Summary Basis of Approval
Cover Form

Appl #: 020450 **Firm: PARKE DAVIS**
Reviewing Div: 120
Trade Name: CEREBYX (FOSPHENYTOIN SODIUM) INJ 75MG/ML
Generic Name:
FOSPHENYTOIN SODIUM

Approval Letter:	Y	Statistician Review:	N
SBA Form:	N	Bio/Dissolution Review:	Y
Final Printed Labeling:	N	Microbiologist Review:	Y
Medical Officer Review:	Y	NAS/NRC Review:	N
Chemist Review:	Y	Pharmacologist Review:	Y
Federal Register Notice:	N	Completion Date:	11-APR-97

20450

Cerebyx

Approval Letter And Related Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-450

AUG - 5 1996

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Ms. Janeth L. Turner
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Ms. Turner:

Please refer to your July 14, 1994 new drug application and your resubmission dated February 22, 1995 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerebyx® (fosphenytoin sodium) Injection 75 mg/mL (50 mg/mL PE).

We also acknowledge receipt of your additional correspondence and amendments dated:

February 27, 1996	April 12, 1996	May 8, 1996
March 13, 1996	May 1, 1996	July 12, 1996
March 14, 1996	May 2, 1996 (2)	July 30, 1996

This new drug application provides for the following:

> Cerebyx® is indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. The safety and effectiveness of Cerebyx® in this use has not been systematically evaluated for more than 5 days.
>
> Cerebyx® can be used for the control of generalized convulsive status epilepticus and prevention and prevention and treatment of seizures occurring during neurosurgery. It can also be substituted, short-term, for oral phenytoin.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated July 12, 1996 with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. The revisions are as follows:

1. Please correct the legend to Figure 1 to read "...1200 mg PE Cerebyx infused..." rather than "...1200 mg Cerebyx infused...."

2. WARNINGS: Usage in Pregnancy, *Clinical* section

B. *Risks to the Fetus.*

Paragraph 1, last sentence: please change "contribution" to "contributions".

3. WARNINGS: Usage in Pregnancy: *preclinical:* section

The wording of dose comparisons and plasma level data should be made consistent as follows:

Para 1, sentence 2: ... (approximately 30% of the maximum human loading dose or higher on a mg/m^2 basis), which produced peak maternal plasma phenytoin concentrations of approximately 20 μg/mL or greater.

Para 1 sentence 4: ... (approximately 10% of the maximum human loading dose on a mg/m^2 basis) ....

Para 2, sentence 1: ... (approximately 50% ....

Para 2, sentence 2: ... (approximately 120% ....

4. PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility; section

Para 3, last sentence: ... at doses of 50 mg PE/kg or higher (approximately 40 % of the maximum human loading dose or higher on a mg/m^2 basis).

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-450. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Phase IV Commitment

We remind you of your Phase 4 commitment specified in your submission dated April 12, 1996 and amended on July 12, & 30, 1996. This commitment is listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment." Yourcommitment is as follows:

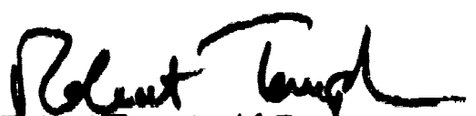
In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact: Robbin Nighswander, R.Ph.
Regulatory Management Officer
(301) 594-2777

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-450

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Ms. Janeth L. Turner
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

FEB 23 1996

Dear Ms. Turner:

Please refer to your July 14, 1994 new drug application (and your resubmission dated February 22, 1995) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerebyx® (fosphenytoin sodium) Injection 75 mg/ml.

We acknowledge the following additional correspondence and amendments:

September 2, 1994	July 21, 1995	October 31, 1995
September 14, 1994	September 5, 1995	November 3, 1995
October 6, 1994	September 14, 1995	November 20, 1995
December 16, 1994	September 27, 1995	January 4, 1996
March 29, 1995	October 19, 1995	January 8, 1996
June 8, 1995	October 27, 1995	February 9, 1996
June 22, 1995	(2 submissions)	

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to adopt as labeling for Cerebyx®, the draft package insert attached to this letter, modified as requested (i.e., as per this letter and the notes embedded within the text of the attached package insert).

Phase IV Commitment

We also ask that you submit the following information:

1. **Labeling:**

Package Insert: Should additional information relating to the safety and effectiveness of Cerebyx® become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Product and Container Labeling: Please revise all product and container labeling to appropriately convey that dosage conversion calculations do not need to be performed when converting patients between fosphenytoin and phenytoin (i.e., all labeling should clearly convey that 50 mg/ml of phenytoin is being delivered and that NO dosage conversion factor need be applied).

2. **Microbiology:**

The following microbiological issues concerning sterility assurance and other issues have not been completely addressed:

a. Bulk solution bioburden limits (prior to filtration) should be specified and the methods to test this, including sample points, should be described. Historical data may be provided in support of the established limit. We prefer the sample collection point be identified in the manufacturing instructions.

b. The frequency of requalifying sterilizers (autoclaves and tunnels) was specified as every 2 years. We generally recommend more frequent evaluation of the instrument and process.

c. The operating parameters for sterilization of filters and filling equipment were not provided and their validation was not discussed.

d. Validation of the integrity of the container and closure systems' barrier to microbial ingress was not discussed. Please provide a summary of the methods and results demonstrating the integrity of this system.

e. Your amendment dated October 27, 1995 describes specifications for media fills (Tab 5, Appendix 1, page 19). The stated Alert Limit permits no investigation of any kind when as many as 2 containers are contaminated in a batch of 5000. We encourage some investigation of any evidence of contamination in product (simulated or otherwise) manufactured by a process for sterile product.

3. Manufacturing and Controls:

Safety Update

Submit a safety update report as provided for under 21 CFR 314.50(d)(5)(vi)(b). This may be limited to deaths, serious adverse events, other adverse events that led to discontinuation of the drug, and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels. Please also include any serious adverse events reported since your last safety update in the final draft version of product labeling you submit in response to this approvable action.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Robbin Nighswander, R.Ph., M.S.
Regulatory Management Officer
Telephone: (301) 594-2850

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachment (1)

Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 9, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Cerebyx® [fosphenytoin injection] NDA 20-450 Approvable Action

TO: Robert Temple, MD, Director, ODE 1
&
File NDA 20-450

This memorandum provides a discussion of several factors affecting the regulatory action that might be taken in regard to Parke-Davis' pending NDA 20-450 for Cerebyx® [fosphenytoin].

Several options, ranging from approval to disapproval are defensible. As a matter of tactics, however, the action letter being forwarded declares the NDA approvable, albeit under a number of conditions that are enumerated both within the text of the letter and within a version of product labeling developed by the division (i.e., in 'notes to the firm' embedded within the text) that would be attached to the letter, if issued. If the Office were to choose an alternative action, the draft approvable letter may be modified accordingly.

Introductory Comments and notes about the administrative strategy applied in the evaluation of this NDA

The structure of the arguments supporting approval

Although Cerebyx® [fosphenytoin] is a new chemical entity, an approval of the NDA for Cerebyx® is only possible, given the type of the information provided in the NDA, because Dilantin®, Parke Davis' innovator brand of phenytoin, is an approved anti-epileptic drug product [AED].

The conclusion that Cerebyx® is effective in use, in particular, turns not on reports of adequate and well controlled clinical investigations, but upon 1) the knowledge that phenytoin is an effective AED, 2) that fosphenytoin is completely converted within minutes of injection to phenytoin and 3) evidence adduced by the sponsor in biopharmacokinetic and clinical trials showing that when Cerebyx® is administered under the directions provided in the proposed Cerebyx® product labeling, the resulting plasma levels of phenytoin approximate those that are obtained when Dilantin injection is administered under its recommended conditions of use for the same claimed use.

Although the agency's earlier determination that the benefits of Dilantin® injection outweigh the risks of its use is a necessary element in the chain of argument and evidence that can be used to support a conclusion that Cerebyx® will be safe for use under its proposed labeling, the determination involving Dilantin® is, in and of itself, insufficient to support the conclusion about Cerebyx®'s safety. Not only is fosphenytoin a different molecular species than phenytoin (and, therefore, may pose an entirely distinct panoply of risks unrelated to its conversion to phenytoin), but fosphenytoin injection yields two/three molecular species, phosphate and formaldehyde/formate that are not produced when Dilantin is administered. How these differences affect the regulatory decision, and how well I believe they have been addressed by the firm, are discussed in a later section of this memorandum.

An administrative issue affecting labeling of both Cerebyx® and Dilantin®

Cerebyx® labeling can be viewed as addressing both fosphenytoin specific (e.g., fosphenytoin, formate, phosphate) and phenytoin related issues. The latter, to the extent that they represent information not currently included in Dilantin® labeling pose a problem in that, with the marketing of Cerebyx®, there would be in existence different, arguably contradictory, statements about the same drug substance (phenytoin) in the labeling of two different approved drug products (Dilantin® and Cerebyx®).

While we do not propose to resolve the problem by linking the approval of

the Cerebyx® NDA to full revision of Dilantin® product labeling, we do recommend, if the Cerebyx® NDA is declared approvable, asking the firm to revise the content of those sections of Dilantin® product labeling (both oral and injectable) that differ substantively from Cerebyx® product labeling (e.g., phenytoin specific matters vis a vis pregnancy, teratogenicity, etc.) and to submit labeling supplements to all[1] their Dilantin product NDAs at the same time as they make a response to a Cerebyx® approvable action letter.

Effectiveness in Use.

As noted in the preceding section, although the Cerebyx® NDA contains no reports of adequate and well controlled clinical investigations that document fosphenytoin injection's capacity to suppress seizures, the effectiveness of the product as an anti-epileptic drug [AED] can be deemed established on the grounds that 1) fosphenytoin is a prodrug for phenytoin[2] and 2) under the conditions of use recommended in the labeling proposed by the Division, Cerebyx® injection will yield plasma levels of free phenytoin that are sufficiently close[3] to those that would be produced

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[1] The firm might not choose to revise Dilantin® injection because they intend that it be replaced by Cerebyx®; I would recommend that we insist that they do, however, in part to ensure that generic labeling for injectable phenytoin is consistent with Cerebyx®.

[2] Each molar unit of administered fospheytoin is converted to an equimolar quantity of phenytoin.

[3] It is acknowledged that 'close' has no clinically defined or generally recognized meaning. The word is intended to convey a judgment by the review team that the rate and extent of free phenytoin delivery to the systemic circulation that follows the administration of Cerebyx® do not differ from the rate and extent of free phenytoin delivery that follows the administration of Dilantin® injection to a degree that will a cause a clinically significant difference in treatment response. This judgment, admittedly, cannot be supported by reference to empirical findings; there is no established quantitative relationship between changes in the rate and extent of phenytoin delivery and changes in the percent of patients experiencing a satisfactory anti-epileptic response in any of the clinical settings in which parenteral phenytoin is recommended. While such a judgment is, therefore, undeniably arbitrary, it is

when Dilantin® injection is administered for the same indication[4] under Dilantin® injection's recommended conditions for use to allow Cerebyx® injection to be used in place of Dilantin® injection.

As noted, the bioequivalence of Cerebyx® and Dilantin® injection have not been demonstrated under every possible set of doses and routes of administration being recommended in Cerebyx® labeling. It is our judgment, however, that the products are 'fungible' when given in equimolar doses in settings where the extent, but not the rate, of phenytoin delivery controls its effectiveness.

In the one situation in which rate of phenytoin availability is deemed of critical clinical importance, that is, intravenous loading for the treatment of status epilepticus, the firm has been able to develop a regimen of use under which the pharmacokinetic performance of Cerebyx® and Dilantin® injection are bioequivalent by ordinary agency criteria (i.e., the 90% CL limits on the ratio of the realized values of the estimates for the usual PK parameters of the new to the old product are ≥ 0.8 and ≤ 1.25).

> A digression concerning the doses of phenytoin and fosphenytoin studied may be helpful at this point. The molecular weight of fosphenytoin is approximately 1.5 times that of phenytoin; accordingly a dose of phenytoin only 0.67 that of fosphenytoin is equimolar to the latter. Unfortunately, it is sometimes difficult to be certain whether or not the dose of fosphenytoin

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every bit as reasonable as the one that allows the agency to declare products that differ in their biopharmacokinetic performance 'bioequivalent' as long as the difference in their performance falls within some arbitrary tolerance limits (e.g., the 90% confidence limits on the ratio of realized estimates for a particular pharmacokinetic parameter , say Cmax or AUC, for two products, falls between 0.8 and 1.25). Having said all this, however, it should be noted that the firm did show that fosphenytoin and phenytoin can deliver free phenytoin to the same rate and extent under one specific set conditions of dose and rate of administration. (see discussion of study 982-240).

[4]

1. IV loading in status epilepticus
2. IM or IV loading for treatment or prophylaxis
3. IM or IV use for maintenance therapy
4. IM or IV use for temporary substitution for oral Dilantin

identified in file documents (e.g., in both FDA review documents and sponsor's reports), is intended to represent the actual weight of fosphenytoin or the weight expressed in phenytoin equivalents (PE), that is, the weight of phenytoin that would yield an equimolar amount of phenytoin as the fosphenytoin dose actually administered. There is not much that can be done about those ambiguities in usage other than to be aware of them.

The table that follows provides a concrete example: it enumerates the actual mass doses for both fosphenytoin and phenytoin that would generate the same molar amount of phenytoin in status epilepticus. Note that the rate of phenytoin specified in the table is not actually deliverable with Dilantin® injection because the maximum rate of intravenous administration for that product is 50 mg/min.

Drug	dose	rate
fosphenytoin	22.5 to 30 mg/kg	150 to 225 mg/min
phenytoin	15 to 20 mg/kg	**100 to 150 mg/min

** theoretical: phenytoin cannot safely be delivered at this rate; 50 mg/min is the maximum recommended rate.

Study 98224 shows Cerebyx® and Dilantin® bioequivalent under the iv loading infusion regimen employed (i.e., see the table above). It bears repetition that this regimen is intended for use when phenytoin is being administered intravenously to a patient in status epilepticus; this is the only clinical setting, in our judgment, in which a decrease in the rate of systemic phenytoin delivery might have an adverse effect on clinical outcome. In all other settings, we assume that it is the extent, not the rate, of phenytoin delivery that is controlling.

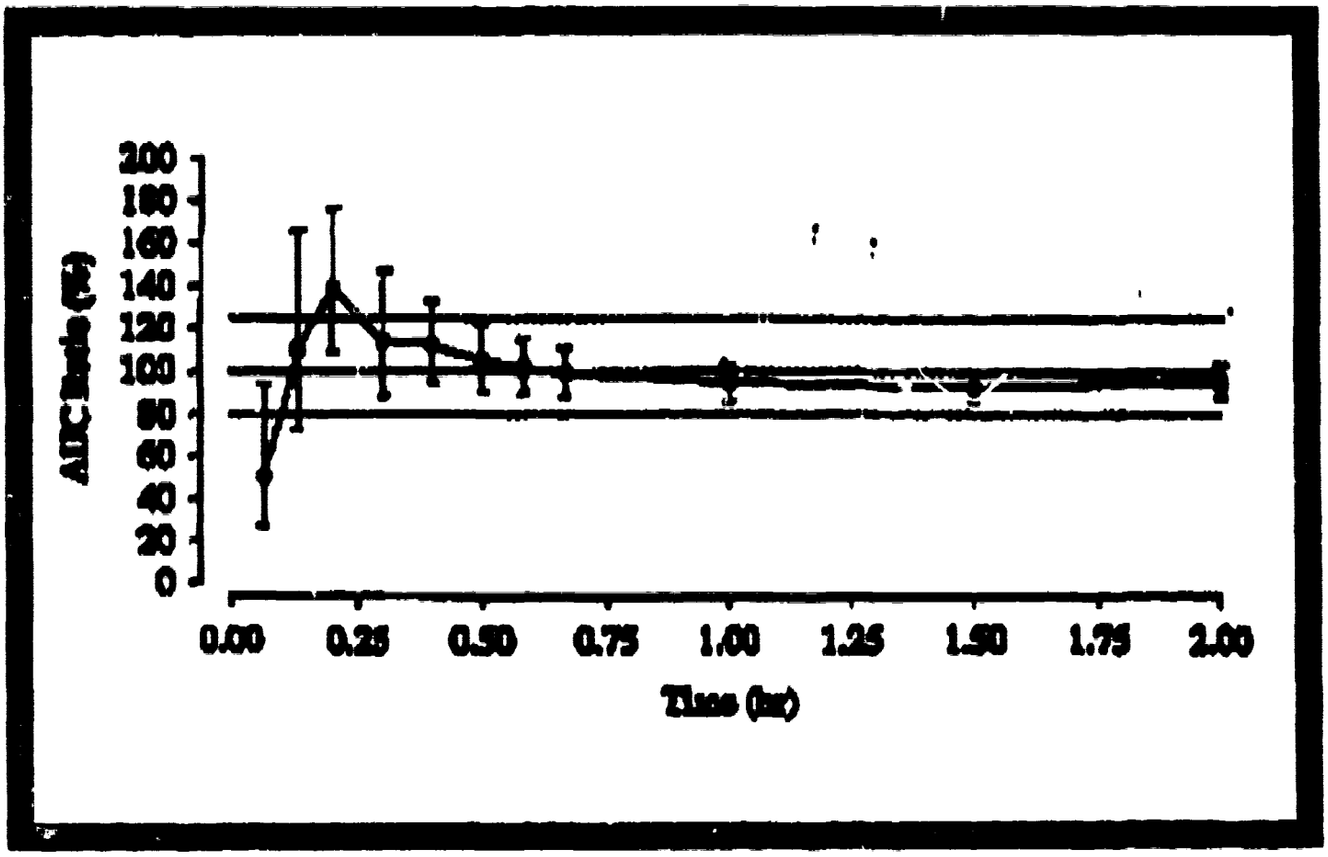
A digression about the method used to assess the relative rate at which Cerebyx® and Dilantin® infusions deliver free phenytoin is useful here. When drugs are administered by constant intravenous infusion, the Cmax and Tmax occur typically at the end of the infusion and the realized values of these parameter estimates are controlled, other variables held constant, by both the total dose and the rate of delivery of that dose.

In ordinary circumstances, therefore, the administration of two drug products that yield the same molar amounts of the same drug substance cannot possibly generate bioequivalent delivery profiles if they are administered at

different rates of infusion. The situation is different where Cerebyx® and Dilantin® are concerned, however.

A number of events and phenomena, including fosphenytoin protein binding, fosphenytoin hydrolysis, phenytoin protein binding, and phenytoin displacement from protein bound sites affect the rate at which Cerebyx® infusion delivers free phenytoin. As a consequence, Cerebyx® must be administered at a faster rate than Dilantin® injection to deliver free phenytoin at an equivalent rate and extent.

The parameter employed to compare the pace of free phenytoin delivery by the two products is the ratio of their cumulative AUCs for free phenytoin. The ratio is obtained by dividing the cumulative AUC for free phenytoin at some time, t, following the start of the infusion of Cerebyx®, by the cumulative AUC for free phenytoin at the same time, t, following the start of an infusion of Dilantin® injection. If the two products deliver free phenytoin at the same rate, the ratio will be unity at all times.



The Division's consultant biopharmaceutical review team has evaluated the firm's report of Study 98224 and concludes that it documents that a

dose of 1200 mg PE of fosphenytoin[5] delivered intravenously at a rate of 150 mg PE/min produces the same cumulative free phenytoin AUC over time as a dose of 1200 mg of phenytoin delivered at 50 mg/min.

Even in study 98224, however, the performance of the two products is not precisely identical throughout the entire post-dosing interval as the plot of the ratio of the cumulative free phenytoin AUC demonstrates (see the figure on the preceeding page which is reproduced from the top panel of Figure 13 on page 12 of the 12/21/95 biopharm review). In short, even in this study, the technical declaration of bioequivalence is somewhat arbitrary as it turns on the time after the start of infusion that is chosen for the evaluation of the cumulative AUC ratio.

In this regard, it is important to note that the regimen selected for Cerebyx® infusion ensures that in comparison to Dilantin® more, rather than less free phenytoin, is generated early on in the course of the infusion (e.g., from 10 to 30 minutes or so), the very period in which it is deemed critically important from a clinical perspective to ensure the rapid delivery of bioavailable phenytoin.

Safety in Use: specific issues.

Whether or not fosphenytoin is safe in use cannot rest on the knowledge that phenytoin is a safe drug, however. Because fosphenytoin is not only a prodrug for phenytoin but for phosphate[6] and formaldehyde/formate[6], the risks that might be associated with the parenteral administration of these products under the conditions of use recommended in Cerebyx labeling must be considered.

Both Dr. Edward Fisher, the primary reviewing pharmacologist, and Dr. John Feeney, the neurology group clinical reviewer responsible for the

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[5] 20 mg/kg given to a 60 kg patient results in 1200 mg total dose

[6] Each molar unit of fosphenytoin forms equimolar units of phosphate and formaldehyde. Formaldehyde is then converted to formate which is then converted to CO_2 and H_2O by a folate dependent step.

application, discuss risks that might derive from the generation of the byproducts of fosphenytoin hydrolysis.

It is important to acknowledge at the outset that concerns about the potential risks posed by these byproducts arise for theoretical reasons; there are no findings of serious injury or toxicity in either clinical or preclinical tests with fosphenytoin that indicate that either formate or phosphate derived from fosphenytoin administration has actually caused harm.

On the other side of coin, however, a systematic effort to detect toxicity that might have been caused by these byproducts (particularly formate) has not been carried out either in animals or humans. Perhaps more important as a reason for caution, the extent of clinical exposure to Cerebyx® at the highest doses and rates of delivery is limited[7] and, accordingly, the warrant provided by the absence of evidence of harm is less than robust.

Formate: the risk of ocular injury

Although no reports of blindness or diminished vision have been reported in association with the clinical testing of Cerebyx, formate, a known mammalian ocular toxin[8] is a by product of fosphenytoin hydrolysis. As much as 5 mmoles of formate may be delivered within 7 minutes under the regimen recommended for Cerebyx® in the management of status epilepticus [SE].

Although the firm had been repeatedly advised of our concern about the potential risk posed by formate exposure, it has yet to provide a systematic evaluation of the extent of, and variability in, formate

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[7] Only 128 patients have been exposed to doses of greater than 15 mg PE/kg at an infusion rates of ≥ 150 mg PE/min and only 66 patients at this rate and the higher dose of 20 mg PE/kg.

[8] Studies in monkeys document that formate levels as low as 7 MMOL/L can cause optic nerve damage; formate is presumably the agent immediately responsible for the blindness that is associated with methanol ingestion

generation following intravenous loading with fosphenytoin. In fact, only 4 patients have had formate levels measured, and then during infusions that delivered only one-half the load of fosphenytoin recommended for the treatment of status epilepticus.

Also, since the metabolism of formate is folate dependent, and a substantive proportion of patients with status epilepticus may be folate deficient (e.g., alcoholics), the issue is not only the extent of monitored experience, but the collateral conditions under which exposure has taken place.

The risk assessment process is further complicated by the sparseness of the information available from preclinical models. At present, we believe (know) that exposures as low 7 MMOL/L can cause ocular damage in monkeys, but do not know whether or not lower exposures can.

On the other hand, Dr. Fisher points out that sustained exposures to elevated levels of formate are probably required to cause injury in humans and that the firm did estimate, based on data available from other sources, the likely increment in serum formate that would follow an infusion of formate equivalent to that delivered by the maximum recommended dose of fosphenytoin, and that such an input would be unlikely to raise formate levels above background, let alone produce those known to cause injury.

Accordingly, in my view, concerns about formate are not of a concern vis a vis the approvability of Cerebyx, although they probably require mention in labeling, unless the firm can provide either argument or data, or both to convince us such mention is unnecessary.

Risks of a phosphate load.

Dr. Feeney draws attention to the risks that might follow rapid IV administration of a phosphate load. Both serum ionized calcium levels and pH may be affected, but neither have been systematically monitored by the sponsor. As with the concerns discussed in regard to formate, I believe we ought to require mention of the possibility of these effects in labeling unless the sponsor can provide evidence or argument to show that

such labeling statements are unnecessary.

Systemic sensations

In his review, Dr. Feeney discusses a set of sensations that are associated with infusion of Cerebyx (burning/pruritus affecting the extremities, the groin and in peri-rectal areas[9]); since these are not observed with phenytoin infusion, it is logical that they are the result of some unique property of fosphenytoin, its byproducts, or some secondary phenomena arising from their introduction into the systemic circulation.

Phosphate, for example, might act directly or indirectly through an effect on serum Calcium levels. The usual signs/symptoms of tetany (peri-oral dysthesias, tingling in the distal extremities, etc.), however, do seem distinguishable from those associated with fosphenytoin infusion; nonetheless, the possibility that changes in serum Calcium are involved cannot be dismissed out-of-hand.

The bottom line, however, is that our ability to assess any hypothesis regarding the cause of these phenomena is limited by the minimal monitoring of serum formate, Calcium, phosphate and pH done by the firm.

Fatalities

The population treated with fosphenytoin is likely to be at substantially greater risk of death than the typical cohort of patients with complex partial seizures who participate in the usual AED development program. In particular, the fosphenytoin cohort includes patients in status, those with head trauma, etc, and as a consequence is a cohort in which deaths, regardless of treatment, are expected.

Accordingly, I am not concerned about the number of deaths reported in

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[9] Dr. Feeney writes that "the character and location of the sensory disturbance described for Decadron and Hydrocortisone matches the dominant description in Cerebyx-treated subjects. With all 3 agents, patients describe a burning or itching which localizes primarily to the groin area."

association with the use of fosphenytoin. This judgment, however, is defended only by my personal intuition, no more, no less.

Safety and Common ADRs

This is largely a labeling display issue. The firm has studied Cerebyx® over a number of disparate conditions in different patient populations. It makes no sense in my view, to combine these experiences in an effort to provide a single, overall, table of untoward clinical event incidence. Instead, it makes far more sense to present the incidence within the various settings. We instruct the firm, within the text of labeling, how best to accomplish this goal.

Safety in Children

This important age group has not been evaluated; if approved, Cerebyx® is likely to be used in children, yet we do not have information on their handling of the product.

Safety in Use- overall considerations:

The extent of clinical experience with an investigational drug, the degree to which that experience is representative of the conditions under which the drug will be used if marketed, and the quality and kind of patient monitoring during the drug's clinical testing determine the strength and value of any warrant that may be offered about the safety of a drug at the time of its approval.

Obviously, the fewer the number of patients exposed, the less reliable any warrant about the drug; this applies both to risks that were and those that were not observed during the product's pre-marketing development.

This generic caveat applies to any regulatory conclusion that a drug is 'safe for use;' but it is especially applicable where Cerebyx® is concerned. First, because this product has been administered to relatively few individuals overall. The total numbers of subjects exposed are enumerated in the following table:

	NDA	SU 1	SU 2
Population			
Total Enrolled	849	861	994
Exposed to Fos	736	748	859
Cutoff Dates			
General Safety	Sept 1, 94	Feb 22, 95	Aug 1, 1995
Deaths/Serious AEs	Nov 18, 94	May 15, 95	Sept. 15, 1995

Of greater concern, Cerebyx® has been administered to even fewer under conditions of use where it is expected to cause the greatest number of problems: high rate intravenous infusion. Specifically, as of the last safety update, only 128 patients had been exposed to doses ≥15 mg PE/kg at an infusion rates of ≥ 150 mg PE/min and only 66 have been exposed to doses ≥ 20 PE/kg at infusion rates of ≥ 150 mg PE/min.

Whether or not this extent of clinical testing provides an adequate basis to allow the marketing of Cerebyx® under these conditions is a determination that turns on personal judgment, and, therefore, ultimately, the personal judgment of the agency official who has the delegated authority to act on the question, in this case, the Office Director.

Discussion of Options

Although the evidence provided by the sponsor is probably sufficient to allow some expert epileptologists to reach, responsibly, a conclusion that Cerebyx® has been shown to be safe for use under high dose, high rate conditions of use recommended in its proposed labeling, I cannot know whether most, or even a majority of experts, would reach the same conclusion.

Accordingly, the division has prepared an approval action letter because it believes such an action can be defended, although it is not necessarily the

action that any of us may individually prefer[10].

In any case, I could also defend an action approving the NDA under labeling that either 1) warns about the residual uncertainties concerning the safety of the high dose regimen, or 2) omits the high dose/high rate regimen on the grounds that there is insufficient evidence to ensure its safety.

Neither of these options is entirely appealing, however, because Cerebyx® is only able to deliver phenytoin as rapidly as Dilantin® injection under the high dose, high rate regimen, and, therefore, we could not be certain, under either of these options, that Cerebyx would be fully effective (or as effective as Dilantin® injection), when used in the management of status.

We could, of course, disapprove the NDA, arguing, as we did when it was first submitted, that more clinical experience (i.e., safe passage) with the product under the high intravenous loading dose regimen is required before we can conclude that it is safe in use regardless of the restrictions placed on its use in labeling. The argument being made here is that whatever the labeling limitations or restrictions applied, the product would, if marketed, be likely to be used under the high dose/high rate regimen, a regimen yet to be shown to be safe.

This would be a difficult regulatory position to defend, however, because we are only obliged, at least ordinarily, to determine whether or not a drug is safe for use under the conditions of use recommended in its labeling. In short, were it not for the status epilepticus indication, it would be easy to conclude that Cerebyx® has been shown to be safe for use. On the other hand, none of us is unaware of the extent of 'off label' use of marketed drug products and the potential for that use to cause harm.

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[10] Personally, I would clearly feel more comfortable with an approvable action if it were taken with the knowledge that 200, rather than 66 patients, had been exposed without serious incident to the highest dose and rate intravenous loading regimen. The problem, of course, is that I would take still greater comfort if there were 2000 such exposures.

Importantly, nothing in this discussion is intended to gainsay or undermine the potential advantages that may well be provided by Cerebyx®. An injectable form of phenytoin that is less locally irritating than Dilantin® (reasonably inferred from what we know but not proven) would be especially useful for intramuscular use. The point is that it is a matter of personal judgment whether the gains are sufficient to outweigh our residual doubts about its safety for use.

Finally, neither I, nor any member of the review team, to my knowledge, is so wedded to any single view of this matter that we are absolutely committed to one and only one course of action. To the contrary, this is a close decision and I can accept any of the 3 options enumerated. I am, as are members of the review team, available to discuss the matter further, as required.

2/9/96

Paul Leber, M.D.
2/9/96

NDA 20-450
HFD-100
Temple
HFD-120
Katz
Feeney
Fitzgerald
Fisher
Blum
Heimann
Nighswander
HFD-860
Harris
Miller
Baweja
Malinowski

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 20 1996

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Fosphenytoin, NDA 20-450 (Cerebyx)

TO: Dr. Paul Leber, HFD-120

I believe this application is approvable and that the available data and documented exposure are sufficient for a proding for a very familiar active moiety. The possibility remains, as you note, that some rare, "idiosyncratic" response to the short-liver parent molecule, or to a minor unsuspected metabolite of the parent, could occur, but a few 100 more patients will not resolve that question.

I have modified the letter slightly, I think still reflecting what was sought by the Division.

I have one regulatory, not scientific question: why is fosphenytoin considered an NME? Type 4 NDAs include new salts or esters of a previously approved active moiety. Although allowance is made for stable esters, especially where these are active (e.g., isorsorbide mono-odinitrate) that doesn't seem the case here, with the 15 minute half-life.

I have made a few labeling changes and note particularly the following changes and questions.

2 Pages
Purged

Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 22, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Reply to your memo of 2/20/96

TO: File, NDA 20-450 Cerebyx(fosphenytoin)
&
Robert Temple, M.D.
Director,
Office of Drug Evaluation 1

The Division's review team has reviewed the comments about the Cerebyx action presented in your memo to me of 2/20/96.

We take your point that the intravenous administration of Cerebyx under any dosing regimen cannot precisely reproduce the phenytoin input to the systemic circulation that is obtained with the direct infusion of phenytoin sodium at 50 mg/min. Accordingly, we have revised the dosing instructions so that the recommended regimen for the treatment of status is between 100 mg PE/min and 150 mg PE/min. This should result in an intermediate choice by many and that will be fine.

For the most part, we have otherwise made the changes in the labeling and letter as you requested, except for one or two places.

Dosing and Administration Section:

Here, we found your additional comments to be verbose and confusing. Accordingly, we simplified the instructions, providing the major points regarding iv use in a series of 4 brief bullets.

We did, however, incorporate the intent of your comments in this section in the Clinical Pharmacology Section.

Warning Section:

The instruction regarding the maximum rate of phosphenytoin infusion seems

unnecessarily confusing when it includes the phrase "at rates greater than 50 mg/min." We would prefer deleting the phrase. The call, however, is clearly yours and toward that end we provide two pages 6's, one with and one without the phrase.

Pharmacology:

I have allowed Ed Fisher and Glenna to repair and revise the pharm sections as they believe best. I find their changes reasonable and assume that you will as well.

Questions in the memorandum:

First, fosphenytoin is an ester, but not of phenytoin. It's an NME and we can take credit accordingly.

As to your other questions, I'm not sure that I can answer them in a meaningful manner; I'll try (John Feeney is my major source of inspiration and data on this).

4. How, if at all, renal and/or liver disease affects fosphenytoin to phenytoin conversion is unknown. The theory is that the free fraction of fosphenytoin is increased in the presence of hypoproteinemia.

5. Yes, because this is part of a regimen that will lead to the chronic use of phenytoin

#6. Dilantin is an ancient drug product--many things in its labeling got there the same way that they get into the labeling of all older drugs--in short, we don't know, and, don't have the resources available currently to find out.

I trust you can sign this approvable action as is; if not, let us know.

Paul Leber, M.D.
2/22/96

Final Printed Labeling

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Medical Officers Review

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	Third Safety Update
Correspondence Date:	April 12, 1996
Date Received:	April 15,1996

Background: This safety update consists of 2 volumes out of a 4 volume submission. The entire submission represents the sponsor's response to a recent Approvable Letter.

Exposure: The cutoff date for the last (second) safety update was September 15, 1995. This SU covers all deaths, serious AEs, and withdrawals for AEs that have occurred since then. Data are also provided from 2 studies of Fos which are being conducted under a separate IND . Events from all studies are summarized through March 8, 1996.

It appears that there is only one ongoing study in status epilepticus. Only 5 additional pts have been enrolled since the last (second) SU. Of these 5, no deaths, serious AEs, or withdrawals because of serious AEs have been reported. Therefore, this SU reports almost entirely on the experience of Cerebyx in stroke.

Deaths: 10 deaths (on placebo or Fos) occurred out of 79 pts enrolled in stroke studies. We know that 1/10 deaths occurred on Fos and 1/10 deaths occurred on placebo. Because the blind has not been broken in the other stroke study, we do not know the treatment assignment of the 8 other deaths. All deaths appear related to the stroke itself or the sequelae of stroke. None of the deaths were attributed to Fos.

Serious, Nonfatal AEs: 5 pts had serious AEs that were nonfatal. One of these, severe hypotension related to Cerebyx was reported as an IND safety report on March 12, 1996 and is outlined in the next paragraph. The blind was not broken for the other AEs, but a review of them suggests that none would be considered attributed to study drug.

Pt 113 in Study 25, a 51-yr-old woman, developed an absolute decrease of 67 in her systolic pressure during a loading dose of Cerebyx for treatment of stroke. BP was 142/86 and dropped to 75/50. The investigator classified the event as life-threatening, although the BP returned to baseline with fluids.

Withdrawals Due to AEs: 5 pts withdrew due to AEs. 3/5 occurred in a completed stroke study so that we know all 3 received Cerebyx. The other 2 occurred in an ongoing stroke study where the blind has not been broken.

Patients 111 in Study 19 in stroke had the infusion stopped (note that the rate was 50 mgPE/min) because of perineal burning and itching. The event was called severe and occurred after only 27% of the injection was given. Symptoms resolved after13 minutes followed an hour later by recurrence of mild itching for 5 min.

Patients 118 in Study 19 in stroke had the infusion stopped (note that the rate was 50 mgPE/min) because of perineal itching. The event was called moderate and occurred after 16% of the injection was given. Symptoms resolved in 5 minutes.

Other events were mild hypotension, severe bradycardia (treatment assignment unknown), and atrial fibrillation in a pt with a history of AFib (treatment assignment unknown).

Summary:

Burning, itching, bradycardia, hypotension are all described in proposed labeling. Therefore, the safety profile of Cerebyx has not changed with the addition of this safety update.

John Feeney, M.D.
Medical Reviewer
April 23. 1996

cc:
HFD-120
IND 28,217
HFD-120/Leber/Katz/Feeney/Nighswander

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	Proposed labeling revisions
Correspondence Date:	April 12, 1996
Date Received:	April 15,1996

Background: The entire 4-volume submission represents the sponsor's response to a recent Approvable Letter. Two volumes represent the requested safety update and are reviewed in a separate document. The other two volumes represent the proposed labeling revisions along with supporting documentation.

Proposed Labeling Changes: Only major changes are addressed here.

Two pervasive changes made by the sponsor are the correct insertion of the word **sodium** whenever describing equivalent doses of Cerebyx and parenteral Dilantin. Phenytoin as the free acid (Dilantin-30 Pediatric and Dilantin-125 Suspensions and Dilantin Infatabs) would have a different dose equivalence. The sponsor would also like to delete the **PE** used throughout labeling to refer to doses of Cerebyx. The very fact that different phenytoin products already on the market provide different amounts of phenytoin for equivalent weight-based dosing regimens would support the use of the PE notation throughout labeling to point out the equivalence only to phenytoin sodium and not to the free acid.

Issues related to formate and phosphate have been addressed by the sponsor by presenting data from Study 27, a PK study of the high-dose, high-rate loading dose. Some of this data was presented in submissions (specifically requested by me) dated **May 2 and May 8, 1996**. This information is discussed in **Appendix I.**

5 Pages Purged

John Feeney, M.D.
Medical Reviewer
June 17. 1996

cc:
HFD-120
IND 28,217
HFD-120/Leber/Katz/Feeney/Nighswander

CLINICAL REVIEW AND EVALUATION

NDA 20-450

Cerebyx (fosphenytoin)

Reviewer:	John Feeney, M.D.
Date:	February 1, 1996
Sponsor:	Parke-Davis
Indication:	Epilepsy
NDA Submission Date:	February 23, 1995

Table of Contents

Overview

Cerebyx (fosphenytoin) has been developed by Parke-Davis

The basis for an approval action on this NDA is the demonstrated bioequivalence of IV Cerebyx and IV Dilantin. When Cerebyx was administered at an IV rate that was three times greater on a molar basis than the rate of Dilantin, bioequivalence based on free phenytoin levels was demonstrated.

It became clear during the review of this NDA that confusion readily arises in discussing the dosage of Cerebyx. The molecular weight of Cerebyx is 50% greater than Dilantin, so that 150mg Cerebyx delivers the same molar amount of phenytoin as 100mg Dilantin. Therefore, an infusion rate of 75mg/min Cerebyx delivers the same molar amount of phenytoin as 50mg/min Dilantin (the maximal labeled rate for Dilantin). However, the bioequivalent rates (as defined above for free phenytoin levels) would be 225mg/min Cerebyx and 50mg/min Dilantin.

Since the use of Cerebyx will, by design, be temporary with conversion to oral phenytoin soon thereafter, I believe that Cerebyx dosing should be expressed in phenytoin equivalents in labeling. Thus, 150mg Cerebyx would be expressed as 100mg phenytoin equivalents (PE). This eliminates the one and only step in converting total oral phenytoin dosing to parenteral Cerebyx dosing, but still leaves one step in converting the Dilantin loading dose rate (50mg/min) to the bioequivalent Cerebyx loading dose rate (150mg/min phenytoin equivalents). By not expressing Cerebyx as PE in labeling, I believe there will be considerable confusion in dosing during the first few years of general use.

Cerebyx is a phosphate ester of phenytoin. The bioavailability of phenytoin after IM Cerebyx is 100% with good local tolerability in over 300 patients exposed. The sponsor contends that IV Cerebyx is better tolerated at the injection site than IV Dilantin. This latter point is supported by the normal volunteer studies when injection site irritation is examined in Cerebyx and Dilantin treated patients at bioequivalent rates. The active-control trials in patients did not adequately control for dose and rate betweeen Cerebyx and Dilantin patients, so that no additional comparative data on IV injection site irritation is yielded by those studies. Study 26 may provide comparative information along these lines, but we are not yet in possession of that final study report.

Cerebyx is rapidly converted to phenytoin with a half-life of 15 minutes. The two byproducts of this conversion are phosphate and formaldehyde. The theoretical safety concerns of formaldehyde formation have been addressed by the sponsor and are the subject of much discussion in the pharm/tox review of Dr. Fisher. On page 60 of his review, Dr. Fisher notes (page 60 of his review) that peak plasma formaldehyde levels would be predicted to be 5.4mg/L, with levels returning to background levels (2.6mg/L) within 20 minutes. In fact, formaldehyde levels are apparently difficult to measure in plasma, and beyond this, the toxicity of formaldehyde may in large part be due to its metabolism to formate as occurs in methanol poisoning.

Formate levels that produce optic nerve pathology are only 10-20 X background levels. Maximal formate levels were predicted by the sponsor to be no higher than background levels. This prediction has not been verified with empiric data to date. Formate levels were not measured in preclinical toxicity studies; in fact, models of formate toxicity in non-primates can only be produced in the presence of folate deficiency. Normal formate levels were measured in 4 normal volunteers, but at a Cerebyx-exposure much less than will occur with the standard loading dose. In the absence of formate levels in adequately loaded subjects, the safety margin cannot be stated.

Not addressed by the sponsor or the pharm/tox review is the phosphate load with Cerebyx. The loading dose of Cerebyx delivers 75mg elemental phosphorus. Assuming retention in the plasma, the theoretical increase in serum phosphorus would be 2mg/dL. If the calcium-phosphorus product

exceeded 60-70 in a given patient, the theoretical concern would be calcium deposition in soft tissues and a possible transient decrease in calcium. The sponsor has measured ionized free calcium at the end of a 7 minute loading dose in 5 volunteers and found these levels to be normal. Obviously, this is a small experience which should probably be expanded. Additionally, the sponsor should be asked to assess the distribution of the phosphorus load in varying states of decreased glomerular filtration. Labeling should certainly make note of this issue, especially in dialysis patients. (The sponsor performed a study in dialysis patients, but used a small loading dose administered over 30 minutes.)

The safety database accrued is complex and makes any exptrapolation of the results difficult. Several important points follow:

First, the two active-control trials with IV Dilantin (Studies 15 and 21) do not allow any direct comparisons between treatments. Both trials incorporated IV loading doses (one of the two also included maintenance IV dosing beyond the IV load) and I believe the loading dose presents the biggest safety concern in the use of Cerebyx. However, neither trial provided for Cerebyx and Dilantin to be administered at the bioequivalent rates. (Study 26 may allow for some direct comparisons, but we do not have the final study report yet.)

Second, as a general rule over the entire database, the high-dose, high-rate Cerebyx patients were also some of the sickest patients, usually patients with status epilepticus. While this may in fact mirror the intended usage of high-dose, high-rate Cerebyx, it makes the interpretation of the safety data more difficult.

Third, the patients exposed to Cerebyx tended to fall into one of two categories: 1) seriously ill patients with status epilepticus or pending neurosurgery and 2) relatively stable patients with epilepsy. The net effect of this is that the safety data from one group cannot really be merged with the other.

Normal volunteer studies were in general limited to escalating IV "loading" doses. Since the population of normal volunteers is relatively homogeneous, I believe it provides important information on rate-related adverse events, making some comparisons between Cerebyx and Dilantin treated subjects possible. For instance, one unique adverse event that

occurs with Cerebyx is a sensation of generalized itching or tingling which is variously coded as pruritus or paresthesia. In the normal volunteer studies, this phenomenon can be seen to be rate-related for both Cerebyx and Dilantin, but with a much higher incidence with Cerebyx at bioequivalent rates of administration.

Similarly, in the normal volunteer studies, injection site pain and injection site reaction are seen to be rate-related for IV Dilantin and occur only rarely for Cerebyx at any rate.

The sponsor has proposed use of Cerebyx for up to 14 days. However, only a few patients were exposed for longer than 5 days. I believe labeling should reflect the database with use allowed for 5 days or less.

For labeling purposes, the sponsor proposes to present adverse event data separately for the 3 controlled trials. Since the AE profiles in these trials only reflect the population studied (seriously ill neurosurgery patients vs stable epilepsy patients) and since the standard deviation around any point estimate from a given trial must be exceedingly large, I would argue to discard these tables from labeling and bring forward the descriptive list of AEs in the parenteral Dilantin labeling.

Finally, the sponsor has not fully addressed the unique adverse event of pruritus/paresthesia seen with Cerebyx. In particular, the ISS often uses descriptive language to the effect that this AE was "usually transient." In my review, I could not ascertain the outcome of all cases of this AE. I found no specific mention of a case of pruritus/paresthesia that persisted, but I would request the sponsor to directly address the question of reversibility of this AE. The second safety update (November 1995) added 100 individual exposures to the high-dose, high-rate experience with Cerebyx and confirmed the frequent occurrence of pruritus in that situation. The sponsor could provide more information on the experience of these individuals with the sensory disturbance.

Conclusions:

Cerebyx is approvable. The following additional information is needed before a final approval action can be taken:

1. The sponsor should provide a more complete description of the sensory

disturbance caused by Cerebyx, to include the reversibility over time.

2. Levels of phosphorus, magnesium, and free calcium should be measured at frequent timepoints during a 7 minute loading dose of Cerebyx and correlated with the character of the sensory disturbance.

3. Formate levels should be measured after a loading dose of Cerebyx. Since the breakdown of formate is folate dependent, and because folate deficiency may be common in the population treated with Cerebyx (alcoholics and/or patients on chronic phenytoin therapy), some attempt should be made to measure formate levels in a folate deficient population after a loading dose of Cerebyx.

The advantages of Cerebyx over parenteral Dilantin are:

1. Given IV, it produces fewer local reactions, can be given in one-third the time of Dilantin, and may be more compatible with other IV solutions.

2. It can be given IM with predictable absorption and fewer local reactions.

Peripheral Sensory Phenomena

Background: We refused to file the original NDA submission for Cerebyx because of the minimal safety database accrued at high dose, high rate (SE dosing) infusions. The sponsor only slightly improved upon this at the time of the resubmission. Again, the first safety update only minimally improved upon this. The second safety update in late 1995 more than doubled the exposure to SE dosing.

Looking only at the NDA submission, it became clear from normal volunteer studies that a dose- and rate-related sensory disturbance occurred with IV Cerebyx. In patient studies, the bulk of patients exposed to SE dosing were too obtunded to report sensory disturbances because they were in fact SE patients. Therefore, in patient studies, a dose- and rate-related sensory disturbance was less obvious.

The second safety update in late 1996 included the results of Study 26 performed from April 1995 to June 1995. Ninety patients were added to the SE dosing database. Half the patients were epilepsy patients (not SE patients and not neurosurgery patients) and would not be expected to be obtunded. Likewise half the patients reported pruritus. Because we are not in possession of all the information from Study 26, we cannot ascertain the exact proportion of patients who were alert enough to report sensory disturbances. It is possible, given the information provided, to assume that all awake patients in Study 26 experienced some degree of sensory disturbance; it is also possible that only half did.

These were not trivial disturbances. The infusion was interrupted or discontinued for 13/44 (30%) patients experiencing pruritus. The intensity was rated severe for 6/44 (14%) patients; moderate for 17/44 (39%) patients; and mild for the remainder.

The mean onset time was 2 minutes for these 44 patients. By the time of follow-up, outcome was unknown for 1/44 patients. Resolution of sensory symptoms is reported for all the rest. Because time-to-resolution is referenced to end of infusion, and because we are told that infusions were slowed or stopped because of pruritus in a third of patients, we cannot determine what happens in the absence of altered rate and time of

infusion. It sounds like most patients improve within 5-10 minutes of stopping the infusion (12-17 minutes from start of infusion, assuming the infusion is given over the prescribed 7 minutes). A fourth of patients have some degree of disturbance beyond this point (median, 1 hour).

The second safety update also mentioned the results of Study 27, a 16-subject PK and safety study. 75% of these normal volunteers experienced pruritus; 75% of these normal volunteers experienced paresthesia. Four of the 16 subjects (25%) reported "severe" pruritus.

Significance: Just based on what we know about this phenomenon, it is clear that the natural history of the disturbance must be elucidated more clearly in order to provide for the safe use of this drug. For instance, the intensity of symptoms for those patients who experience symptoms beyond one hour of dosing has not been provided to us. Do some patients have severe pruritus for days or do only mild symptoms persist beyond one hour ? Since many patients who receive IV loading with Cerebyx will not need rapid loading, labeling will need to reflect a rate for those patients which results in minimal discomfort.

Also, could the pathophysiology that underlies the sensory disturbances with SE dosing of Cerebyx herald some more serious pathology ?

In awake patients treated with SE dosing of Cerebyx, patient reporting of sensory disturbance could lead to lowering of rate. In obtunded patients, this margin of safety has been removed.

Example of Foscavir (foscarnet): Foscavir is an example of a drug where the onset of sensory disturbance does herald more serious problems, specifically with hypocalcemia. Foscavir was developed for IV administration for the treatment of CMV retinitis in the mid-1980s. Early on it became clear that many patients experienced distal and perioral paresthesias, tetany, and seizures. The constellation of symptoms and signs was identical to that seen with hypocalcemia and, in fact, total serum calcium levels were low in some patients. Cases of fatal hypocalcemia have been reported with this drug.

Experience with Foscavir has demonstrated that the labeled loading infusion may cause decreases in ionized free calcium even though total

serum calcium remains normal.[1,2] The mechanism of this ionized hypocalcemia is believed to be **chelation** of free calcium by foscarnet itself (structurally appearing as a phosphate moiety with a carboxyl group substituted for an oxygen). Foscarnet is excreted unchanged in the urine, presumably carrying calcium with it. There is no evidence that foscarnet is broken down to phosphate, and there is no evidence of phosphate precipitating out of solution with calcium. While foscarnet itself is toxic to renal tubule cells, there is no evidence of nephrocalcinosis (deposition of calcium-phosphate precipitates in the kidney) or other soft tissue calcium deposition.

The current labeling for Foscavir states (WARNINGS; Mineral and Electrolyte Imbalance), "Therefore, patients should be advised to report symptoms of low ionized calcium such as perioral tingling, numbness in the extremities and paresthesias. Physicians should be prepared to treat these as well as severe manifestations of electrolyte abnormalities such as tetany and seizures. The rate of Foscavir infusion may affect the transient decrease in ionized calcium. Slowing the rate may decrease or prevent symptoms."

Possible Mechanisms of Cerebyx-Induced Sensory Disturbance: There are many ways that Cerebyx could cause sensory symptoms. **Any explanation has to account for a lack of symptoms at bioequivalent dosing regimens of parenteral Dilantin.** Perhaps IV fosphenytoin (the parent compound) alone causes sensory disturbance. Or perhaps IV fosphenytoin results in a distribution of phenytoin in tissues that is different from the distribution that results from parenteral Dilantin. Formate and phosphate are the two byproducts of fosphenytoin metabolism. Either one of these could cause transient sensory disturbances either directly or via an intermediate step.

A. Formate: Note that several steps are necessary in the metabolism of Cerebyx before the formation of formate. Given the almost immediate

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[1]Jacobson, Gambertoglio, Aweeka, Causey, and Portale. Foscarnet-induced hypocalcemia and effects of foscarnet on calcium metabolism. J Clin Endocrinol Metab 72: 1130-1135, 1991.

[2]Lor and Liu. Neurologic sequelae associated with foscarnet therapy. Ann-Pharmacother 28(9): 1035-7, 1994.

onset of the sensory phenomenon, it seems unlikely that formate would be the causative agent.

B. Phosphate: When I investigated the degree of phosphate loading with Cerebyx, I was impressed. Approximately 1 gram of phosphorus is ingested each day in an average United States diet. Of this, 700mg is absorbed. In comparison, an IV loading dose of Cerebyx includes 75mg of phosphorus; the SE dosing regimen would introduce the fosphenytoin over 7 minutes. One outdated regimen for treating hypercalcemia[3] was to give phosphates IV at a dose of 20 to 30 mg of elemental phosphorus per kg over 12 to 16 hours. In a 70kg person, this would result in 100mg/hr. A stated hazard of this therapy was extraskeletal calcifications, including nephrocalcinosis with resulting renal failure.

C. Sponsor's Comments on Mechanisms: The sponsor first addresses underlying mechanisms of these sensory disturbances from Cerebyx on the third-to-the-last page of the second safety update. "Although the underlying mechanism of fosphenytoin-induced pruritus and paresthesia is unknown, similar symptoms have also been reported for other phosphate-ester prodrugs and for foscarnet." The "other phosphate-ester prodrugs" referenced by the sponsor are Decadron and Hydrocortone.

Curiously, the character and location of the sensory disturbance described for Decadron and Hydrocortone matches the dominant description in Cerebyx-treated subjects. With all 3 agents, patients describe a burning or itching which localizes primarily to the groin area.

By my calculation, IV loading doses of Decadron and Hydrocortone provide 1/20th-1/10th the elemental phosphorus provided by a loading dose of Cerebyx. Therefore, assuming phosphate is the common link, it would not be surprising that Cerebyx would produce more severe burning and itching.

Calcium Metabolism: Calcium is usually measured in the clinic as total serum calcium (normal 9-10.4mg/dL). About 50% of serum calcium is ionized and 10% is complexed with citrate, phosphate, bicarbonate, and lactate. The rest (40%) is protein-bound, mainly to albumin. The concentration of serum calcium is reflected in the proportion: [Ca] x

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[3]Renal and Electrolyte Disorders Schrier (editor). Little, Brown and Company, 1976; p 198.

[Phosphate]/[Calcium-Phosphate]. The normal range for phosphorus is 3-4.5mg/dL. The product of [Ca] (mg/dL) x [Ph] (mg/dL) therefore normally approaches 50. When the product approaches 60-70, most textbooks raise concern about precipitation with resultant soft tissue calcification, to include nephrocalcinosis.

By weight, phosphorus represents 15/406 or 3-4% of fosphenytoin so that a loading dose of Cerebyx delivers 75mg phosphorus. If this load remained in the vascular space, the serum phosphorus could theoretically rise by 2mg/dL, thereby raising the calcium-phosphorus product to 70. This would drive the equilibrium toward calcium-phosphate and tend to lower calcium. As with Foscavir, the ionized free calcium would probably reflect this drop better than total serum calcium values.

Note, however, that hypocalcemia typically causes a tingling sensation around the face and in the hands, not a burning in the groin as we have seen in many Cerebyx patients.

Although the sponsor has not acknowledged this theoretical concern, it must have crossed their minds. The second safety update briefly summarizes an open-label safety and PK study performed in June 1995 which incorporated 16 healthy subjects, each given a single SE dose of Cerebyx (Study 27). In reviewing individual lab listings for these subjects, I notice that 9/16 subjects had ionized free calcium levels performed at 18 minutes, while 5 of the same subjects had ionized free calcium levels performed at 8 minutes. None of the levels are remarkable, either when viewed as absolute values or as change from baseline. Certainly these measurements are not comparable to those reported for Foscavir. However, note that the SE dose of Cerebyx is delivered over 7 minutes. With only 5 ionized free calcium level checked at 8 minutes and the rest performed at 18 minutes, I do not believe we can rule out the occurrence of a transient hypocalcemia during the 7 minute infusion. Further, the clinical status of these 5 (or 9) subjects is not stated. Were they subjects with or without pruritus ?

In the absence of more data on ionized free calcium, I reviewed total calcium levels in Study 26. Note that, aside from the 8 and 18 minute clinical labs in Study 27, I am not aware of clinical labs in any other studies being performed early enough to be informative on this subject. Still, 25% of Cerebyx-treated patients in Study 26 are listed with low

calcium levels. Since this does not differ from the Dilantin-treated group, I would doubt it is important.

A review of all deaths and serious AEs in Study 26 raises no particular concerns regarding other manifestations of hypocalcemia. In particular, I do not see any description of seizures occurring in proximity to Cerebyx infusions, cardiac rhythm disturbance, or tetany. In fact, the profile of serious AEs appears roughly the same for Cerebyx and Dilantin treated patients in Study 26. Again, though, **patients in Study 26 "had near normal levels of consciousness to report adverse events and infusion tolerance" (2nd safety update,p35) which may not mirror the SE population most likely to receive the SE doses of Cerebyx. Patients in Study 26 could report sensory symptoms early and thereby cause their rate to be lowered.**

Summary:

1. The natural history of the sensory disturbance caused by Cerebyx at SE dosing has not been fully characterized. In particular, we do not know if the intensity (severe for many) correlated with duration (many hours for some), especially in the absence of dose and rate reductions.

Relevant to this last point is that the number of known obtunded patients given SE dosing regimens remains small. (We don't know the level of consciousness for all Study 26 patients.) For these patients, the longterm follow-up was short, 3-5 days by protocol. More obtunded patients, given SE dosing without rate reductions and followed for longer periods of time, would add a margin of safety to the Cerebyx experience. (Perhaps Study 25 contains some of this information.) Pertinent to this, the patients in Study 16 who were given the SE dosing regimen could have their status at the 3-5 day visit teased out and presented separately. Patient 2 at Center 8 has pruritus beginning on day 2, continuing, and not yet recovered, but the duration of follow-up is not clearly stated. The "mild itching feeling" reported for Patient 22, Center 9 in Study 16 on Day 4, just after experiencing post-ictal psychosis is intriguing along these lines.

2. One very plausible theory for the sensory disturbance (one which the sponsor has begun to investigate in Study 27) is a drug-induced transient drop in ionized free calcium. I believe this needs to be investigated more

comprehensively, prior to drug approval. This could be accomplished by checking free calcium levels more frequently, at earlier time points, and in more patients. There may be value in also checking magnesium levels at the same time, since magnesium is another example of a divalent cation. Sensory symptoms could be correlated with calcium and magnesium levels. (Indeed, presenting free calcium levels for 9/16 subjects in Study 27 raises the concern that values are not presented for the subjects with sensory disturbances.)

Relevant to the this, the sponsor could measure serum phosphate levels in closer proximity to the infusion since phosphate levels would predict potential for hypocalcemia.

Formate

For each mmole of Cerebyx administered, one mmole of formate is produced. Therefore, a loading dose of Cerebyx delivers about 5 mmoles of formate to the individual. Assuming all the formate stayed within the circulation (5 liters), a maximal theoretical increase of 1 MMOL/L in background formate levels could occur. This was recognized at the time the IND for fosphenytoin was first filed in 1986 (see the pharm/tox review of Dr. Fitzgerald from 1986).

In 1986, the sponsor at that time) measured formate levels in 4 subjects administered a small loading dose of fosphenytoin over 30 minutes (half as much fos as constitutes a current loading dose, given over a greater time interval). Background levels were 0.5 MMOL/L and did not increase. Since then, formate levels have not been measured in any human studies of Cerebyx.

Given the measured background levels in that study and the maximal theoretical increase, the maximal theoretical level that could be achieved after a Cerebyx loading dose is 1.5 MMOL/L.

In monkey studies referenced by Dr. Fisher in the current pharm/tox review, formate levels as low as 7 MMOL/L could cause the characteristic optic nerve lesions of formate toxicity (implied, but not clearly stated, is that levels below 7 MMOL/L did not cause the lesion in the monkey studies).

There are ongoing investigations into the mechanism of methanol toxicity, due in part to interest in methanol as an automotive fuel. Methanol is converted to formaldehyde and then to formate. Investigators have found that rats, normally resistant to methanol toxicity, can be made sensitive

to methanol toxicity by creating a state of folate deficiency.[1,2] This folate-reduced (FR) rat model has been the subject of some recent studies on methanol toxicity. In this model, 2.5-3.0 MMOL/L formate probably represents the NOEL (personal communication from Robert Louis-Ferdinand to Dr. Ed Fisher). Formate levels of 7-10 MMOL/L are associated with changes in the electroretinogram of the FR rat and with the histological abnormalities in the optic nerve.

In the NDA, preclinical studies were performed in non-primates which are not susceptible to formate toxicity unless they are made folate deficient. Formate levels were not measured in these studies.

The human clinical literature on methanol toxicity includes reported formate levels in patients who died, suffered visual loss, and who survived without deficits.[3,4] Formate levels as low as 2-4 MMOL/L are reported in some fatalities. Unfortunately, the timing of these levels in relation to the methanol exposure are not always clear. Some reported formate levels may be peak levels while others are trough levels. Levels of 10 MMOL/L and above do seem to consistently be associated with poor outcomes. Levels below 10 have outcomes that vary from complete recovery to death. Based on the information from monkey and FR rat studies, I believe the human levels below 10 in association with poor

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[1]Lee, Garner, and Terzo. A rat model manifesting methanol-induced visual dysfunction suitable for both acute and long-term exposure studies. Toxicol.Appl.Pharmacol. 128: 199-206, 1994.

[2]Garner, Lee, and Louis-Ferdinand. Muller cell involvement in methanol-induced retinal toxicity. Toxicol.Appl.Pharmacol. 130: 101-107, 1995.

[3]Brown-Woodman, Huq, Hayes, Herlihy, Picker, and Webster. In vitro assessment of the effect of methanol and the metabolite, formic acid, on embryonic development of the rat. Teratology 52: 233-243, 1995. (See their Table 9 for a range of reported formate levels in human methanol toxicity.)

[4]McMartin, Ambre, and Tephly. Methanol poisoning in human subjects: Role for formic acid accumulation in the metabolic acidosis. Am.J.Med. 68: 414-418, 1980.

outcomes may simply represent trough levels in patients who experience much higher levels at other times in their clinical course.

Folate-deficient populations are a topic of some discussion in the literature on methanol toxicity. Alcoholism, pregnancy, and chronic phenytoin therapy are all states known to be associated with folate deficiency. Treatments that alter folate metabolism, such as dietary manipulation, nitrous oxide, and methotrexate, have been shown to modify methanol toxicity in monkeys and rats. Methanol-derived levels of formate are higher in folate-deficient monkeys than in normal monkeys after similar exposures to methanol.[5] These authors found that elevations in formate levels after very high inhalation exposures, whether in normal or folate-deficient monkeys, were only a fraction of background formate levels.

Acidosis: Severe methanol toxicity is associated with a severe acidosis, as well as high formate levels. To quote one paper on methanol poisoning, "Formate accumulation occurs in a manner reciprocal to the depletion of bicarbonate."[4] When searching the line listings for Study 27 in the recent safety update, I found fairly complete data on bicarbonate levels from the 16 subjects given loading doses. These levels were collected at regular 30 minute intervals. For the 16 subjects entered, many of them showed some small decrement in bicarb with the nadir occurring at different times for different subjects. The biggest decrement occurred for subject 16, with a baseline bicarb of 25.4 and an end-of-infusion reading of 18.6. (19-26MMOL/L is given as the normal range.) It is unclear if these small decrements represent normal variability over time or some consistent effect of the infusions.

I wonder if the decrements seen in bicarbonate in Study 27 might be used as markers for elevations in formate levels. Again, the sponsor has not specifically called attention to the existence of the bicarbonate data or to its significance. (It is not clearly stated why the bicarb levels were checked in the first place.)

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[5]Dorman, Moss, Farris, Janszen, Bond, and Medinsky. Pharmacokinetics of inhaled [^{14}C] methanol and methanol-derived [^{14}C] formate in normal and folate-deficient cynomolgus monkeys. Toxicol.Appl.Pharmacol. 128: 229-238, 1994.

Labeling for Cerebyx will have to reflect the fact that patients with status epilepticus usually have an underlying metabolic acidosis, the degree of which varies with the severity of the status and the cause of the status (see Patient 11, Study 16; multiple drug overdose), and that Cerebyx may add to this derangement.

Anion Gap: If there is a transient decrease in bicarbonate in the absense of a change in sodium and chloride, we have defined an increase in the anion gap. Formation of formate and/or phosphate loading could increase the anion gap. For subject 16 in Study 27, the anion gap at the end of the infusion was 16 with a normal of 8-16.

Sensory Symptoms: In the animal toxicology studies, Dr. Fisher has not seen any evidence of severe sensory symptoms such as writhing. If the animals experience the same phosphate load as humans (or slightly greater), and if phosphate is the origin of sensory symptoms, some painful behavior would have been expected. Since we know that formate metabolism is one area where these non-primates differ from humans in Cerebyx-processing, the question arises whether formate accumulation in humans could be contributing to the sensory disturbance.

Summary:

1. Formate levels have not been measured in humans after a loading dose of Cerebyx.

2. Formate levels have not been measured in folate-deficient humans after a loading dose of Cerebyx.

Introduction

A. Administrative History

Following is a brief chronology of the IND and NDA:

1984	
1986	files IND for Fos
1990	transfers IND tc
1990	transfers IND to Warner Lambert/Parke-Davis
1991	Orphan drug designation for grand mal status
5/91	IM clinical studies begin
2/92	IV clinical studies begin
7/94	NDA filed
9/94	Refuse to file letter
2/95	Resubmission of NDA
6/95	First safety update
10/95	Second safety update

The basis for the refuse to file action in September 1994 was the small number of patients and volunteers treated with Fos at a rate of 150 mg/min PE. Only 4 pts with status epilepticus had been treated at that rate while about 20 normal volunteers had been treated at that rate.

The sponsor continued to enroll pts in an ongoing status epilepticus study after the NDA was filed. On the basis of the increased numbers of pts treated as well as a recalculation of infusion rates for some previously-treated pts, it was agreed that the sponsor would resubmit the NDA in 1995.

B. Material Utilized in Review

The NDA dated July 14, 1994 and received July 15, 1994 included 93 volumes. Volumes 1.1, 1.47-1.72, and 1.89-1.92 from that submission were used for purposes of this review.

After the refusal to file, a resubmission dated February 22, 1995 and received February 23, 1995 was submitted. The resubmission included 15 volumes. Volumes 3.1 and 3.9-3.12 from the resubmission were frequently used for purposes of this review. Those volumes included a rewritten Integrated Summary of Safety and rewritten study reports for Studies 982-15, 982-21, and 982-16.

The 4-month safety update dated June 22, 1995 and received June 23, 1995 was also used for this review. At my request, Tables 5 and 6 from the safety update were changed by the sponsor and submitted September 14, 1995.

The FDA Biopharm Review is also integral to the review of this NDA.

C. Background

Fosphenytoin Sodium (Fos) is the disodium phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin. It is a prodrug of phenytoin. It is rapidly and completely converted to phenytoin in vivo by ubiquitous phosphatases. Because of the phosphate ester, 150 mg Fos yields 100 mg phenytoin sodium. In this report, doses of Fos and dose rates of Fos will always be expressed as phenytoin equivalents (PE) as opposed to actual mg Fos.

According to the sponsor, the presumed advantages of Fos over parenteral phenytoin are:

* pH 8.8 as opposed to pH 12 of Dilantin
* freely soluble and stable in common IV fluids
* can be used IM
* shorter administration times; can be given at 150 mg/min while Dilantin is limited to 50 mg/min
* minimal tissue trauma at injection site (presumably due to lower pH
* no cardiovascular toxicity including hypotension

While shorter administration times could be a distinct advantage in emergent situations, it will be seen below that this is actually a necessity in order to meet bioequivalence standards based on free phenytoin levels after IV administration.

The relative local injection site toxicities and cardiovascular toxicities of Fos and parenteral Dilantin remain a topic for this review.

In fact, this NDA is unique in many ways. First, there are no controlled trials to support the efficacy of Fos. The "controlled trials" submitted were really not designed to show a difference between treatment groups on a protocol-specified efficacy outcome. The majority of patients studied were not having seizures, but were only at risk for seizures for one reason or another.

Secondly, the bioequivalence data submitted in support of this application really only applies to the isolated instance of IV loading. To my knowledge, no bioequivalence data for IV maintenance dosing, IM loading, or IM maintenance dosing has been submitted.

Thirdly, the limited safety database submitted in support of this application can be partitioned in two ways. The first way partitions the data by route of administration, IV versus IM. (In addition to the systemic toxicities that could be part and parcel of the route-determined bioavailability, there exists the route-specific local toxicities.) The second way partitions the data by loading versus maintenance dosing.

While the safety of a loading dose also speaks to the safety of a maintenance dose by the same route of administration, the converse is not true. Because of this last point, I have divided the patient safety database as seen in the table below. Subjects in normal volunteer studies are not included in this table. Since almost all normal volunteer studies (n=148 Fos-exposed subjects) were single loading dose studies, these studies would be expected to add information primarily to the IV loading group.

	Loading	Maintenance	Loading Plus Maintenance
IV Route	181	88	181
IM Route	178	297	357

Note that the definition of "Loading" for purposes of such a table can be complicated. We could look only at the "bioequivalent" IV loading dose,

with a very precise rate and total dose. Or we could include anyone with a total dose of 20mg/kg PE given over an hour or less (a subacute loading dose). Or we could include anyone with the "bioequivalent" rate even if the total dose was as low as 10mg/kg PE. Interestingly enough, for the IM route, a bioequivalent loading dose cannot be defined because parenteral Dilantin is rarely given IM. The systemic bioavailability of IM Fos is reported to be 100%

D. Proposed Directions for Use

The proposed labeling seeks an indication of Fos for short-term parenteral use for up to 14 days:

- o for status epilepticus
- o for the treatment or prophylaxis of seizures in patients with epilepsy or in neurosurgical patients
- o as a substitute for oral phenytoin when oral administration is not feasible

The Dosage and Administration Section of the proposed labeling describes 4 situations for use:

1. IV loading in status epilepticus
2. IM or IV loading for treatment or prophylaxis
3. IM or IV use for maintenance therapy
4. IM or IV use for temporary substitution for oral Dilantin

For status epilepticus, "the standard loading dose is 22.5 to 30 mg/kg (15-20 PE) infused at 150 to 225 mg/min (100-150 PE) in adults ... with vital signs ... and cardiac rhythm (ECG) monitored during and immediately after the infusion ... Cerebyx (19.5-25.5 mg/kg or 13-17 PE) administered at 225 mg/min (150 PE) is bioequivalent to an equimolar dose of Dilantin administered parenterally at 50 mg/min."

Further, "Guidelines for the treatment of status epilepticus suggest that patients still in status epilepticus after a phenytoin loading dose of 20 mg/kg may receive additional loading doses of 5 mg/kg up to a maximal dose of 30 mg/kg. **Based on these guidelines**, patients treated with Cerebyx still in status epilepticus after a Cerebyx loading dose of 30 mg/kg (20mg PE) may receive additional Cerebyx loading doses of 7.5 mg/kg (5mg PE) up to a maximal Cerebyx dose of 45 mg/kg (30mg PE)."

The sponsor has studied the loading doses above and, **based on free phenytoin concentrations,** has found that Cerebyx infusions at 225 mg/min (150mg PE) are bioequivalent to standard Dilantin loading doses. However, if the standard of care for **refractory** status includes additional boluses, the sponsor has not studied the PK of Cerebyx at these higher doses.

E. Foreign Marketing

Fosphenytoin is not marketed in any country.

F. Related INDs

Fosphenytoin is being developed under 2 separate INDs: IND epilepsy and IND

PK Studies

IM Fos Maintenance

The bioavailability of phenytoin, given as IM Fos, is 100%. In contrast, the bioavailability of phenytoin, given as Dilantin Kapseals is 90%.

Bioequivalence Studies for Emergent IV Loading

Study 18 was a 4-way crossover study of different doses and infusion rates. The concentration-time curves depicted in the publication of this study depict nearly superimposable curves for 1200 mg given at 100 mg/min and 150 mg/min. While not designed as a bioequivalence study, it appears that these 2 infusion rates would be bioequivalent and, additionally, both result in similar rise times for free phenytoin concentrations.

Data from a second published PK study shows Fos at 100 mg/min to have a slower rise time of free phenytoin concentration than Fos at 150 mg/min; the Cmax and AUCs appear similar otherwise. This study was designed as a bioequivalence study: Only Fos at 150 mg/min was bioequivalent to Dilantin at 50 mg/min. The rise time of free phenytoin levels was steeper for Fos, resulting in maximal levels about 5-7 minutes faster for Fos than Dilantin.

Safety Concerns for Emergent IV Loading in Light of PK Data

As described in later sections, there is minimal safety data for IV Fos given at a rate of 150 mg/min PE. The safety experience widens considerably if 100 mg/min is used as a cutoff.

The 2 PK studies present discrepant data. In one, 100 vs 150 appear equivalent with similar rise times for free phenytoin levels. In the other, only 150 is bioequivalent to Dilantin 50 mg/min.

The rise time for free phenytoin levels is significantly faster in one PK study compared to Dilantin. In the other study, the rise time is less steep and is similar for both 100 and 150 mg/min infusion rates. If the rise time is steeper with Fos 150 mg/min than for Dilantin at 50 mg/min, the potential exists for increased cardiovascular toxicity with Fos than with Dilantin. **The only way to resolve the safety issue would be to conduct a large enough safety study powered to detect a difference between parenteral Dilantin and Fos, given at 50mg/min and 150mg/min respectively.** A study with pts randomized to these 2 infusion rates has been designed by the sponsor to begin in April 1995, but it is unlikely that this study will have the power to detect a difference between the two drugs with respect to this AE.

Safety

Preclinical Safety Profile (see Dr. Fisher's review)

The toxicological profile of Fos was essentially the same as that of phenytoin. Acute IV toxicity studies were conducted in mice, rats, rabbits, and dogs. Multidose toxicity studies were conducted by both the IV and IM routes in rats and dogs. The IV studies were 4 weeks in duration while the IM studies were 13 weeks in duration.

Special studies of local tissue irritation were conducted. Fos produced significantly less venous and perivascular irritation than phenytoin at equimolar concentrations. Local irritation after IM injection of Fos to rabbits was significantly lower than after IM phenytoin.

The cardiovascular effects of equimolar doses of phenytoin and Fos were comparable following IV bolus injection to anesthetized female dogs. Any less pronounced effects seen after Fos administration are presumed to be due to the lower peak blood levels of phenytoin resulting from its administration (22 vs 49 mcg/ml).

The formation of formaldehyde after Fos administration raises a theoretical safety concern. The theoretical maximum dose of formaldehyde (assuming complete, instantaneous conversion) after an IV dose of 2100 mg Fos (proposed maximum human dose) based on a 1:1 molar ratio would be 5.17 mmol or about 0.1 mmol/kg (3 mg/kg) for a 50 kg person. Using modeling techniques, peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 minutes. Plasma formate levels measured in 4 healthy volunteers following administration of 1200 mg of Fos by IV infusion over 30 min were not significantly different from those observed in a placebo group or from baseline levels

(25 mg/L).

Dr. Fisher has reviewed the genetic toxicity and reproductive toxicity studies. Developmental toxicity seen in rats given Fos is consistent with that previously reported with phenytoin.

Fos was clastogenic in Chinese hamster lung cells. Phenytoin was reportedly not clastogenic in previous studies with CHO cells. One explanation for this discrepancy is that the clastogenicity of Fos is due to formaldehyde formation.

1.0 Exposure

849 volunteers and patients have participated in all Fos studies included in the NDA. These volunteers and patients account for 942 exposures to some study drug (Fos, phenytoin, or placebo) if patients in crossover studies are counted as 2 separate exposures.

736 volunteers or patients have been exposed to Fos, including 148 volunteers and 588 patients. 534 patients were part of the completed clinical studies while an additional 54 patients were part of ongoing Study 16 (status epilepticus).

The sponsor's list of all studies is attached.

Note that almost all 148 volunteers in the early dose-escalation and PK studies received single IV doses of Fos.

Two of the studies in patients were unusual in their dosing regimens. In study 005, patients received half of their maintenance oral dose of phenytoin as IV Fos and the other half as IM Fos. Study 10 was an isotope study.

TABLE 1. Description of Clinical Studies
(Page 1 of 7)

Study No. and Description	No Entered	Demography	Drug Administration						
			Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
STUDIES IN SUBJECTS									
Clinical Pharmacology Studies[a]									
982-001	Total	Age Range	FOS, IV	150	100	Single dose	3.3	5	Single dose
[9653-86-01]	25	19-35	FOS, IV	300	200	Single dose	6.7	5	Single dose
Single-blind, randomized, placebo-controlled, single-center dose-ranging tolerance study in healthy subjects	Treatment	Gender	FOS, IV	600	400	Single dose	13.3	5	Single dose
	5 PBO	25 Males	FOS, IV	1200	800	Single dose	26.7	5	Single dose
	20 FOS	0 Females	PBO, IV[b]	NA	NA	Single dose	NA	5	Single dose
		Race							
		20 White							
		3 Black							
		2 Other							
982-002	Total	Age Range	FOS, IV	375	250	Single dose	8.3	12	Single dose
[9653-86-02]	12	20-31	DIL, IV	250	250	Single dose	8.3	12	Single dose
Single-blind, randomized, 2 way crossover, single center study of absolute bioavailability after IV administration in healthy subjects	Treatment	Gender							
	12 FOS	12 Males							
	12 DIL	0 Females							
		Race							
		9 White							
		2 Black							
		1 Other							
982-003	Total	Age Range	FOS, IV	375	250	Single dose	50	5	Single dose
[9653-86-03]	31	18-44	FOS, IV	750	500	Single dose	100	5	Single dose
Open-label, baseline controlled, escalating infusion rate, single-center, safety and tolerance study in healthy subjects	Treatment	Gender				Single dose	150	1	Single dose
	3 PBO	31 Males	FOS, IV	1125	750	Single dose	50	5	Single dose
	28 FOS	0 Females				Single dose	75	5	Single dose
						Single dose	100	5	Single dose
		Race				Single dose	150	2	Single dose
		26 White	PBO, IV[b]	NA	NA	Single dose	NA	3	Single dose
		3 Black							
		2 Other							

PE = Phenytoin equivalents; FOS = Fosphenytoin; PBO = Placebo; NA = Not applicable; DIL = Dilantin.

[a] Subjects in clinical pharmacology studies may have received more than 1 treatment.

[b] PBO was administered intravenously, in single doses, and at a rate similar to that of FOS.

TABLE 1. Description of Clinical Studies
(Page 2 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration						
			Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-006	Total	Age Range	FOS, IM	375	250	Single dose	NA	12	Single dose
(9653-86-06)	12	22-40	DIL, IV	250	250	Single dose	25	12	Single dose
Open-label, randomized, 2-way crossover, single-center study of bioavailability after IM administration in healthy subjects	Treatment 12 FOS 12 DIL	Gender 12 Males 0 Females Race 12 White							
982-007	Total	Age Range							
(9653-87-07)	15	24-68	FOS, IV	375	250	Single dose	8.3	15	Single dose
Open-label, single center, pharmacokinetic study in subjects with renal or hepatic disease and in healthy subjects	Treatment 15 FOS	Gender 15 Males 0 Females Race 10 White 4 Black 1 Other							
982-011	Total	Age Range							
(9653-87-11)	11	20-31	FOS, IV	1125	750	Single dose	50	10	Single dose
			DZ, IV	10	NA	Single dose	2[a]	9	Single dose
Open-label, randomized, 3-way crossover, single-center, drug-interaction study of fosphenytoin and diazepam in healthy subjects	Treatment 10 FOS 9 DZ 11 FOS/DZ	Gender 11 Males 0 Females Race 11 White	FOS/DZ, IV	1125/10	750	Single dose	50/2[a]	11	Single dose

PE = Phenytoin equivalents; FOS = Fosphenytoin; DIL = Dilantin; DZ = Diazepam; NA = Not applicable.

[a] Rate for diazepam represents mg DZ/min rather than phenytoin equivalents.

TABLE 1. Description of Clinical Studies
(Page 3 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration: Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
9R2-017	Total	Age Range	FOS, IV	900	600	Single dose	50	6	Single dose
	6	19-35	DIL, IV	600	600	Single dose	50	6	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, escalating single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects. Study ended prematurely	Treatment	Gender	PBO, IV[b]	NA	NA	Single dose	NA	6	Single dose
	6 PBO	6 Males							
	6 FOS	0 Females							
	6 DIL								
		Race							
		5 White							
		1 Black							
9R2-017	Total	Age Range							
	2	18-23	DIL, IV	600	600	Single dose	25	2	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, escalating single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects. Study ended prematurely.	Treatment	Gender							
	2 DIL	2 Males							
		Race							
		1 White							
		1 Black							
9R2-018	Total	Age Range	FOS, IV	600	400	Single dose	12.5	4	Single dose
	21	19-43				Single dose	25	4	Single dose
Double-blind, randomized, placebo-controlled, 4-way crossover, escalating single-dose and infusion rate, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin in healthy subjects	Treatment	Gender				Single dose	50	4	Single dose
	21 PBO	21 Males				Single dose	100	4	Single dose
	20 FOS	0 Females				Single dose	150	4	Single dose
			FOS, IV	1200	800	Single dose	12.5	4	Single dose
						Single dose	25	4	Single dose
		Race				Single dose	50	4	Single dose
		19 White				Single dose	100	4	Single dose
		2 Other				Single dose	150	4	Single dose
			FOS, IV	1800	1200	Single dose	12.5	4	Single dose
						Single dose	25	4	Single dose
						Single dose	50	4	Single dose
						Single dose	100	4	Single dose
						Single dose	150	4	Single dose
			PBO, IV[b]	NA	NA	Single dose	NA	21	Single dose

PE = Phenytoin equivalents; FOS = Fosphenytoin; PBO = Placebo; DIL = Dilantin; NA = Not applicable.
[b] PBO was administered intravenously, in single doses, at a rate similar to IV fosphenytoin.

TABLE 1. Description of Clinical Studies
(Page 4 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration						
			Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-020	Total	Age Range	FOS, IV	1800	1200	Single dose	50	12	Single dose
	12	18-49	DIL, IV	1200	1200	Single dose	50	12	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects			PBO, IV[b]	NA	NA	Single dose	NA	12	Single dose
	Treatment	Gender							
	12 PBO	12 Males							
	12 FOS	0 Females							
	12 DIL								
		Race							
		10 White							
		1 Black							
		1 Other							
982-024	Total	Age Range							
	12	20-42	FOS, IV	1800	1200	Single dose	100	12	Single dose
			FOS, IV	1800	1200	Single dose	150	12	Single dose
Nonblind, randomized, 3-way crossover, single-dose, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects	Treatment	Gender	DIL, IV	1200	1200	Single dose	50	12	Single dose
	12 FOS	12 Males							
	12 DIL	0 Females							
		Race							
		10 White							
		2 Other							
COMPLETED STUDIES IN PATIENTS									
Clinical Pharmacology Studies									
982-005	Total	Age Range	FOS, IV	NS[c]	NS	Single dose	50	43	Single dose
19653-86-05	43	20-73	FOS, IM	NS[c]	NS	Single dose	NA	42	Single dose
Open-label, baseline-controlled, single-dose, multicenter, safety, tolerance, and pharmacokinetic study of IV and IM fosphenytoin in patients with epilepsy maintained on oral Dilantin	Treatment	Gender							
	43 FOS	32 Males							
		11 Females							
		Race							
		38 White							
		5 Black							

Subjects in clinical pharmacology studies may have received more than 1 treatment.
FOS = Fosphenytoin; DIL = Dilantin; PBO = Placebo; NA = Not applicable; NS = Not specified.
[b] PBO was administered intravenously, in single doses, at a rate similar to IV fosphenytoin.
[c] Doses administered were equivalent to half the patients daily dose of PO Dilantin prior to study entry.

TABLE 1. Description of Clinical Studies
(Page 5 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration: Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-010	Total	Age Range	FOS, IV	208	139	Single dose	12[d]	7	Single dose
[9653-87-10]	7	20-61	DIL, IV	144	144	Single dose	12[d]	7	Single dose
Open-label, baseline-controlled, single-center study of absolute bioavailability in patients using stable isotope techniques	Treatment 7 FOS 7 DIL	Gender 7 Males 0 Females Race 7 White							
Controlled Clinical Studies									
982-013	Total	Age Range	FOS, IM	NS[e]	NS	QD/BID	NA	179	5 days
	240	18-83	DIL, PO	NS[e]	NS	QD/BID	NA	61	5 days
Double-blind, placebo-controlled, multiple-dose, parallel-group, multicenter, safety, tolerance, and pharmacokinetic study of IM fosphenytoin substituted for oral Dilantin in epilepsy and neurosurgical patients	Treatment 179 FOS 61 DIL	Gender 141 Males 99 Females Race 196 White 36 Black 8 Other							

Subjects in clinical pharmacology studies may have received more than 1 treatment.
PE = Phenytoin equivalents; FOS = Fosphenytoin; DIL = Dilantin; NA = Not applicable; NS = Not specified.
[d] Both drugs were infused simultaneously over a 12-minute period.
[e] Eligible patients were receiving 200 to 500 mg/day PO Dilantin. Doses administered were equivalent to the dose of PO Dilantin taken prior to study entry.

TABLE 1. Description of Clinical Studies
(Page 6 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration: Drug, Route	Planned Dose (mg/kg)	Planned Dose (mg PE/kg)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-015	Total	Age Range	FOS, IV[f]						
	116	15-89	Loading	18-21	12-14	Single dose	≤50	88	Single dose
			Maintenance	NS	NS	QD/BID	≤50	88	3-14 days
Double-blind, active-controlled, parallel-group, multiple-dose, multicenter, safety, tolerance, and pharmacokinetic study of IV fosphenytoin versus Dilantin in neurosurgical patients	Treatment	Gender							
	88 FOS	72 Males	DIL IV[f]						
	28 DIL	44 Females	Loading	12-14	12-14	Single dose	≤50	28	Single dose
			Maintenance	NS	NS	QD/BID	≤50	27	3-14 days
		Race							
		88 White							
		26 Black							
		2 Other							
982-021	Total	Age Range							
	52	16 73	FOS, IV	≥15	≥10[g]	Single dose	≤100	39	Single dose
			DIL, IV	≥10	≥10[g]	Single dose	≤50	13	Single dose
Double-blind, active-controlled, parallel group, single-dose, multicenter safety and tolerance study of IV fosphenytoin versus Dilantin in patients requiring a loading dose of phenytoin	Treatment	Gender							
	39 FOS	33 Males							
	13 DIL	19 Females							
		Race							
		28 White							
		16 Black							
		8 Other							

PE = Phenytoin equivalents; FOS = Fosphenytoin; DIL = Dilantin; NA = Not applicable; NS = Not specified.

[f] Suggested loading dose range. Protocol specified that loading and maintenance doses should achieve and maintain plasma phenytoin concentrations ≥ 10 mg/mL.

[g] Maximum single dose of 2000 mg.

TABLE 1. Description of Clinical Studies
(Page 7 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration: Drug, Route	Planned Dose (mg/kg)	Planned Dose (mg PE/kg)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
Uncontrolled Clinical Studies									
982-014	Total 118	Age Range 16-98	FOS, IM[f]						
Open-label, multiple-dose, multicenter, safety, tolerance, and pharmacokinetic study of IM fosphenytoin in neurosurgery patients	Treatment 118 FOS	Gender 78 Males 40 Females	Loading	12-18	8-12	QD/BID	NA	118	Single dose
			Maintenance	NS	NS	QD/BID	NA	117	3-14 days
		Race 93 White 25 Black							
982-022	Total 60	Age Range 16-80	FOS, IM	≥ 15	≥ 10[g]	Single dose	NA	60	Single dose
Open-label, single dose, multicenter, safety, and tolerance study of IM fosphenytoin in patients requiring a loading dose of phenytoin	Treatment 60 FOS	Gender 34 Males 26 Females							
		Race 32 White 24 Black 4 Other							
Ongoing Studies in Patients									
982-016	Total 54	Age Range 5-75	FOS, IV	15-30	10-20[h]	Single dose	≤ 150[i]	54	Single dose
(Interim) Open label, single dose, rate escalation, multicenter safety, tolerance, and pharmacokinetic study of IV fosphenytoin in patients with status epilepticus	Treatment 54 FOS	Gender 32 Males 22 Females							
		Race 21 White 23 Black 8 Other							

PE = Phenytoin equivalents; FOS = Fosphenytoin; NA = Not applicable; NS = Not specified.

f Suggested loading dose range. Protocol specified that loading and maintenance doses should achieve and maintain plasma phenytoin concentrations ≥ 10 mg/mL.

g Maximum single dose of 2000 mg.

h Target dose of 18 mg/kg to a maximum single dose of 2000 mg.

i Protocol specified an initial rate of 2 mg/kg/min to a maximum of 100 mg/min, with subsequent escalation to 3 mg/kg/min to a maximum of 150 mg/min based on safety at the lower rate.

Excluding those 2 studies, the remaining patients in clinical studies can be divided as follows:

IV "Load"

Study 21: 39 Fos patients*
Study 15: 88 Fos patients**
Study 16: 54 Fos patients***

IV Maintenance

Study 15: 88 Fos patients (1 week)**

IM Load

Study 22: 60 Fos patients*
Study 14: 118 Fos patients**

IM Maintenance

Study 13: 179 Fos patients*
Study 14: 118 Fos patients**

* epilepsy patients
** neurosurgery patients
*** status epilepticus

With the exception of 6 patients in Study 16 (status epilepticus), all patients were 16 years of age or older. Study 16 included 6 patients between the ages of 5 and 10 years.

Duration of exposure by route of administration (see sponsor's Figure 4):

Approximately 200 patients received IM Fos for 5 days, but only about 20 patients received IM Fos for 6 days or greater. IM exposure to Fos was heavily influenced by Study 13 which was designed as a 5-day study.

Approximately 60 patients received IV Fos for 4 days, but only about 18 patients received IV Fos for 5 days or greater. IV exposure to Fos was dependent on Study 15 where there was a protocol-specified option to switch to PO Dilantin after 3 days at the investigators' discretion.

Dose and Rate (see sponsor's Figure 7 which incorporates both volunteers and patients):

The total dose given obviously depended on whether the dose was designed as a loading dose or a maintenance dose.

The rate of administration for IV dosing was generally about 50 mg/min ± 20 except where specifically pushed higher to the bioequivalent rates necessary in status (150 mg/min).

2.0 Volunteer Studies

148 unique volunteers were exposed to Fos. Some of these individuals may have received more than one exposure to Fos. As mentioned above, most of these volunteers received single IV doses as part of dose-escalation or PK studies. Sponsor's Table 3 represents the number of unique volunteers exposed to Fos, Dilantin, and placebo in these studies.

2.1 Deaths

There were no deaths in volunteer studies.

2.2 Serious AEs and Discontinuations

There were 3 serious AEs reported in volunteer studies, 2 were on Fos and

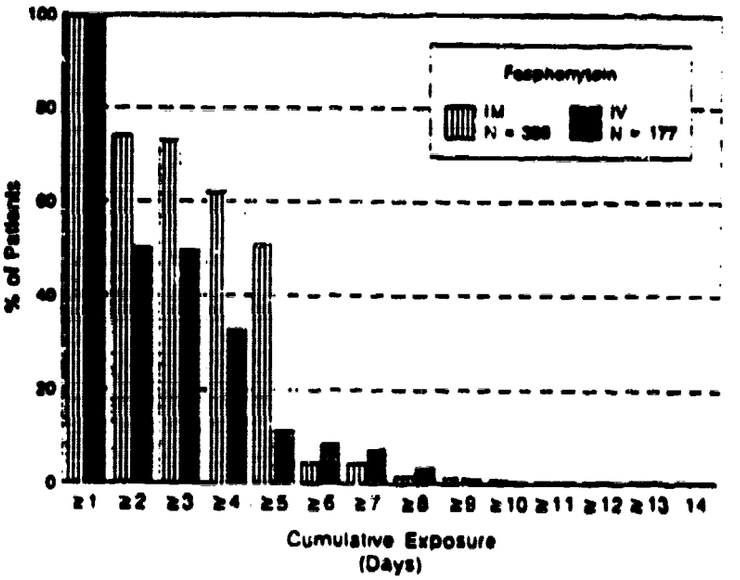

FIGURE 4. Exposure to Fosphenytoin by Route: Patients

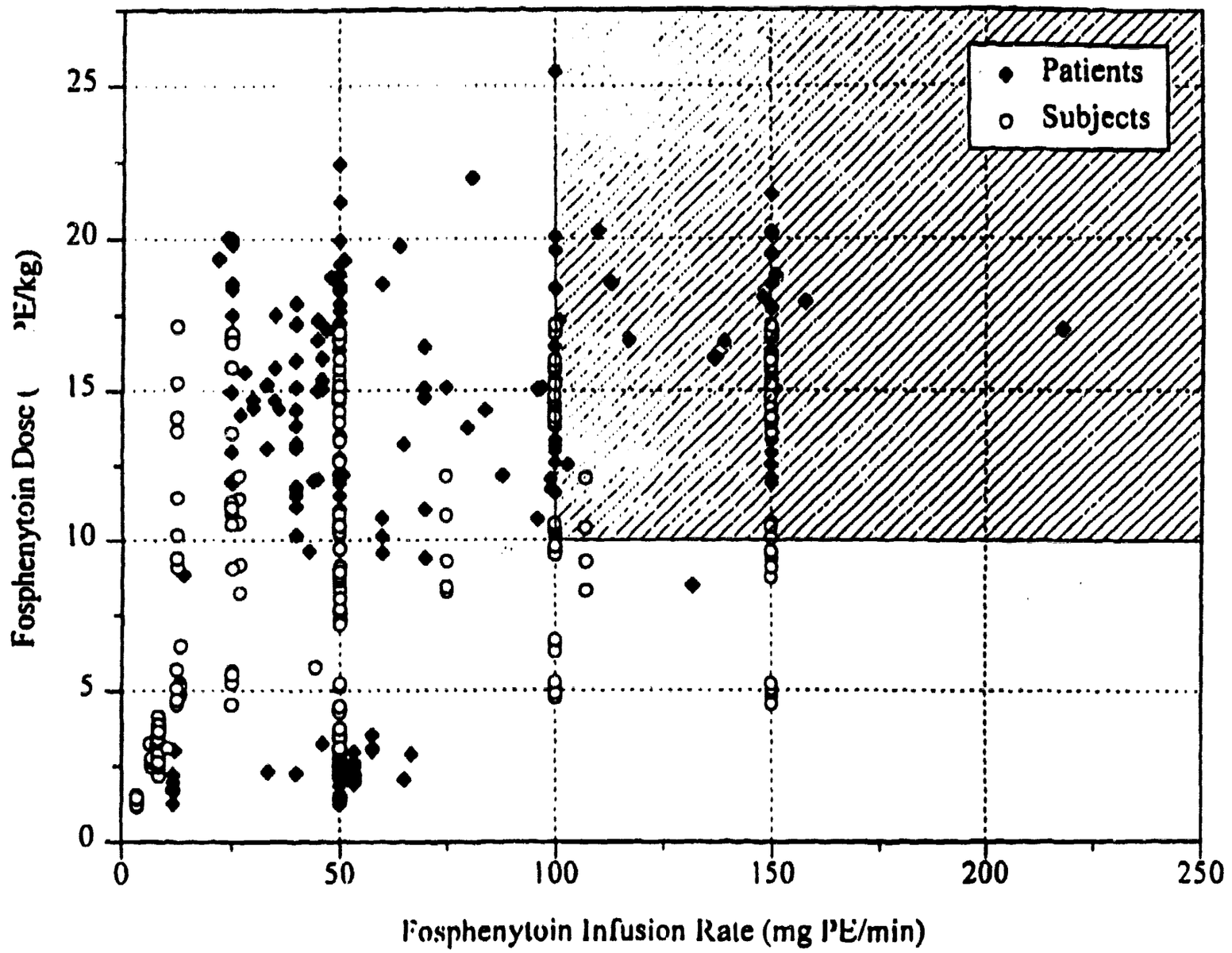

FIGURE 7. Subject and Patient Exposure to Fosphenytoin by Dose and Rate

TABLE 3. Source and Number of Subjects

Study	Placebo	Fosphenytoin		Dilantin	Total in Study[a]	Total Exposed to Fosphenytoin[a]
	IV	IM	IV	IV		
982-001	5	0	20	0	25	20
982-002	0	0	12	12	12	12
982-003	3	0	28	0	31	28
982-006	0	12	0	12	12	12
982-007	0	0	15	0	15	15
982-011	0	0	11	0	11	11
982-012	6	0	6	6	6	6
982-017	0	0	0	2	2	0
982-018	21	0	20	0	21	20
982-020	12	0	12	12	12	12
982-024	0	0	12	12	12	12
Total	47	12	136	56	159	148

[a] Each subject counted once

1 was on Dilantin. The patient narratives for all 3 patients are included below. The first Fos volunteer experienced progressive bradycardia leading to asystole for 23 seconds. During the asystole, the volunteer experienced 15 seconds of tonic-clonic movement. Because of subsequent abnormal electrophysiologic testing, the case was deemed unrelated to study drug. The subject had received 500mg of a planned 750mg bolus at 150mg/min.

The second Fos patient had hypotension and syncope after receiving 650mg of a planned 750mg bolus at 50mg/min. Bradycardia accompanied the event.

The Dilantin subject experienced hypotension after receiving 600mg of Dilantin at 50mg/min.

All 3 events seem most consistent with vasovagal reactions.

The classification of "discontinuations" or "withdrawals" would be somewhat uninformative for these volunteer studies since most of the studies were single dose IV studies. Nevertheless, there were 3 discontinuations. The 2 previously mentioned Fos serious AEs account for 2 of the 3 discontinuations. The third discontinuation was a Dilantin treated subject who developed a wandering cardiac pacemaker during infusion.

2.3 Severe AEs

Severe AEs were reported in 5 Fos subjects and 3 Dilantin subjects. 1/5 severe Fos reactions was described as a serious AE; the other 4 severe AEs were: ataxia, stupor, tinnitus, and pruritus. The 3 severe Dilantin AEs were: injection site pain in 2 subjects and hypotension in 1 subject.

2.4 All AEs

The sponsor has chosen to present the AE data relative to the number of exposures vs the number of subjects. For this reason, the denominators differ from Table 3 above in that there were 211 Fos exposures in 148 subjects. The number of exposures = number of subjects for placebo and Dilantin subjects. Sponsor's Table 6 shows all AEs, as well as those characterized as associated with test drug.

TABLE 6. All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 1 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47		Fosphenytoin* N = 211		Dilantin N = 56	
	All	Associated	All	Associated	All	Associated
ANY BODY SYSTEM	14 (29.8)	12 (25.5)	141 (66.8)	136 (64.5)	38 (67.9)	36 (64.3)
NERVOUS	6 (12.8)	6 (12.8)	123 (58.3)	121 (57.3)	32 (57.1)	32 (57.1)
Nystagmus	3 (6.4)	3 (6.4)	53 (25.1)	53 (25.1)	29 (51.8)	29 (51.8)
Dizziness	2 (4.3)	2 (4.3)	80 (37.9)	80 (37.9)	20 (35.7)	20 (35.7)
Paresthesia	1 (2.1)	1 (2.1)	68 (32.2)	66 (31.3)	11 (19.6)	11 (19.6)
Somnolence	0 (0.0)	0 (0.0)	7 (3.3)	7 (3.3)	0 (0.0)	0 (0.0)
Ataxia	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	2 (3.6)	2 (3.6)
Tremor	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)
Incoordination	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)
Hypertonia	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Stupor	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Euphoria	0 (0.0)	0 (0.0)	5 (2.4)	5 (2.4)	3 (5.4)	3 (5.4)
Anxiety	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (1.8)	1 (1.8)
Hypesthesia	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)
Thinking Abnormal	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	2 (3.6)	2 (3.6)
Nervousness	1 (2.1)	1 (2.1)	2 (0.9)	2 (0.9)	2 (3.6)	2 (3.6)
Abnormal Gait	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Dysarthria	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	3 (5.4)	3 (5.4)
Twitching	0 (0.0)	0 (0.0)	4 (1.9)	4 (1.9)	2 (3.6)	2 (3.6)
Convulsion	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Circumoral Paresthesia	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	3 (5.4)	3 (5.4)
CNS Depression	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

* Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

TABLE 6. All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 2 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47		Fosphenytoin[a] N = 211		Dilantin N = 56	
	All	Associated	All	Associated	All	Associated
BODY AS A WHOLE	6 (12.8)	5 (10.6)	45 (21.3)	39 (18.5)	25 (44.6)	24 (42.9)
Headache	1 (2.1)	1 (2.1)	26 (12.3)	24 (11.4)	8 (14.3)	5 (8.9)
Pain	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	1 (1.8)	1 (1.8)
Accidental Injury	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Injection-Site Reaction	2 (4.3)	1 (2.1)	4 (1.9)	3 (1.4)	7 (12.5)	7 (12.5)
Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)
Injection-Site Pain	3 (6.4)	3 (6.4)	4 (1.9)	4 (1.9)	17 (30.4)	17 (30.4)
Asthenia	0 (0.0)	0 (0.0)	3 (1.4)	2 (0.9)	0 (0.0)	0 (0.0)
Chills	0 (0.0)	0 (0.0)	7 (3.3)	7 (3.3)	2 (3.6)	2 (3.6)
Chest Pain	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Injection-Site Inflammation	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	2 (3.6)	2 (3.6)
Flu Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)
Photosensitivity Reaction	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
DIGESTIVE	1 (2.1)	1 (2.1)	24 (11.4)	21 (10.0)	10 (17.9)	10 (17.9)
Nausea	1 (2.1)	1 (2.1)	15 (7.1)	14 (6.6)	4 (7.1)	4 (7.1)
Constipation	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)
Dry Mouth	0 (0.0)	0 (0.0)	6 (2.8)	6 (2.8)	4 (7.1)	4 (7.1)
Dyspepsia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Gastrointestinal Disorder	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

[a] Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

TABLE 6. All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 3 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47				Fosphenytoin* N = 211				Dilantin N = 56			
	All		Associated		All		Associated		All		Associated	
DIGESTIVE (continued)												
Increased Salivation	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Dysphagia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Cheilitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
CARDIOVASCULAR	1	(2.1)	1	(2.1)	6	(2.8)	6	(2.8)	5	(8.9)	5	(8.9)
Hypotension	0	(0.0)	0	(0.0)	3	(1.4)	3	(1.4)	3	(5.4)	3	(5.4)
Bradycardia	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
Arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.6)	1	(1.8)
Vasodilatation	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	2	(3.6)	2	(3.6)
Vascular Disorder	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Syncope	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Heart Arrest	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
AV Block Second Degree	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Pallor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Phlebitis	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SPECIAL SENSES	1	(2.1)	1	(2.1)	58	(27.5)	57	(27.0)	17	(30.4)	16	(28.6)
Tinnitus	1	(2.1)	1	(2.1)	29	(13.7)	29	(13.7)	9	(16.1)	9	(16.1)
Ear Disorder	0	(0.0)	0	(0.0)	22	(10.4)	20	(9.5)	8	(14.3)	8	(14.3)
Taste Perversion	0	(0.0)	0	(0.0)	10	(4.7)	10	(4.7)	0	(0.0)	0	(0.0)
Amblyopia	0	(0.0)	0	(0.0)	3	(1.4)	2	(0.9)	1	(1.8)	1	(1.8)
Abnormal Vision	0	(0.0)	0	(0.0)	7	(3.3)	7	(3.3)	4	(7.1)	4	(7.1)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

* Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

TABLE 6. All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 4 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47				Fosphenytoin[a] N = 211				Dilantin N = 56			
	All		Associated		All		Associated		All		Associated	
SPECIAL SENSES (continued)												
Diplopia	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	1	(1.8)	1	(1.8)
Hyperacusis	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(1.8)	1	(1.8)
Mydriasis	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Conjunctivitis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(1.8)	0	(0.0)
Ear Pain	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES	1	(2.1)	1	(2.1)	31	(14.7)	30	(14.2)	6	(10.7)	6	(10.7)
Pruritus	0	(0.0)	0	(0.0)	30	(14.2)	30	(14.2)	1	(1.8)	1	(1.8)
Rash	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(1.8)	1	(1.8)
Urticaria	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Sweating	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(5.4)	3	(5.4)
Contact Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Skin Disorder	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
RESPIRATORY	1	(2.1)	0	(0.0)	9	(4.3)	4	(1.9)	1	(1.8)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	5	(2.4)	1	(0.5)	0	(0.0)	0	(0.0)
Hyperventilation	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
Rhinitis	1	(2.1)	0	(0.0)	2	(0.9)	1	(0.5)	1	(1.8)	0	(0.0)
UROGENITAL	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	1	(1.8)	1	(1.8)
Urination Impaired	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	1	(1.8)	1	(1.8)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

[a] Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

The most common AEs for Fos were:

Dizziness	38%
Paresthesia	32%
Nystagmus	25%
Tinnitus	14%
Pruritus	14%
Headache	12%
Ear disorder	10%

Except for paresthesia and pruritus, the incidence for all the above AEs was equal to or less than that for Dilantin.

Injection site pain was 2% for Fos vs 30% for Dilantin. Injection site reaction was 2% for Fos vs 13% for Dilantin.

2.5 Rate-related AEs After IV Administration

Some AEs were rate-related after IV administration in both Fos and Dilantin treated subjects. More informative, however, are the discrepancies between Fos and Dilantin treated subjects, situations where an AE was clearly rate-related for one treatment but not the other.

Taste perversion was rate-related for Fos, reaching 19% of Fos subjects when Fos was administered at 100-150 mg/min, but did not occur at any rate for Dilantin administration.

Likewise, pruritus was rate-related for Fos, reaching 38% of Fos subjects when Fos was administered at 100-150 mg/min, but only occurred in a single Dilantin-treated subject.

Paresthesia were rate-related for Dilantin as follows:

0/12 cases at 15 mg/min or less
0/14 cases at 15-30 mg/min
11/30 (37%) cases at 30-50 mg/min

Paresthesia were also rate-related for Fos as follows:

3/54 (6%) at 15 mg/min or less
3/17 (18%) at 15-30 mg/min
18/62 (29%) at 30-50 mg/min

23/35 (66%) at 50-100 mg/min
21/31 (68%) at 100-150 mg/min

Note that at bioequivalent rates, 37% Dilantin subjects vs 68% Fos subjects reported paresthesia. Of course, the total dose was not controlled for in these comparisons.

2.6 Dose-related AEs After IV Administration

No new trends over those reported in the rate-related AE section are obvious here. Taste perversion and pruritus increase with dose (as opposed to rate) in the absence of any significant number of events in Dilantin subjects at any dose.

2.7 Clinical Labs

The sponsor reports no clinically significant changes after Fos administration. Recall that most exposures in volunteers were single dose exposures.

2.8 Injection Site Reactions

Sponsor's Table 10 summarizes injection site reactions for the volunteer studies. Based on 102 Fos exposures and 39 placebo exposures, the profile of reactions for Fos and placebo are not significantly different. 97% of exposures in both groups resulted in none-mild reactions. For the Dilantin-exposures (n=32), 15% resulted in moderate reactions and 6% resulted in severe reactions.

When rate-relatedness was examined, up to 23% of high-rate Dilantin exposures resulted in reactions. Reactions were not rate-related with Fos. Up to 43% of high-rate Dilantin exposures resulted in injection site pain. Pain was not rate-related with Fos.

2.9 Vital Signs

The ISS does not address vital signs in volunteer studies.

TABLE 10. Evaluation of Infusion-Site Reactions: Subjects (Parke-Davis Studies)
[Number (%) of Exposures in Subjects]

Study	Treatment	No. of Exposures in Subjects Evaluated	Maximum Intensity of Infusion-Site Adverse Reaction									
			None		Mild		Moderate		Severe		Missing/Not Done	
982-012	Placebo	6	6	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Fosphenytoin	6	6	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Dilantin	6	1	(16.7)	5	(83.3)	0	(0.0)	0	(0.0)	0	(0.0)
982-017	Dilantin	2	0	(0.0)	2	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
982-018	Placebo	21	20	(95.2)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
	Fosphenytoin	60	56	(93.3)	3	(5.0)	1	(1.7)	0	(0.0)	0	(0.0)
982-020	Placebo	12	10	(83.3)	1	(8.3)	1	(8.3)	0	(0.0)	0	(0.0)
	Fosphenytoin	12	8	(66.7)	3	(25.0)	1	(8.3)	0	(0.0)	0	(0.0)
	Dilantin	12	2	(16.7)	4	(33.3)	4	(33.3)	2	(16.7)	0	(0.0)
982-024	Fosphenytoin	24	18	(75.0)	6	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Dilantin	12	0	(0.0)	11	(91.7)	1	(8.3)	0	(0.0)	0	(0.0)
Total	Placebo	39	36	(92.3)	2	(5.1)	1	(2.6)	0	(0.0)	0	(0.0)
	Fosphenytoin	102	88	(86.3)	12	(11.8)	2	(2.0)	0	(0.0)	0	(0.0)
	Dilantin	32	3	(9.4)	22	(68.8)	5	(15.6)	2	(6.3)	0	(0.0)

2.10 Conclusions From Normal Volunteer Studies

The great majority of data collected in normal volunteers is applicable to the IV bolus situation (at varying rates). In the categories severe AEs, all AEs, rate-related AEs, and dose-related AEs, there is a consistent trade-off between the occurrence of local injection site reactions and pain with IV Dilantin and the occurrence of generalized paresthesia and pruritus with IV Fos.

Paresthesia are reported with IV Dilantin, but only at high rate or high dose. Even at high rate or high dose though, the incidence of paresthesia is less than expected for Dilantin given the incidence for Fos. Taste perversion is an additional AE that appeared for Fos subjects but not Dilantin subjects.

The sponsor does not address the reversibility of Fos-associated paresthesia, pruritus, and taste perversion directly in the ISS. Statements are made to the effect that these 3 AEs tend to be limited to the post-infusion times. Whether some subjects continued with these AEs is not directly obvious from reading the ISS.

3.0 Completed Studies in Patients

534 patients participated in completed clinical studies. The breakdown of these 534 patients has been presented above in "Section 1.0 Exposure." In the ISS, the sponsor presents different cross-sectional views of AE data, but each is inadequate for not accounting for other relevant variables. For instance, a breakdown by route of administration does not account for whether the individual patients were given loading doses or maintenance doses. For this reason, I believe that only individual study reports are interpretable. Even these present problems by not controlling for rate and dose in may circumstances (see individual study reviews).

The appropriateness of combining results from different studies in patients even when ostensibly the same medications were given by the same route and same dosing regimen (loading vs maintenance) can be questioned. For instance, patients in Studies 15 and 21 received IV loading doses of Fos or Dilantin. But the AE profile for the Dilantin arms of the two trials differ significantly (see tables of common AEs from these 2 trials on following pages). One possible explanation is that one study was in neurosurgical patients and the other in epilepsy patients.

In Study 21 in epilepsy patients, nystagmus, dizziness, vertigo, and ataxia are reported in 38%, 38%, 23%, and 15% of patients respectively. In Study 15 in neurosurgery patients, the same AEs are reported in 14%, 11%, 0%, and 7% of patients respectively. All these AEs would be more likely to be ascertained in an ambulatory, alert population like the epilepsy population.

3.1 All AEs

Sponsor's Table 12 presents all AEs occurring in patients in completed studies. Suffice it to say that no alarming safety concerns arise in reviewing data presented this way. At the same time, no convincing advantages of Fos over Dilantin emerge.

While injection site pain is reported in 1.5% of Fos patients and 6.9% of Dilantin patients, the comparability of rate and dose of administration between groups is not obvious. Likewise, while injection site reaction is reported in 2.8% of Fos patients and 4.9% of Dilantin patients, the rates and doses may not be comparable. Note that when data is grouped as it is

TABLE 12. All and Associated Adverse Events Occurring in ≥1% of Patients by Body System and Treatment[a,b]
[Number (%) of Patients]
(Page 1 of 2)

BODY SYSTEM/ Preferred Term	Fosphenytoin N = 534				Dilantin N = 102			
	All		Associated		All		Associated	
NERVOUS								
Nystagmus	99	(18.5)	71	(13.3)	14	(13.7)	7	(6.9)
Dizziness	48	(9.0)	43	(8.1)	10	(9.8)	9	(8.8)
Ataxia	48	(9.0)	20	(3.7)	9	(8.8)	2	(2.0)
Somnolence	45	(3.4)	25	(4.7)	10	(9.8)	8	(7.8)
Tremor	31	(5.8)	19	(3.6)	9	(8.8)	5	(4.9)
Incoordination	28	(5.2)	15	(2.8)	4	(3.9)	2	(2.0)
Paresthesia	26	(4.9)	19	(3.6)	3	(2.9)	2	(2.0)
Neuropathy	25	(4.7)	2	(0.4)	4	(3.9)	0	(0.0)
Reflexes Increased	16	(3.0)	1	(0.2)	3	(2.9)	0	(0.0)
Speech Disorder	15	(2.8)	4	(0.7)	3	(2.9)	2	(2.0)
Hypertonia	12	(2.2)	2	(0.4)	0	(0.0)	0	(0.0)
Reflexes Decreased	10	(1.9)	2	(0.4)	4	(3.9)	2	(2.0)
Intracranial Hypertension	9	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Stupor	8	(1.5)	3	(0.6)	1	(1.0)	0	(0.0)
Anxiety	7	(1.3)	2	(0.4)	0	(0.0)	0	(0.0)
Confusion	6	(1.1)	2	(0.4)	0	(0.0)	0	(0.0)
Agitation	6	(1.1)	0	(0.0)	1	(1.0)	0	(0.0)
BODY AS A WHOLE								
Headache	41	(7.7)	13	(2.4)	6	(5.9)	2	(2.0)
Fever	35	(6.6)	0	(0.0)	6	(5.9)	0	(0.0)
Pain	29	(5.4)	10	(1.9)	2	(2.0)	2	(2.0)
Accidental Injury	22	(4.1)	2	(0.4)	7	(6.9)	2	(2.0)
Infection	17	(3.2)	0	(0.0)	5	(4.9)	0	(0.0)
Injection-Site Reaction	15	(2.8)	10	(1.9)	5	(4.9)	2	(2.0)
Asthenia	9	(1.7)	7	(1.3)	2	(2.0)	1	(1.0)
Back Pain	9	(1.7)	1	(0.2)	0	(0.0)	0	(0.0)
Face Edema	9	(1.7)	0	(0.0)	4	(3.9)	0	(0.0)
Injection-Site Pain	8	(1.5)	7	(1.3)	7	(6.9)	7	(6.9)
Reaction Unevaluable	7	(1.3)	2	(0.4)	1	(1.0)	1	(1.0)
Sepsis	7	(1.3)	0	(0.0)	1	(1.0)	0	(0.0)
DIGESTIVE								
Nausea	30	(5.6)	12	(2.2)	6	(5.9)	1	(1.0)
Constipation	26	(4.9)	2	(0.4)	3	(2.9)	0	(0.0)
Vomiting	17	(3.2)	2	(0.4)	5	(4.9)	0	(0.0)

[a] Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment. Events occurring in ≥1% of patients were based upon all adverse events occurring in fosphenytoin-treated patients.
[b] See Appendix B.2 for a complete listing of all and associated adverse events.

TABLE 12. All and Associated Adverse Events Occurring in ≥1% of Patients by Body System and Treatment[a,b]
[Number (%) of Patients]
(Page 2 of 2)

BODY SYSTEM/ Preferred Term	Fosphenytoin N = 534				Dilantin N = 102			
	All		Associated		All		Associated	
CARDIOVASCULAR								
Hypotension	13	(2.4)	4	(0.7)	3	(2.9)	2	(2.0)
Hypertension	10	(1.9)	1	(0.2)	2	(2.0)	0	(0.0)
Tachycardia	9	(1.7)	0	(0.0)	2	(2.0)	0	(0.0)
Bradycardia	7	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES								
Pruritus	27	(5.1)	24	(4.5)	0	(0.0)	0	(0.0)
Rash	7	(1.3)	1	(0.2)	2	(2.0)	1	(1.0)
HEMIC AND LYMPHATIC								
Ecchymosis	30	(5.6)	13	(2.4)	4	(3.9)	2	(2.0)
SURGERIES/PROCEDURES								
Surgeries/Procedures	26	(4.9)	0	(0.0)	5	(4.9)	0	(0.0)
RESPIRATORY								
Pneumonia	10	(1.9)	0	(0.0)	6	(5.9)	0	(0.0)
Lung Disorder	7	(1.3)	0	(0.0)	1	(1.0)	0	(0.0)
UROGENITAL								
Urinary Retention	8	(1.5)	0	(0.0)	3	(2.9)	0	(0.0)
Urinary Tract Infection	6	(1.1)	0	(0.0)	2	(2.0)	0	(0.0)
MUSCULOSKELETAL								
Myasthenia	11	(2.1)	1	(0.2)	2	(2.0)	0	(0.0)
SPECIAL SENSES								
Amblyopia	9	(1.7)	4	(0.7)	3	(2.9)	3	(2.9)
METABOLIC AND NUTRITIONAL								
Hypokalemia	8	(1.5)	0	(0.0)	2	(2.0)	0	(0.0)

[a] Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment. Events occurring in ≥1% of patients were based upon all adverse events occurring in fosphenytoin-treated patients.

[b] See Appendix B... for a complete listing of all and associated adverse events.

here for all patients, the term "injection site" could apply to either IM or IV injection site !

On page 48 of the ISS, the sponsor describes the experience with paresthesia and pruritus in more detail. For 13 patients treated with IV Fos, the investigator chose to manage the events by changing the infusion rate or administering medication (steroids or antihistamines). The number of events after IM Fos is not stated here, but no interventions were utilized. One patient withdrew because of severe pruritus that occurred with severe allergic reaction (Pt 13, Study 13, Center 1).

Also on page 48, the sponsor reports that in completed patient studies, discrepancies between Fos and Dilantin treated patients with regard to pruritus and paresthesia were not as great as in the normal volunteer studies. This fact is misleading because the 2 different comparative studies in patients reported different experiences. With regard to paresthesia, Study 21 reported a 10% vs 0% incidence in paresthesia in favor of Dilantin. With regard to pruritus, Study 21 reported a 31% vs 0% incidence in pruritus in favor of Dilantin. In short, in some patient studies, discrepancies in Fos and Dilantin treated subjects with regard to paresthesia and pruritus were as great as or greater than those seen in the normal volunteer studies.

3.2 Common AEs Within the Two Active-Control Trials

The 2 active-control trials in the NDA differ in two respects: first, one had only an IV loading dose while the other had an IV load followed by IV maintenance dosing; second, one was in neurosurgery patients and one was in epilepsy patients.

When the 2 Dilantin-control trials (Studies 15 and 21) are looked at separately, the magnitude of the discrepancies between Fos and Dilantin for certain AEs varies.

For all studies combined, pruritus was reported in 5% Fos patients and 0% Dilantin patients. In Study 15 (neurosurgery patients), pruritus was reported in 6% Fos patients and 0% Dilantin patients. But in Study 21 (epilepsy patients), pruritus was reported in 31% Fos patients vs 0% Dilantin patients.

TABLE 16. Most Frequent Adverse Events With IV Administration to Neurosurgical Patients (Study 982-015)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 88		Dilantin N = 28	
NERVOUS				
Nystagmus	12	(13.6)	4	(14.3)
Neuropathy	9	(10.2)	4	(14.3)
Reflexes Increased	7	(8.0)	0	(0.0)
Dizziness	6	(6.8)	3	(10.7)
Somnolence	6	(6.8)	3	(10.7)
Speech Disorder	5	(5.7)	1	(3.6)
BODY AS A WHOLE				
Fever	11	(12.5)	6	(21.4)
Face Edema	7	(8.0)	4	(14.3)
Injection-Site Reaction	6	(6.8)	5	(17.9)
Infection	6	(6.8)	2	(7.1)
DIGESTIVE				
Constipation	11	(12.5)	3	(10.7)
Nausea	9	(10.2)	4	(14.3)
Vomiting	6	(6.8)	5	(17.9)
CARDIOVASCULAR				
Tachycardia	7	(8.0)	2	(7.1)
Hypotension	6	(6.8)	2	(7.1)
SKIN AND APPENDAGES				
Pruritus	5	(5.7)	0	(0.0)
SURGERIES/PROCEDURES				
Surgeries/Procedures	9	(10.2)	3	(10.7)
RESPIRATORY				
Pneumonia	6	(6.8)	6	(21.4)
UROGENITAL				
Urinary Retention	7	(8.0)	3	(10.7)
MUSCULOSKELETAL				
Myasthenia	7	(8.0)	2	(7.1)
METABOLIC AND NUTRITIONAL				
Hypokalemia	8	(9.1)	2	(7.1)

TABLE 15. Most Frequent Adverse Events With IV Administration to Patients With Epilepsy (Study 982-021)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 39		Dilantin N = 13	
NERVOUS				
Nystagmus	18	(46.2)	5	(38.5)
Dizziness	10	(25.6)	5	(38.5)
Ataxia	7	(17.9)	2	(15.4)
Vertigo	4	(10.3)	3	(23.1)
Paresthesia	4	(10.3)	0	(0.0)
Tremor	3	(7.7)	0	(0.0)
Neuropathy	3	(7.7)	0	(0.0)
Somnolence	2	(5.1)	1	(7.7)
Speech Disorder	2	(5.1)	2	(15.4)
BODY AS A WHOLE				
Headache	7	(17.9)	1	(7.7)
Pain	5	(12.8)	1	(7.7)
Reaction Unevaluable	4	(10.3)	1	(7.7)
Chills	2	(5.1)	0	(0.0)
Chest Pain	2	(5.1)	0	(0.0)
CARDIOVASCULAR				
Hypotension	3	(7.7)	1	(7.7)
SKIN AND APPENDAGES				
Pruritus	12	(30.8)	0	(0.0)
SPECIAL SENSES				
Amblyopia	4	(10.3)	3	(23.1)
Ear Disorder	2	(5.1)	0	(0.0)

Overall, in Study 21, the big differences in AEs between Fos and Dilantin occurred for pruritus (31 vs 0 %), paresthesia (10 vs 0 %), neuropathy (8 vs 0 %), and tremor (8 vs 0 %).

Overall, in Study 15, the big differences in AEs between Fos and Dilantin occurred for pruritus (6 vs 0 %), increased reflexes (8 vs 0 %), and injection site reaction (7 vs 18 %).

Note that injection site reactions were not unusual in Study 15 and demonstrated a difference between Fos and Dilantin. In Study 21, only a single injection site reaction was reported (it happened to be in a Fos patient) so that no difference between Fos and Dilantin was really demonstrated. In all likelihood, this difference between studies was because Study 21 was only a single dose study while Study 15 incorporated a loading dose followed by several days of maintenance dosing. (Another alternative explanation is that the Dilantin rates in Study 21 were lowered in 5 patients because of local pain, thereby decreasing the later emergence of injection site reactions in those patients.)

One might infer from the last paragraph that, for IV dosing, the advantage of Fos over Dilantin with regard to local tissue reactions is confered only upon patients who receive maintenance dosing. However, in both Study 15 and Study 21, the rates of infusion of the loading doses were so low as to contribute almost nothing to our understanding of IV loading in an emergent setting i.e. status epilepticus where the bioequivalent rate of 100-150 mg/min should be approached. In those situations of rapid infusion, local injection site reactions might occur with both Dilantin and Fos, perhaps even with an advantage for Fos. Unfortunately, a head-to-head comparison of Dilantin and Fos in comparable rapid infusions has only recently begun. Until that study is completed, no definitive statements about a Fos advantage over Dilantin for injection site reactions in emergent settings can be made.

3.3 Common AEs in IV Maintenance Study

The only study that really speaks to the safety of IV maintenance therapy is Study 15. As alluded to previously, this study in neurosurgical patients appears to underrepresent (in the face of comparable dose and rate) certain AEs which were shown in another study (Study 21) to occur with

high frequency in another population (epilepsy).

If exposure is assumed to be the same after IM maintenance therapy in neurosurgery patients, Study 14 (uncontrolled) can also be used to support IV maintenance therapy and, alternatively, Study 15 can be used to support IM maintenance therapy (albeit without the local IM safety data).

3.4 "Slow" Loading Doses

For all their differences, there are 4 studies (2 active-control and 2 uncontrolled) which support subacute loading doses. Studies 14 and 15 were performed in neurosurgery patients and studies 21 and 22 were performed in epilepsy patients. Studies 15 and 21 had IV loading doses while studies 14 and 22 had IM loading doses.

3.5 "Rapid" IV Loading Doses

Only one study, Study 16, really addresses the safety of IV loading doses in status epilepticus. This was an uncontrolled study.

Some comparative safety data on IV loading is accrued in Studies 15 and 21 and, although bioequivalent rates were only rarely achieved in those studies, do provide some picture of comparative safety.

In particular, one concern might be that significant AEs might be missed in Study 16 if the patients with status epilepticus were too obtunded to report them. In Study 21 in epilepsy patients, obtundation is not a problem so that reporting rates for some AEs would be expected to be higher, albeit with the less-than-bioequivalent rates.

This indication is also the subject of a new active-control trial with Dilantin in which bioequivalent rates will be maintained.

3.6 Rate-related AEs After IV Administration

As in the normal volunteer studies, paresthesia and pruritus were rate-related AEs in Fos patients. At rates that might be bioequivalent, Dilantin patients had a 3-fold less incidence of paresthesia and no cases of pruritus (compared to a 28% incidence of pruritus in Fos patients).

3.7 Severe AEs

Across all patient studies, there were 39 severe AEs among 534 Fos treated patients (7%). These AEs included ataxia, dizziness, somnolence, pain, nausea, ecchymosis, paresthesia, and pruritus.

3.8 Frequent AEs by Gender

Paresthesia and nystagmus were more common in men. Headache, pruritus, somnolence, and ecchymosis were more common in women. However, the sponsor has not adjusted the gender analysis for dose, rate, route, or clinical setting.

3.9 Frequent AEs by Age

Except for somnolence, the incidence of AEs in Fos patients was no different for the 40-65 year old group compared to the > 65 year old group (n=67). Somnolence was more common in the > 65 age group. However, the sponsor has not adjusted the gender analysis for dose, rate, route, or clinical setting.

3.10 Frequent AEs by Race

404 patients were white and 110 patients were black. 20 remaining patients represented other races. Headache, nausea, and paresthesia showed discrepant rates between white and black patients. Paresthesia occurred in 6% or white patients and only 1% of black patients. However, the sponsor has not adjusted the gender analysis for dose, rate, route, or clinical setting.

3.11 Clinical Labs

No overall pattern of change in laboratory values emerges for any of the parameters reported by the sponsor in the ISS. More detailed reviews of patients with extremely high or low values of lab parameters did not raise any additional concern. Recall that many patients were only treated with a single loading dose of Fos and many patients had concomitant conditions that would be expected to cause some lab abnormalities. No pattern of change in serum phosphorus was noted.

3.12 IM Local Tolerability

Of the 357 patients who received at least one IM injection, there were no severe injection site reactions. Two moderate injection reactions occurred and thirty-one mild reactions occurred.

3.13 IV Local Tolerability

Of the 127 patients who received at least one IV injection, there were no severe infusion-site reactions. There was one moderate reaction and nine mild reactions.

3.14 Deaths, Serious AEs, and Withdrawals

Eleven Cerebyx treated patients died. Ten of these deaths occurred in neurosurgery studies or status epilepticus studies. A review of these deaths raises no new concerns about Cerebyx. None of the deaths can be reasonably attributed to Cerebyx.

A review of the serious AEs and the withdrawals raised no new concerns with regard to Cerebyx. The serious AEs that occur with Dilantin may also occur with Cerebyx.

4.0 Study 16: Ongoing Study in Status Epilepticus

No new safety issues were defined in this uncontrolled study. See the review of the study for additional information. The two safety updates add additional information about this study.

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	4-Month Safety Update
Correspondence Date:	June 22, 1995
Date Received:	June 23, 1995

As per the adopted convention, all Fos doses and rates are expressed as mg phenytoin equivalents in this review.

The cut-off for the safety database for this submission was Feb 22, 1995. Additionally, all deaths and serious adverse events through May 15, 1995 are reported.

In fact this SU only adds data on 12 additional patients, patients who were enrolled in the ongoing study of status epilepticus (SE). Thus a total of 66 pts with SE are included in the SU as opposed to 54 in the NDA. The SU presents cumulative data on exposure to Fos, demographics, safety, deaths, withdrawals due to AEs, and serious AEs for the 861 participants in trials. Also, AE data for the 90 participants exposed to Fos at doses of at least 10mg/kg and rates of at least 100mg/min were examined.

The table below summarizes cutoff dates and patient numbers for the NDA and this SU:

	NDA	SU 1
Population		
Total Enrolled	849	861
Exposed to Fos	736	748
Cutoff Dates		
General Safety	Sept 1, 94	Feb 22, 95
Deaths/Serious AEs	Nov 18, 94	May 15, 95

Deaths and Serious AEs from NDA Cutoff Until Feb 22, 1995:

Deaths: One additional death occurred since the filing of the NDA. Patient 16 from Study 16, died from an intracranial bleed that was present prior to Fos administration.

Serious AEs: Four additional pts had serious AEs between NDA cutoff and Feb 22, 1995. Pt 16 from Study 16 is mentioned above under the category "deaths." Pt 20 from Study 16 developed apnea, CHF, and pulmonary edema. The pt had been treated for SE in the setting of a subdural hematoma; a history of IDDM was obtained. Apnea occurred on day 2 and CHF on day 3. Pts 21 and 22 from Study 16 both developed postictal psychosis. All 3 pts with nonfatal serious AEs recovered.

Withdrawals: No pts were withdrawn from Study 16 since the NDA was compiled.

Deaths and Serious AEs from Feb 22, 1995 Until May 15, 1995:

Deaths: One additional death occurred. Pt 1 from Study 26 (an ongoing active control study of IV loading with Fos vs IV loading with Dilantin) developed cryptococcal meningitis in the setting of AIDS and died.

Serious AEs: Pt 2 from Study 26 was hospitalized for CNS toxicity, which the investigator considered severe and possibly related to study medication. 5 days after treatment in the ER for seizures, the pt was admitted with phenytoin toxicity manifested by ataxia with a level of 30; he had been taking maintenance phenytoin, 400 mg/day.

Note: Sponsor's Appendix C.2 (not included) tabulates all deaths, serious AEs, and withdrawals because of AEs for the NDA and through May 15, 95.

Demographics: The demographics of the pts with SE do not change with the addition of the 12 pts.

Adverse Events: The AE tables on page 6-7 of the SU (not included) encompass all 748 subjects/pts exposed to Fos. Such a table is fairly uninformative, given the different routes of administration included. The addition of 12 pts to the 736 reported in the NDA did not change the AE profile.

More relevant is the updated list of all AEs (as well as those deemed associated with use of drug) from **Study 982-16** which occurs as Appendix B.1 (not included) of the SU. The 12 additional pts with SE were treated under this protocol, with pts receiving IV loading doses of Fos. The predominant (>5%) AEs in Study 16 are nystagmus (29%), headache (15%), ataxia (14%), somnolence (12%), agitation (12%), vomiting (11%), pruritus (9%), dizziness (8%), dysarthria (6%), and fever (6%).

Vital signs: Sponsor's Appendix B.2 from the SU (not included) provides the incidence of changes in systolic BP >20 mmHg from Study 16. 37/65 (57%) pts had such a decrease. The sponsor further divides this group by those with a "symptomatic decrease," associated with the AE dizziness, vertigo, lightheadedness, or hypotension.

Infusion site evaluations: Appendix B.3 (not included) from the SU provides the incidence of local skin reactions from Study 16. Data are grouped for 24-hour posttreatment or discharge. If both 24 hour data and discharge data are available, it is not clear how the sponsor chose one over the other. The way the data are collected, mild tenderness, swelling, bruising, and erythema are reported for 3-8% of pts. One pt had moderate bruising.

Clinical lab data: The sponsor states that no clinically significant changes were noted for the 12 additional pts in the SU.

Cohort of Patients Adequately Loaded IV: Sponsor's Appendix D.1 (not included) tabulates patients/subjects treated with Fos at doses >10mg/kg and rates > 100mg/min. 105 **individual exposures** are listed. 15 normal volunteers had 2 exposures at either different doses or different rates; therefore a total of 90 **individual subjects** are included.

37 of the exposures were in normal volunteers, so that 68 patients were treated in this cohort. 51 of these pts came from Study 16, a study of SE. 17 came from Study 21, a study in pts who simply "required a loading dose of phenytoin." The 12 new treated pts in this SU all came from Study 16, but only 11/12 are included in this cohort of high dose/high rate pts.

At this point in time, only 35 individuals have been dosed at 15mg/kg or greater, as well as 150mg/min.

Sponsor's Tables 5 and 6 summarize the breakdown of AEs by dose and rate for the 90 individual subjects exposed. (Note that these Tables were reformatted by the sponsor at my request so that pts treated at the higher doses and rates are not included in the columns for the lower doses and rates as they were in the original tables.) The sponsor concludes that "an increased incidence of AEs was not shown for successive increments of participants in this subgroup treated with increasing doses and rates. In particular, cardiovascular events occurred at a similar incidence across groups and did not appear to be related to the dose or rate of fosphenytoin administration."

However, there are several problems with inferences drawn from Tables 5 and 6. First, the denominators at any dose or rate window will be low, so that we cannot be sure we have captured the true AE profile with any certainty. Second, there is no control group. In particular, it would be interesting to compare the AE profile between pts randomized to phenytoin at 50mg/min vs Fos at 150mg/min. This latter information is being collected in the sponsor's ongoing study, Study 26. Finally, recall that these pts are often obtunded and cannot report some AEs that an awake, alert pt could report.

Literature Review: The sponsor's literature review covers the time period through March 10, 1995. One report of phlebitis in a Fos treated pt

is included. The sponsor maintains that, because of the mild tenderness alone, a clinical diagnosis of phlebitis was not applicable. This is an important issue in that the sponsor has proposed a lower incidence of phlebitis with Fos than with parenteral Dilantin.

Sponsor's Conclusions: The sponsor maintains that the safety profile has not changed with the additional information provided in the SU. The sponsor maintains that:

1. Overall, the AE profile of Fos is similar to that of parenteral Dilantin.

2. IV Fos is associated with fewer infusion site reactions than IV Dilantin (i.e. less pain and burning).

3. IM Fos produced no more injection site reactions than placebo.

4. High-dose, high-rate Fos IV (i.e. the bioequivalent dose and rate) has no more AEs associated with it than lower-dose, lower-rate Fos.

Reviewer's Conclusions: No significant change in the safety profile of Fos has arisen with the addition of the 12 new patients. The sponsor's 4 points above can be addressed as follows:

1. The AE profiles of Fos and parenteral Dilantin must be compared by route of administration. Further, only randomized trials that are adequately powered to detect a difference between treatments can truly assess the comparability of treatments.

2. IV Fos at high-dose, high-rate administration (the bioequivalent dose and rate) has only been given to 35 individuals. The sponsor's literature review demonstrates that IV Fos is not without some risk of local irritation; any estimate of the incidence of infusion site reactions must be so imprecise as to preclude any statements in favor of Fos.

3. The statement about IM Fos may be correct based on a study where IM **maintenance** therapy was studied. Whether this holds true for IM loading with Fos is unknown.

4. The populations of pts that received high-dose, high-rate Fos and lower-dose, lower-rate Fos may be so different as to preclude any statements about the safety of one regimen vs the other. (I suspect that pts with SE were more likely to receive the more aggressive regimens. These pts might be sicker on average and thus less likely to report events such as dizziness or tinnitus.) Only a randomized study can answer this question.

Looking at **IV loading doses** alone, Fos, at the bioequivalent dose and rate, has the potential to cause local reactions and has been shown to cause hypotension (as defined by > 20mmHg drop in SBP) in 57% of pts. The advantages of IV Fos are: 1) It can be given in 1/3 the time required to give an equimolar dose of Dilantin; and 2) It is more compatible with other IV fluids and drugs than Dilantin.

IV maintenance Fos has the same two advantages over Dilantin.

IM loading with Fos is tolerated, while Dilantin is reported to cause local irritation and unpredictable systemic absorption. The SU has not changed the database to either support or refute the use of IM loading with Fos.

IM maintenance with Fos presents the same situation as IM loading. Again the SU has not changed the position of Fos in this regard.

John Feeney, M.D.
Medical Reviewer

cc:
HFD-120
NDA 20-460
HFD-120/Leber/Katz/Feeney/Nighswander

REFORMATTED TABLE 5. Number of Subjects and Patients Exposed to Fosphenytoin at High Doses and Rates

	SU1 Infusion Rate (mg/min)	
Dose (mg/kg)	≥100 to < 150	≥150
≥10 to < 15	19	15
≥15	21	35

REFORMATTED TABLE 6 (a). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Rate and Increments of Dose
[Number (%) of Participants]
(Page 1 of 4)

	SU1			
BODY SYSTEM/ Preferred Term	FOS at ≥100 to 150 mg/min			
	≥10 to <15 mg/kg N = 19		≥15 mg/kg N = 21	
ANY ADVERSE EVENT	18	(94.7)	21	(100)
NERVOUS				
Nystagmus	7	(36.8)	11	(52.4)
Dizziness	7	(36.8)	5	(23.8)
Paresthesia	4	(21)	6	(28.6)
Somnolence	0	(0)	3	(14.3)
Ataxia	0	(0)	6	(28.6)
BODY AS A WHOLE				
Headache	6	(31.6)	6	(28.6)
DIGESTIVE				
Nausea	1	(5.3)	1	(4.8)
SPECIAL SENSES				
Tinnitus	1	(5.3)	1	(4.8)
SKIN AND APPENDAGES				
Pruritus	7	(36.8)	5	(23.8)

REFORMATTED TABLE 6 (b). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Rate and Increments of Dose
[Number (%) of Participants]
(Page 2 of 4)

	SU1			
BODY SYSTEM/ Preferred Term	FOS at ≥ 150 mg/min			
	≥10 to <15 mg/kg N = 15		≥15 mg/kg N = 35	
ANY ADVERSE EVENT	14	(93.3)	32	(91.4)
NERVOUS				
Nystagmus	9	(60)	14	(40)
Dizziness	6	(40)	6	(17.1)
Paresthesia	4	(26.7)	6	(17.1)
Somnolence	2	(13.3)	2	(5.7)
Ataxia	2	(13.3)	1	(2.9)
BODY AS A WHOLE				
Headache	5	(33.3)	1	(2.9)
DIGESTIVE				
Nausea	1	(6.7)	1	(2.9)
SPECIAL SENSES				
Tinnitus	2	(13.3)	1	(2.9)
SKIN AND APPENDAGES				
Pruritus	7	(46.7)	5	(14.3)

REFORMATTED TABLE 6 (c). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Dose and Increments of Rate

[Number (%) of Participants]

(Page 3 of 4)

	SU1			
BODY SYSTEM/ Preferred Term	FOS at ≥10 to <15 mg/kg			
	≥100 to <150 mg/min N = 19		≥150 mg/min N = 15	
ANY ADVERSE EVENT	18	(94.7)	14	(93.3)
NERVOUS				
Nystagmus	7	(36.8)	9	(60)
Dizziness	7	(36.8)	6	(40)
Paresthesia	4	(21)	4	(26.7)
Somnolence	0	(0)	2	(13.3)
Ataxia	0	(0)	2	(13.3)
BODY AS A WHOLE				
Headache	6	(31.6)	5	(33.3)
DIGESTIVE				
Nausea	1	(5.3)	1	(6.7)
SPECIAL SENSES				
Tinnitus	1	(5.3)	2	(13.3)
SKIN AND APPENDAGES				
Pruritus	7	(36.8)	7	(46.7)

REFORMATTED TABLE 6 (d). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Dose and Increments of Rate

[Number (%) of Participants]

	SU1	
	FOS at ≥15 mg/kg	
BODY SYSTEM/ Preferred Term	≥100 to <150 mg/min N = 21	≥150 mg/min N = 35
ANY ADVERSE EVENT	21 (100)	32 (91.4)
NERVOUS		
Nystagmus	11 (52.4)	14 (40)
Dizziness	5 (23.8)	6 (17.1)
Paresthesia	6 (28.6)	6 (17.1)
Somnolence	3 (14.3)	2 (5.7)
Ataxia	6 (28.6)	1 (2.9)
BODY AS A WHOLE		
Headache	6 (28.6)	1 (2.9)
DIGESTIVE		
Nausea	1 (4.8)	1 (2.9)
SPECIAL SENSES		
Tinnitus	1 (4.8)	1 (2.9)
SKIN AND APPENDAGES		
Pruritus	5 (23.8)	5 (14.3)

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	Second Safety Update
Correspondence Date:	October 31, 1995
Date Received:	November 4, 1995

As per the adopted convention, all Fos doses and rates are expressed as mg phenytoin equivalents (PE) in this review.

The cut-off for the safety database for this submission was Aug 1, 1995. Additionally, all deaths and serious adverse events through Sept 15, 1995 are reported.

In fact this SU adds data on 111 additional patients since the first safety update. The sponsor reports that the safety profile of Cerebyx in the safety update is consistent with that reported in the NDA and first safety update.

Since the first safety update, 3 deaths, 4 serious AEs, and 8 withdrawals due to AEs have occurred in 8 Cerebyx treated patients. The 3 deaths were due to cerebral edema, accidental drowning, and GI bleeding. Reasons for withdrawal included generalized itching, burning and itching, nausea and itching, hypotension, and agitation.

All 111 new exposures to Cerebyx were to the IV formulation. No new IM data is provided.

Data from 2 studies initiated and completed since the submission of the NDA and first safety update are included, Study 27 and Study 26.

TABLE 1. Number of Participants and Time Periods Covered in Safety Documents

	NDA	SU1	SU2
Population			
Total Enrolled	849	861[b]	994
Healthy Subjects[a]	159	159	175
Patients (epilepsy or neurosurgical) From Completed Studies	636	636	748
Status Epilepticus Patients From Ongoing Study	54	66[b]	71
Exposed to Fosphenytoin	736	748	859
Healthy Subjects[a]	148	148	164
Patients (epilepsy or neurosurgical) From Completed Studies	534	534	624
Status Epilepticus Patients From Ongoing Study	54	66[b]	71
Exposed to Fosphenytoin at High Dose (≥10 mg/kg) and High Rate (≥100 mg/min)	79	90[b]	194
Healthy Subjects[a]	22	22	38
Patients (epilepsy or neurosurgical) From Completed Studies	17	17	101
Status Epilepticus Patients From Ongoing Study	40	51[b]	55
Cut-Off Dates			
General Safety Information	09/01/94	02/22/95	08/01/95
Deaths and Serious Adverse Events	11/18/94	05/15/95	09/15/95

[a] Some subjects received multiple exposures to fosphenytoin but are only counted once in this table.
[b] All additional exposures were from an ongoing study of patients with status epilepticus (982-16).

Study 27

The final study report for Study 27 is not provided.

This was an open-label single dose study in which 16 normal volunteers received 1200mg Fos at 150mg/min. There were no deaths, no serious AEs, or withdrawals due to AEs. No slowing or discontinuation of infusions because of AEs is specifically reported.

226 AEs were reported. 108 were mild. 106 were moderate. 12 were severe in intensity. The severe AEs included:

pruritus	4 events
paresthesia	2 events
dizziness	2 events
aching knees	1 event
pelvic pain (burning)	1 event
asthenia	1 event
tinnitus	1 event

"The duration of the event ... was <30 minutes for 7 subjects, <2 hours for 2 subjects, <5 hours for 1 subject, and <21 hours for 2 subjects."

Injection-site symptoms including inflammation and reaction were experienced by 3 subjects and were all rated mild in intensity.

75% of subjects experienced paresthesia. 75% of subjects experienced pruritus.

The sponsor reports no changes in ECGs or clinical labs of clinical significance. One subject experienced a drop in BP to 67/43 10 minutes after infusion.

In reviewing the clinical lab data listings, I note that 9 subjects had ionized free calcium levels checked at variable times after infusion. All of the values reported are unremarkable. 5 of the 9 had free calcium levels checked immediately after the infusion. The sponsor makes no comment about these specific levels and their significance.

In reviewing the clinical lab data listings, I also noted bicarb levels were checked at frequent intervals after dosing. It appears that baseline levels

dip by a small increment for some patients, while patient 16 had a level below the stated normal range. Again the sponsor does not comment on these levels.

Study 26

This was a 112 patient, double-blind, randomized, parallel study of an IV loading dose of fosphenytoin vs. an IV loading dose of phenytoin. Patients were randomized in a 4:1 ratio to fos vs phenytoin. The inclusion/exclusion criteria did not specify particular diagnostic categories of patients to be included; rather pts who required a loading dose of phenytoin were to be included. Broadly speaking, this would include pts who were in status epilepticus as well as many other patients.

Pts received equimolar amounts of fos or phenytoin. The bioequivalent infusion rates (based on free phenytoin levels) were used so that the time of infusion was approximately 7 minutes for fos and 20 minutes for phenytoin. The total dose was to be 20mg/kg phenytoin equivalents (PE) except for patients with baseline phenytoin levels or patients over 65 years of age who received 15mg/kg.

90 patients received Cerebyx while 22 received Dilantin. The study was started in April, 1995 and completed in June, 1995.

Roughly half the patients in each treatment group were epilepsy patients; roughly a third of the patients in each treatment group were neurosurgery patients. Only 2 patients with status epilepticus were entered and both were in the Cerebyx arm of the trial.

14% of Cerebyx patients had the infusion modified because of AEs; 2% had the infusion modified because of AEs and pump problems. 50% of Dilantin patients had the infusion modified because of AEs; 14% had the infusion modified because of AEs and pump problems. The predominant reason for modifying the infusion in Dilantin patients was the occurrence of local injection site pain. The predominant reason for modifying the infusion in Cerebyx patients was the occurrence of more generalized itching and tingling, especially in the groin and lower extremities.

TABLE 5. Study 982-26: All and Associated[a] Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM/ Adverse Events	IV Fosphenytoin N = 90				IV Dilantin N = 22			
	All		Associated		All		Associated	
ANY ADVERSE EVENT	81	(90)	75	(83)	18	(82)	18	(82)
NERVOUS SYSTEM[b]	69	(77)	63	(70)	17	(77)	17	(77)
Nystagmus	40	(44)	39	(43)	13	(59)	13	(59)
Dizziness	28	(31)	28	(31)	6	(27)	6	(27)
Somnolence	18	(20)	18	(20)	6	(27)	6	(27)
Ataxia	10	(11)	9	(10)	4	(18)	4	(18)
Stupor	7	(8)	7	(8)	1	(5)	1	(5)
Incoordination	4	(4)	4	(4)	1	(5)	1	(5)
Paresthesia	4	(4)	4	(4)	0	(0)	0	(0)
Extrapyramidal Syndrome	4	(4)	3	(3)	0	(0)	0	(0)
Tremor	3	(3)	1	(1)	2	(9)	2	(9)
Agitation	3	(3)	0	(0)	0	(0)	0	(0)
Hypesthesia	2	(2)	2	(2)	2	(9)	2	(9)
Dysarthria	2	(2)	2	(2)	0	(0)	0	(0)
Vertigo	2	(2)	2	(2)	0	(0)	0	(0)
Brain Edema	2	(2)	0	(0)	1	(5)	0	(0)
Neuropathy	2	(2)	0	(0)	0	(0)	0	(0)
Akathisia	1	(1)	1	(1)	0	(0)	0	(0)
Coma	1	(1)	1	(1)	0	(0)	0	(0)
Intracranial Hypertension	1	(1)	1	(1)	0	(0)	0	(0)
Abnormal Gait	1	(1)	0	(0)	0	(0)	0	(0)
Hemiplegia	1	(1)	0	(0)	0	(0)	0	(0)
Hypertonia	1	(1)	0	(0)	0	(0)	0	(0)
Reflexes Increased	1	(1)	0	(0)	0	(0)	0	(0)
Twitching	1	(1)	0	(0)	0	(0)	0	(0)
Anxiety	0	(0)	0	(0)	1	(5)	1	(5)
Euphoria	0	(0)	0	(0)	1	(5)	1	(5)
Speech Disorder	0	(0)	0	(0)	1	(5)	1	(5)
SKIN AND APPENDAGES[b]	45	(50)	43	(48)	1	(5)	1	(5)
Pruritus	44	(49)	43	(48)	1	(5)	1	(5)
Fungal Dermatitis	1	(1)	0	(0)	0	(0)	0	(0)
Rash	1	(1)	0	(0)	0	(0)	0	(0)

[a] Considered by the investigator to be definitely, probably, possibly related to treatment, or of insufficient information to determine relationship.

[b] The totals for this body system are less than the number of patients with adverse events because at least 1 patient had more than 1 adverse event.

TABLE 5. Study 982-26: All and Associated[a] Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Events	IV Fosphenytoin N = 90				IV Dilantin N = 22			
	All		Associated		All		Associated	
DIGESTIVE[b]	17	(19)	14	(16)	3	(14)	3	(14)
Nausea	8	(9)	6	(7)	3	(14)	3	(14)
Tongue Disorder	4	(4)	4	(4)	0	(0)	0	(0)
Dry Mouth	4	(4)	3	(3)	1	(5)	1	(5)
Vomiting	2	(2)	2	(2)	2	(9)	2	(9)
Rectal Disorder	1	(1)	1	(1)	0	(0)	0	(0)
Tenesmus	1	(1)	1	(1)	0	(0)	0	(0)
SPECIAL SENSES[b]	14	(16)	12	(13)	3	(14)	3	(14)
Tinnitus	8	(9)	8	(9)	2	(9)	2	(9)
Diplopia	3	(3)	3	(3)	0	(0)	0	(0)
Taste Perversion	3	(3)	2	(2)	0	(0)	0	(0)
Amblyopia	2	(2)	2	(2)	2	(9)	2	(9)
Deafness	2	(2)	1	(1)	0	(0)	0	(0)
Ear Disorder	1	(1)	1	(1)	0	(0)	0	(0)
Eye Disorder	1	(1)	0	(0)	0	(0)	0	(0)
Visual Field Defect	1	(1)	0	(0)	0	(0)	0	(0)
CARDIOVASCULAR[b]	13	(14)	12	(13)	4	(18)	4	(18)
Hypotension	7	(8)	7	(8)	2	(9)	2	(9)
Vasodilatation	5	(6)	5	(6)	1	(5)	1	(5)
Tachycardia	2	(2)	1	(1)	0	(0)	0	(0)
Hypertension	1	(1)	0	(0)	0	(0)	0	(0)
Palpitation	0	(0)	0	(0)	1	(5)	1	(5)
BODY AS A WHOLE[b]	13	(14)	8	(9)	2	(9)	2	(9)
Pelvic Pain	4	(4)	4	(4)	0	(0)	0	(0)
Asthenia	2	(2)	2	(2)	0	(0)	0	(0)
Back Pain	2	(2)	2	(2)	0	(0)	0	(0)
Headache	2	(2)	0	(0)	1	(5)	1	(5)
Overdose	1	(1)	1	(1)	0	(0)	0	(0)
Pain	1	(1)	0	(0)	1	(5)	1	(5)
Chills	1	(1)	0	(0)	0	(0)	0	(0)
Cryptococcosis	1	(1)	0	(0)	0	(0)	0	(0)
Death	1	(1)	0	(0)	0	(0)	0	(0)
Face Edema	1	(1)	0	(0)	0	(0)	0	(0)

[a] Considered by the investigator to be definitely, probably, possibly related to treatment, or of insufficient information to determine relationship.

[b] The totals for this body system are less than the number of patients with adverse events because at least 1 patient had more than 1 adverse event.

TABLE 5. Study 982-26: All and Associated[a] Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Events	IV Fosphenytoin N = 90				IV Dilantin N = 22			
	All		Associated		All		Associated	
BODY AS A WHOLE[b] (continued)								
Fever	1	(1)	0	(0)	0	(0)	0	(0)
Injection-Site Reaction	1	(1)	0	(0)	0	(0)	0	(0)
RESPIRATORY	3	(3)	0	(0)	0	(0)	0	(0)
Pneumonia	1	(1)	0	(0)	0	(0)	0	(0)
Sinusitis	1	(1)	0	(0)	0	(0)	0	(0)
Sputum Increased	1	(1)	0	(0)	0	(0)	0	(0)
METABOLIC AND NUTRITIONAL	2	(2)	0	(0)	1	(5)	1	(5)
Hyperglycemia	1	(1)	0	(0)	0	(0)	0	(0)
Hypokalemia	1	(1)	0	(0)	0	(0)	0	(0)
Peripheral Edema	0	(0)	0	(0)	1	(5)	1	(5)
HEMIC AND LYMPHATIC	2	(2)	0	(0)	0	(0)	0	(0)
Ecchymosis	1	(1)	0	(0)	0	(0)	0	(0)
Hypochromic Anemia	1	(1)	0	(0)	0	(0)	0	(0)
UROGENITAL	2	(2)	0	(0)	0	(0)	0	(0)
Urinary Tract Infection	1	(1)	0	(0)	0	(0)	0	(0)
Vaginal Moniliasis	1	(1)	0	(0)	0	(0)	0	(0)

[a] Considered by the investigator to be definitely, probably, possibly related to treatment, or of insufficient information to determine relationship.

[b] The totals for this body system are less than the number of patients with adverse events because at least 1 patient had more than 1 adverse event.

The AE profile in this study reveals pruritus in 50% of Cerebyx patients and 5% of Dilantin patients.

Of the 44 Cerebyx patients who reported pruritus, 6 reported severe intensity. 8 patients had pruritus continue for up to 1-2 hours. Not stated is the intensity of the pruritus for these last 8 patients. 5 patients had no stop time recorded for the pruritus. 4 were listed as recovered at the follow-up visit. One was listed as clinical outcome unknown.

The infusion was modified for 13/44 Cerebyx patients with pruritus. None of the patients with pruritus reported any additional skin reactions, fever, or other AEs suggestive of drug hypersensitivity or anaphylaxis.

The AE listing is attached.

9% of Cerebyx patients reported localized pain and/or burning at the injection site during infusion compared to 90% of Dilantin patients.

Cohort of Patients Adequately Loaded IV: All the new exposures in this safety update were IV, primarily at high doses and rates as a result of the Study 26 and Study 27 protocols. Therefore, there are currently 194 individuals in the safety database (38 volunteers and 156 patients) who received Cerebyx at doses >10mg/kg and rates > 100mg/min. Of these 194 individuals, 128 received Cerebyx at >15mg/kg and > 150mg/min. 66 received Cerebyx at ≥ 19.5mg/kg and ≥ 150 mg/min.

Sponsor's Table 11 summarizes the breakdown of AEs by dose and rate for the 128 patients exposed.

Sponsor's Table 12 summarizes the breakdown of AEs according to the reported intensity of the AEs.

Given the heterogenicity of the total population treated at the highest dose and rate (status epilepticus, neurosurgery, epilepsy), care must be exercised in extrapolating from these results.

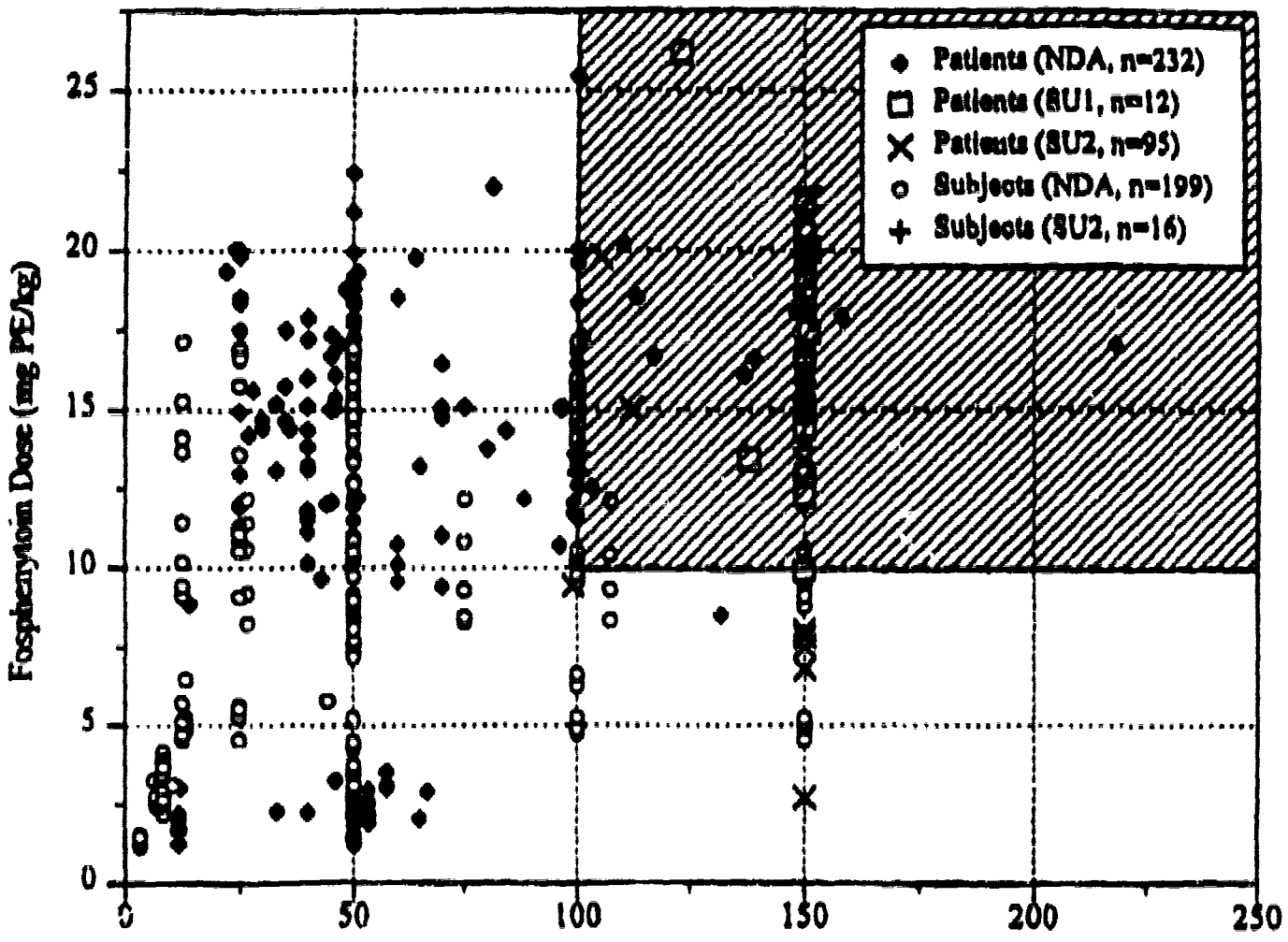

FIGURE 1. Subject and Patient Exposure to Fosphenytoin by Dose and Rate

TABLE 10. Number of Participants[a] Exposed to Fosphenytoin at High Doses and Rates

Dose (mg/kg)	Infusion Rate (mg/min)			
	≥100 to <150		≥150	
	SU1	SU2	SU1	SU2
≥10 to <15	19	24	15	25
≥15	21	32	35	128

[a] Total number of participants is less than total number of exposures because some subjects received multiple exposures to fosphenytoin.

TABLE 11. Most Frequent Adverse Events[a] by Any IV Dose or Rate, Lower Doses or Rates, and Higher Doses and Higher Rates

[Number (%) of Participants]

BODY SYSTEM/ Adverse Event	IV Fosphenytoin at any Dose or Rate N = 490		IV Fosphenytoin at Lower Doses (<15 mg/kg) or Rates (<150 mg/min) N = 373[b]		IV Fosphenytoin at Higher Doses (≥15 mg/kg) and Higher Rates (≥150 mg/min) N = 128	
ANY ADVERSE EVENT	381	(77.8)	278	(74.5)	114	(89.1)
NERVOUS	296	(60.4)	213	(57.1)	94	(73.4)
Nystagmus	144	(29.4)	92	(24.7)	61	(47.7)
Dizziness	121	(24.7)	85	(22.8)	39	(30.5)
Paresthesia	81	(16.5)	65	(17.4)	21	(16.4)
Somnolence	54	(11.0)	32	(8.6)	22	(17.2)
Ataxia	44	(9.0)	23	(6.2)	21	(16.4)
BODY AS A WHOLE	143	(29.2)	111	(29.8)	34	(26.6)
Headache	50	(10.2)	39	(10.5)	12	(9.4)
Pain	25	(5.1)	12	(3.2)	13	(10.2)
DIGESTIVE	88	(18.0)	59	(15.8)	30	(23.4)
Nausea	41	(8.4)	25	(6.7)	16	(12.5)
SPECIAL SENSES	87	(17.8)	57	(15.3)	35	(27.3)
Tinnitus	47	(9.6)	26	(7.0)	21	(16.4)
SKIN AND APPENDAGES	113	(23.1)	62	(16.6)	53	(41.4)
Pruritus	103	(21.0)	54	(14.5)	51	(39.8)

[a] Most frequent adverse events are defined as those that occurred in ≥5% of fosphenytoin-treated subjects or patients.

[b] Includes 11 subjects who are also included in the higher dose/higher rate (N = 128) category.

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TABLE 12. Most Frequent Adverse Events[a] by Lower Doses or Rates, Higher Doses and Higher Rates, and Maximum Intensity

[Number (%)[b] of Patients or Exposures in Subjects)

Preferred Term	IV Fosphenytoin at Doses (<15 mg/kg) or Rates (<150 mg/min) N = 373[c]						IV Fosphenytoin at Doses (≥15 mg/kg) and Rates (≥150 mg/min) N = 128							
	Mild		Moderate		Severe		Mild		Moderate		Severe		Unknown	
Any Adverse Event	203	(73.0)	61	(21.9)	14	(5.0)	66	(57.9)	36	(31.6)	11	(9.6)	1	(0.9)
Nystagmus	84	(91.3)	8	(8.7)	0	(0.0)	38	(62.3)	23	(37.7)	0	(0.0)	0	(0.0)
Dizziness	67	(78.8)	16	(18.8)	2	(2.4)	19	(48.7)	18	(46.2)	2	(5.1)	0	(0.0)
Paresthesia	54	(83.1)	10	(15.4)	1	(1.5)	10	(47.6)	10	(47.6)	1	(4.8)	0	(0.0)
Somnolence	21	(65.6)	11	(34.4)	0	(0.0)	10	(45.5)	11	(50.0)	1	(4.5)	0	(0.0)
Ataxia	18	(78.3)	4	(17.4)	1	(4.3)	10	(47.6)	10	(47.6)	1	(4.8)	0	(0.0)
Headache	24	(61.5)	14	(35.9)	1	(2.6)	7	(58.3)	5	(41.7)	0	(0.0)	0	(0.0)
Pain	7	(58.3)	2	(16.7)	3	(25.0)	5	(38.5)	8	(61.5)	0	(0.0)	0	(0.0)
Nausea	18	(72.0)	6	(24.0)	1	(4.0)	11	(68.8)	4	(25.0)	1	(6.3)	0	(0.0)
Tinnitus	21	(80.8)	4	(15.4)	1	(3.8)	10	(47.6)	10	(47.6)	1	(4.8)	0	(0.0)
Pruritus	30	(55.6)	19	(35.2)	5	(9.3)	29	(56.9)	18	(35.3)	4	(7.8)	0	(0.0)

[a] Most frequent adverse events are defined as those that occurred in ≥5% of fosphenytoin-treated subjects or patients

[b] Percents are based on number of participants with the adverse event in the lower dose or rate, or higher dose and rate category

[c] Includes 11 subjects who are also included in the higher dose/higher rate (N = 128) category.

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Sponsor's Discussion: In this second safety update, the sponsor acknowledges the occurrence of pruritus in Cerebyx-treated subjects and patients. The sponsor comments that other phosphate ester prodrugs, Decadron and Hydrocortone, cause a burning sensation in the groin area. The sponsor states that Foscavir in the treatment of CMV retinitis causes tingling. The sponsor draws attention to the fact that, in Study 26, infusions were interrupted more often with Dilantin than with Cerebyx. The sponsor acknowledges that interruptions require patients to be awake; the sponsor states that patients were, as a rule, awake in Study 26, although specific treatment group comparisons of level of consciousness are not presented.

My Comments: After reviewing the sponsor's references on Decadron and Hydrocortone, I am impressed by the similarities between the character and the location of the sensory disturbance that those drugs create and that Cerebyx creates. Specifically, Cerebyx, like Decadron and Hydrocortone, seems to cause a burning and itching which predominates in the groin area. The intensity of the disturbance seems less with Decadron and Hydrocortone, but the loading dose of these drugs would deliver only 1/20th-1/10th the phosphate that a loading dose of Cerebyx would deliver. Could phosphate alone cause this characteristic sensory disturbance ? If so, are there any intermediate steps required, for instance, the induction of hypocalcemia via calcium-phosphate precipitation ?

My answer to the last question would be, perhaps not. The sensory disturbance described in hypocalcemia is usually a tingling that localizes to the face and hands. While tingling is also described in Cerebyx-treated patients, burning and itching predominate in the descriptions provided. Further, the burning and itching with Cerebyx is often immediate in onset, suggesting a minimal number of steps to cause the phenomenon. Also, free calcium levels were checked in 5 subjects in Study 27 immediately after infusion and were normal. (Not stated was whether these same 5 subjects had sensory disturbances.)

The sponsor mentions Foscavir as another drug that causes sensory disturbances. My understanding is that Foscavir is not broken down to

phosphate, but rather is excreted unchanged in the urine. It is believed that Foscavir actually chelates calcium causing a transient hypocalcemia which, in turn, causes the characteristic sensory disturbance of hypocalcemia (tingling in the face and hands). Therefore, I do not think Foscavir-induced sensory phenomena are parallel to Cerebyx-induced sensory phenomena.

From Studies 26 and 27, I believe the sponsor could provide a much better description of the sensory disturbance caused by the SE dosing regimen of Cerebyx. Currently, I have only been provided narrative accounts for patients and subjects who had "serious" AEs. Patients who had "severe" but not "serious" sensory disturbances are of special interest. For these patients, I think we need to know the duration of sensory disturbance.

John Feeney, M.D.
Medical Reviewer
January 25, 1996

cc:
HFD-120
NDA 20-450
HFD-120/Leber/Katz/Feeney/Nighswander

APPENDIX E.2

NARRATIVES FOR DEATHS, SERIOUS ADVERSE EVENTS, AND WITHDRAWALS BECAUSE OF ADVERSE EVENTS THROUGH 09/15/95

Overall Listing of Deaths, Serious Adverse Events, and Withdrawals Because of Adverse Events

Study	Center/Patient	Indication	Death	Serious AE	Withdrawal	Narrative Number (ISS, Appendix F)	
Studies in Subjects							
982-003	003/016	HS		X	X	1	(SW)
982-011	011/010	HS		X	X	2	(SW)
982-012	012/006	HS		X		3	(S)
982-017	017/001	HS			X	4	(W)
Studies in Patients							
982-013	007/014	E		X	X	5	(SW)
	011/013[a]	E			X	6	(W)
982-014	001/006	N		X		7	(S)
	001/012	N	X	X		8	(DS)
	001/014	N	X	X	X	9	(DSW)
	005/003	N			X	10	(W)
	005/005	N	X	X		11	(DS)
	007/003	N	X	X	X	12	(DSW)
	007/027	N	X	X		13	(DS)
	009/002	N	X	X	X	14	(DSW)
	009/009[b]	N	X	X	X	15	(DSW)
	009/011	N	X	X	X	16	(DSW)
	009/027	N		X	X	17	(SW)
	009/028	N		X		18	(S)
982-015	003/005	N		X		19	(S)
	003/015	N	X	X	X	20	(DSW)
	003/018	N	X	X	X	21	(DSW)
	003/022	N			X	22	(W)
	009/001	N			X	23	(W)

HS = Healthy subjects; E = Epilepsy; N = Neurosurgery; D = Death; S = Serious adverse event; W = Withdrawal.

[a] Patient entered the study a second time at Center 10 as Patient 28 and was withdrawn again because of similar events.

[b] Patient had a serious adverse event and died prior to receiving study drug.

APPENDIX E.2

NARRATIVES FOR DEATHS, SERIOUS ADVERSE EVENTS, AND WITHDRAWALS BECAUSE OF ADVERSE EVENTS THROUGH 09/15/95

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Overall Listing of Deaths, Serious Adverse Events, and Withdrawals Because of Adverse Events

Study	Center/Patient	Indication	Death	Serious AE	Withdrawal	Narrative Number (ISS, Appendix F)	
Studies in Patients (continued)							
982-016	001/001	SE		X		24	(S)
	001/016	SE		X		31	(S)
	001/017	SE		X		32	(S)
	001/020	SE		X		33	(S)[c]
	002/006	SE	X	X		25	(DS)
	002/011	SE	X	X		26	(DS)
	002/013	SE	X	X		30	(DS)
	009/009	SE		X		27	(S)
	009/021	SE		X		[b]	(S)
	009/22	SE		X		[b]	(S)
	012/016	SE	X	X		34	(DS)[c]
982-021	002/003	LD			X	28	(W)
982-022	004/011	LD		X		29	(S)
982-026	001/009	LD	X	X	X	37	(DSW)[d]
	001/014	LD			X	38	(W)[d]
	001/015	LD			X	39	(W)[d]
	001/033	LD	X	X	X	40	(DSW)[d]
	001/049	LD	X	X	X	41	(DSW)[d]
	002/001	LD	X	X		35	(DS)[c]
	005/001	LD			X	42	(W)[d]
	007/002	LD		X		36	(S)[c]
	007/003	LD			X	43	(W)[d]
	007/004	LD			X	44	(W)[d]
	007/009	LD			X	45	(W)[d]
	007/018	LD			X	46	(W)[d]

SE = Status epilepticus; LD = Required loading dose; D = Death; S = Serious adverse event; W = Withdrawal.

[b] Occurred after data cut-off for the NDA (narratives in ISS, Section 9.2.2)

[c] Occurred during period covered by SU1

[d] Occurred during period covered by SU2

Study 982-13: A 5-Day Study of the Tolerance and Safety of IM Fosphenytoin

Investigators

1	Abou-Khalil	Tennessee	20
2	Dyken	Alabama	3
3	Garnett/Pellock	Virginia	24
4	Lai	Missouri	15
5	Leroy	Texas	18
6	Matsuo	Utah	17
7	Michie/Tipton	Florida	20
8	Ojemann	Washington	20
10	Ramsay	Florida	31
11	Singer	Florida	20
12	Verma	Michigan	20
13	Wilder	Florida	32
Total			240

A. Study Design

This was a 5-day, double-blind, placebo-controlled, parallel-group study of IM Fos. By protocol, adult pts were considered for inclusion if they were taking oral Dilantin for the treatment of epilepsy or seizure prophylaxis, had stable blood phenytoin levels, and were maintaining a record of their seizures.

Pts in one group (25% of total N) were to continue receiving their oral Dilantin dose along with IM placebo. Pts in the other group (75% of the total N) were to receive placebo orally along with IM Fos.

Sponsor's Table 3, a schedule of time and events, is attached. After each injection, subjective evaluations of any irritation produced by the injections were to be made by the patient and the investigator. Seizures were to be recorded. One week after the last injection, a final physical exam was to be performed.

A subset of pts at a single study site (N=24) was to have a more extensive PK evaluation. The rest of the pts had determinations made of plasma phenytoin levels immediately before double-blind treatment and again on the fifth day of treatment. The subset of 24 pts had to be on a QD regimen and had plasma samples collected on Day -1 before dosing and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 hrs post dosing. On Days 1-4, samples were collected before dosing. On Day 5, samples were collected before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, and 24 hrs post dosing. Samples were analyzed for total and free phenytoin levels and Fos levels.

Inclusion/Exclusion Criteria were as follows:

- o Pts with epilepsy or recovering from neurosurgery
- o 18 years of age and older
- o On a stable dose of oral Dilantin for treatment or prophylaxis
- o Oral regimen QD or BID
- o Phenytoin levels between 10-20, with 2 samples between 1-4 weeks apart within 4 weeks of study entry which are within 30% of one another
- o Have a written record of seizures for at least 28 days (if being treated for epilepsy)
- o Not on more than 2 drugs to control seizures
- o Absence of life-threatening disease

Injections were given in the gluteus maximus and could be divided into 2 equal injections given in separate locations if the dose required a large volume. The pt was to rate on a 4 point scale the extent of pain, itching, and burning immediately after injection and again at 5, 30, 60, and 120 min post-injection, and immediately prior to the next injection.

The attending investigator would examine the site of injection at 5 and 30 min, and 1 and 2 hr after injection and again immediately prior to the next injection. A subjective rating of injury and local irritation was to be made using a 4 point scale applied to the 4 symptoms: redness, swelling, tenderness, and necrosis.

The dose of oral and IM study medication could be adjusted to maintain therapeutic blood concentrations and to minimize phenytoin toxicity.

The protocol-specified analysis plan was vague beyond stating that local

irritation would be compared between groups. It was stated that analyses of both safety and efficacy would be stratified based on whether the drug was given as prophylaxis or as treatment for epilepsy.

The efficacy analysis was likewise vague other than to say that comparisons between treatment groups would be made for seizure control, looking at the treatment period as well as the immediate pre- and post-treatment periods.

"The sample size of 200 was not chosen based on statistical considerations. This number of pts, added to those in other studies, is intended to demonstrate safe passage of pts treated with Fos in a sample of over 500 pts and normal volunteers."

B. Subject Disposition and Baseline Comparison

The first pt entered the study on April 23, 1991 and the last pt completed the study on December 30, 1991. 240 pts were randomized; 5 pts in the Fos group did not receive all 5 days of dosing and 1 additional pt who did receive 5 days of dosing did not return for the follow-up visit.

By design, pts could receive medication QD or BID; in fact, all pts received their medication QD. One treatment group consisted of 179 pts. The other treatment group consisted of 61 pts. The two treatment groups were similar in demographic characteristics. 95% of pts in both groups carried a diagnosis of epilepsy; only 6 pts in one group and 3 pts in the other were neurosurgery pts who required seizure prophylaxis. The mean daily dose of Dilantin was 375mg, with a range of 200-500mg.

The two treatment groups were balanced with respect to the concurrent AED medications used. 70% of pts took no other AEDs. 9-10% of pts took concurrent phenobarb. 9-10% of pts took concurrent VPA. 7-8% of pts took concurrent carbamazepine.

174/179 pts in the Fos group received all 5 days of treatment. 61/61 pts in the Dilantin group received all 5 days of treatment.

During the treatment phase, 13 Fos pts had their dose adjusted. 5/13 had doses lowered because of AEs such as confusion, ataxia, dizziness, and

nystagmus. 2/13 had doses raised because of poor seizure control. 5/13 had dose adjustments because plasma levels were either too high (2) or too low (3); recall that the protocol called for levels during the treatment phase only in pts in the PK special study group. 1/13 had the dose lowered simply due to noncompliance.

2 pts withdrew because of AEs. 2 pts withdrew because of "administrative" reasons. A fifth pt in the Fos group did not receive all 5 doses, but completed the study visits.

Protocol variations that could impact on interpretation of local irritation were as follows:

nonalternating sides for medication injection in 75 pts
multiple injection sites in 7 pts
multiple injections for a given dose not of equal volume in 5 pts

In 26 pts, at least one phenytoin level during screen was less than 10. In 3 pts, the 2 plasma levels during screen were not within 30% of each other.

C. Results

Given the multiple tests for local irritation performed by both the pts and physicians, along with the multiple time points at which these tests were performed for each injection, and the 5 different injections, it is hard to envision a statistic that would capture all this data in a meaningful way. Suffice it to say that a visual screen of all the listings for local skin irritation reveal no clinically significant differences between Fos and placebo injections, other than a slight increase in mild to moderate itching within the first hour after injection.

No deaths occurred during the study. 2 pts withdrew from the Fos group because of AEs. 1 pt experienced a serious AE in the Fos group. The one serious AE reported was phenytoin toxicity. The pt recovered completely after withdrawal from the study; the investigator noted that the pt had taken some additional doses of Dilantin from her own supply on Days 1 and 2 of treatment. The other withdrawal was due to an allergic reaction and pruritus, with full recovery off treatment. (Recall that pts had been exposed to phenytoin chronically before entering the study; exposure to

Fos was not the pt's first exposure to phenytoin.)

The percent of pts reporting any AEs was slightly higher in the Fos group (68%) compared to the placebo group (62%).

There was a higher incidence of nystagmus, incoordination, headache, nausea, and pruritus in the Fos group.

During the study, 6 pts experienced AEs that were rated "severe" in intensity, 4 on Fos and 2 on placebo. In the Fos group, one pt was discussed above as the withdrawal for allergic reaction and pruritus. There was one case each of severe nausea, vomiting, and migraine. In the placebo group, there was one case of dizziness that responded to a reduced dose, and one case of local excision of a breast lesion.

The incidence of seizures during treatment differed between the Fos and placebo groups (18% vs 10%). In particular, Fos pts had a high incidence of partial complex seizures (11%) compared to placebo (2%). Two Fos pts required dose adjustments because of poor seizure control. Most pts experienced no seizures in either treatment group so that the sponsor's comparison of average number of seizures per day between treatment groups is not very instructive. The sponsor acknowledges that the latter is highly influenced by a single patient with a large number of seizures. The sponsor reports some additional analyses which compare change from baseline to treatment period or change from treatment period to post-treatment; no statistically significant differences were found.

Blood pressure, heart rate, and respiration rate were recorded in relation to Fos injections. No clinically important trends were noted in any of these parameters following Fos injection, although 2-3 pts were noted to have blood pressures as low as 90/60 30-60 minutes after Fos injection. Pt 11-13 who discontinued because of dizziness had a BP of 90/60 30 minutes post-dose with a pre-dose pressure of 110/70. No pressures lower than 90/60 were noted for any pt at any time.

To determine any trend toward abnormal lab values during the study, pts were categorized as to whether their lab values were below, within, or above normal range at baseline and at the end of treatment. Changes to low or high from the screening value to the first follow-up visit were summarized. The sponsor notes that no consistent differences or

clinically important trends were evident. Changes from normal at screen to low at f/u occurred for at least 10% of pts in either group for RBC count, WBC count, and calcium.

Detailed PK Analysis: At Center 3, evaluable data was available for 13 pts out of a targeted population of 24. The sponsor explains that for 7 of the remaining 11 pts, samples were collected in heparinized tubes which were later found to interfere with Fos measurements. The remaining 4 pts were in the oral Dilantin/IM placebo group and were therefore not included in the analyses. For the 13 available, samples had been drawn at baseline at numerous times in relation to oral dose administration; on day 5, samples again were drawn at numerous times in relation to IM Fos administration. The ratios for Day 5 (IM Fos)/Baseline (oral Dilantin) are as follows:

Total Phenytoin	
Cmax	1.21
Tmax	0.66
AUC	1.05
Free Phenytoin	
Cmax	1.32
Tmax	0.42
AUC	1.18

The increases in Cmax and AUC might be explained by the increased bioavailability of Fos (100%) relative to oral Dilantin (90%). The more marked increases in free phenytoin following IM Fos might be consistent with displacement of phenytoin from plasma protein binding sites by Fos.

Overall PK Analysis at All Centers: A trend analysis was used to determine if there were differences in trough concentrations between treatment groups over time. 20 pts who required changes in dosage during the study were excluded from the analysis; data were available for 165 Fos treated pts and 55 Dilantin treated pts. The results showed that the mean trough concentrations of total phenytoin provided by Fos increased slightly from the first day through the follow-up visit, while the mean trough levels provided by Dilantin orally tended to stay the same. The increase in trough levels seen with Fos may be consistent with the complete bioavailability of IM Fos.

D. Conclusions

The PK data from this trial needs further Biopharm review. Based on the sponsor's presentation of the data, it appears that an IM dose of Fos may be substituted for an equimolar oral dose of Dilantin, achieving plasma levels of total phenytoin and free phenytoin which are roughly 20% higher. The AE profile of IM Fos reflects an increased incidence of nystagmus, incoordination, nausea, and headache, all of which might be expected with higher phenytoin and free phenytoin levels. The increased incidence of pruritus with IM Fos is unexpected based on higher phenytoin levels alone, but would not preclude use of IM Fos.

Perhaps the pts who would benefit most by IM Fos would be chronically Dilantin-treated pts who have a transient 2-3 day gastrointestinal disturbance which prevents oral medication, but is transient and not expected to require IV access for hydration or caloric intake.

Because of the delayed Tmax of total phenytoin and free phenytoin after IM Fos, IM Fos is **not** an alternative route of phenytoin administration in pts with status epilepticus.

TABLE 3. Schedule of Study Procedures

Study Procedure	Patient Selection	Double-Blind Treatment Phase					Follow-up Visit	
		Day						
	-28 to -1	1 through 5					6	13
		Minutes From IM Injection						
		-15	5	30	60	120		
Medical History	X							
Current Medications	X							
Seizure History	X							
Physical Exam	X						X	X
Pregnancy Test	X							
Full Neuro Exam	X							X
Brief Neuro Exam		X					X	
Vital Signs	X	X		X	X	X	X	X
Record Seizures	X	X					X	X
Clinical Labs[a]	X						X	X
Drug Screen	X						X	X
Phenytoin Concentration	2X	X					X	
Patient Ratings		X	X	X	X	X	X	
Injection Site Exam		X	X	X	X	X	X	X
Global Evaluation								

[a] Hematology, blood chemistry, and urinalysis

TABLE 11. All and Associated Adverse Events by Body System and Treatment Group

[Number (%) of Patients]

(Page 1 of 3)

BODY SYSTEM/ Preferred Term	IM FOS/PO PBO N = 179				PO DIL/IM PBO N = 61			
	All		Associated		All		Associated	
ANY BODY SYSTEM	121	(67.6)	71	(39.7)	38	(62.3)	19	(31.1)
NERVOUS	77	(43.0)	51	(28.5)	26	(42.6)	13	(21.3)
Nystagmus	27	(15.1)	15	(8.4)	5	(8.2)	1	(1.6)
Tremor	17	(9.5)	12	(6.7)	8	(13.1)	5	(8.2)
Ataxia	15	(8.4)	6	(3.4)	5	(8.2)	0	(0.0)
Incoordination	14	(7.8)	10	(5.6)	3	(4.9)	1	(1.6)
Somnolence	12	(6.7)	10	(5.6)	6	(9.8)	6	(9.8)
Dizziness	9	(5.0)	8	(4.5)	2	(3.3)	1	(1.6)
Paresthesia	7	(3.9)	3	(1.7)	2	(3.3)	2	(3.3)
Reflexes decreased	5	(2.8)	1	(0.6)	3	(4.9)	2	(3.3)
Depersonalization	2	(1.1)	2	(1.1)	0	(0.0)	0	(0.0)
Abnormal gait	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Confusion	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Dysarthria	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Hyperkinesia	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Hypertonia	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Stupor	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Vertigo	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Reflexes increased	1	(0.6)	0	(0.0)	3	(4.9)	0	(0.0)
Nervousness	1	(0.6)	0	(0.0)	2	(3.3)	1	(1.6)
Anxiety	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypesthesia	0	(0.0)	0	(0.0)	2	(3.3)	2	(3.3)
BODY AS A WHOLE	45	(25.1)	18	(10.1)	12	(19.7)	4	(6.6)
Headache	16	(8.9)	5	(2.8)	3	(4.9)	1	(1.6)
Asthenia	7	(3.9)	5	(2.8)	2	(3.3)	1	(1.6)
Accidental injury	6	(3.4)	1	(0.6)	4	(6.6)	1	(1.6)
Back pain	6	(3.4)	1	(0.6)	0	(0.0)	0	(0.0)
Pain	4	(2.2)	0	(0.0)	1	(1.6)	1	(1.6)
Abdominal pain	3	(1.7)	3	(1.7)	1	(1.6)	0	(0.0)
Infection	3	(1.7)	0	(0.0)	3	(4.9)	0	(0.0)

TABLE 11. All and Associated Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Preferred Term	IM FOS/PO PBO N = 179				PO DIL/IM PBO N = 61			
	All		Associated		All		Associated	
BODY AS A WHOLE (continued)								
Flu syndrome	3	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Allergic reaction	2	(1.1)	2	(1.1)	0	(0.0)	0	(0.0)
Injection site reaction	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Malaise	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Overdose	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
DIGESTIVE	15	(8.4)	6	(3.4)	1	(1.6)	0	(0.0)
Nausea	8	(4.5)	5	(2.8)	0	(0.0)	0	(0.0)
Vomiting	5	(2.8)	2	(1.1)	0	(0.0)	0	(0.0)
Constipation	3	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspepsia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhea	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
HEMIC AND LYMPHATIC	15	(8.4)	12	(6.7)	3	(4.9)	2	(3.3)
Ecchymosis	13	(7.3)	11	(6.1)	3	(4.9)	2	(3.3)
Leukocytosis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES	10	(5.6)	4	(2.2)	0	(0.0)	0	(0.0)
Pruritus	5	(2.8)	4	(2.2)	0	(0.0)	0	(0.0)
Rash	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin discoloration	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Contact dermatitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Maculopapular rash	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pustular rash	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Sweating	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR	7	(3.9)	4	(2.2)	0	(0.0)	0	(0.0)
Hypertension	3	(1.7)	1	(0.6)	0	(0.0)	0	(0.0)
Migraine	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Palpitation	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Syncope	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Postural hypotension	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

TABLE 11. All and Associated Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Preferred Term	IM FOS/PO PBO N = 179				PO DIL/IM PBO N = 61			
	All		Associated		All		Associated	
MUSCULOSKELETAL	4	(2.2)	3	(1.7)	3	(4.9)	2	(3.3)
Leg cramps	3	(1.7)	3	(1.7)	2	(3.3)	2	(3.3)
Joint disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Arthralgia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
RESPIRATORY	4	(2.2)	0	(0.0)	2	(3.3)	0	(0.0)
Pharyngitis	1	(0.6)	0	(0.0)	1	(1.6)	0	(0.0)
Dyspnea	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lung disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Sinusitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
SPECIAL SENSES	4	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)
Amblyopia	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Diplopia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Edema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral edema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
ENDOCRINE	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroid disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
UROGENITAL	1	(0.6)	0	(0.0)	1	(1.6)	0	(0.0)
Breast neoplasm	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Fibrocystic breast	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Impotence	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
SURGERIES/PROCEDURES	1	(0.6)	0	(0.0)	2	(3.3)	0	(0.0)
Surgeries/Procedures	1	(0.6)	0	(0.0)	2	(3.3)	0	(0.0)

Study 982-14: An Open-Label Study of the Tolerance and Safety of IM Fosphenytoin Given as a Single Loading Dose Followed by a Maintenance Regimen For Up To 2 Weeks

Investigators

1	Boucher	Memphis, TN	30
5	Matsuo	Salt Lake City, UT	5
6	Michie	Cape Coral, FL	20
7	Dean	Winston-Salem, NC	30
8	Ramsay	Miami, FL	2
9	Smith	St.Louis, MO	31
Total			118

A. Study Design

The study was intended to be a safety study. The projected enrollment was 150 patients.

Patients were to be candidates for neurosurgery or patients who had already undergone neurosurgery. Open-label treatment was to consist of a single loading dose followed by maintenance dosing for at least 3 days and for a maximum of 7 days (changed by amendment to 14 days). Patients were to return 2-4 days after the last injection for follow-up exams and procedures. A subset of patients at a single site (n=10) were to have PK determinations performed at various timepoints following injections.

Inclusion/exclusion criteria dictated that patients be 12 years of age or older. Pts were not to be have terminal illnesses or other life-threatening diseases.

To be excluded were pts with hypotension, bradycardia, and A-V block. Pts were excluded if they took any AED except benzodiazepines within 1 week prior to screen.

No medications were specifically excluded during the study. Any IV medications other than the study medication were to be administered at a

site different from that used for study drug.

By protocol the study drug could be administered either QD or BID as deemed appropriate by the investigator to achieve therapeutic concentrations of at least 10-20 microgms/mL. A protocol amendment required QD dosing only. Page 7 of the protocol implies that the loading dose would be 8-12 mg/kg PE.

The dosing administration could be divided and given in separate locations on the buttock.

During the treatment period, a trough blood phenytoin was to be drawn each day, prior to the patient receiving the first daily dose of study medication.

B. Subject Disposition and Baseline Comparison

The study was conducted between July 1991 and April 1992.

The study population included 78 males and 40 females, 93 whites and 25 blacks. The mean age was 48 years.

The pts were seriously ill neurosurgery pts who were victims of trauma to the head or other neurological emergencies, the most common of which were motor vehicle accidents and gunshot wounds. Over 1/5 pts were unconscious when they entered the study, and over 1/2 pts had a level of consciousness that was lethargic or worse.

110 pts completed treatment. 80 pts completed the follow-up assessments. 8 pts withdrew, 6 for admin reasons and 2 for AEs.

118 patients were given a loading dose between 8-21.6 mg/kg PE. Maintenance doses ranged from 1.7-17.2 mg/kg. Maintenance doses were given either QD or BID. 64 pts received QD doses, 45 pts received BID doses, and 9 pts received both QD and BID doses.

While the maximum treatment duration was extended by protocol amendment from 7 days to 14 days, only 5 pts received treatment for 8 days or greater.

C. Results

Eight pts withdrew from the study, 2 for administrative reasons and 6 because of AEs. Only 1/6 experienced an event that was considered drug related, an erythematous rash. At the follow-up visit, most of the rash had resolved.

Four pts who withdrew from the study died. Three other pts died after completing the study.

At any one timepoint, a maximum of 3 pts experienced mild irritation at the injection site.

Note that the AE data was grouped across the entire study and was not separated according to loading vs maintenance dosing. Altogether, 75% of pts reported AEs; only 8% of pts overall had AEs that were considered associated with study drug. The most frequent AEs were fever, somnolence, and nystagmus. 5% of pts experienced at least one seizure during open-label treatment; without a comparative treatment group, it is hard to interpret this finding.

Ten pts experienced serious AEs, but none of these were considered associated with study drug.

Changes from baseline in laboratory parameters occurred not infrequently during this study. However, given the population of seriously ill trauma patients requiring neurosurgery, no inferences can be made from the lab data.

For each patient studied, the mean trough phenytoin concentration for the study duration was > 10. Recall that daily trough concentrations were measured and doses adjusted to keep the daily levels > 10.

D. Conclusions

In a seriously ill neurosurgical population, the sponsor has demonstrated that plasma levels of phenytoin > 10 can be achieved and maintained. No safety concerns obviously related to Fos arose during the conduct of the study, but the natural tendency in this population is to attribute all AEs to

the underlying condition or the treatment of the underlying condition. Mild to moderate AEs will be overshadowed by more serious AEs in this population.

No efficacy data arises from this study. The occurrence of seizures in some patients despite plasma levels of phenytoin > 10 was documented, but is not surprising given the severity of the underlying conditions.

Study 982-15: A Study of the Tolerance and Safety of IV Fosphenytoin Given as a Single Loading Dose Followed by a Maintenance Regimen For Up To 2 Weeks

Investigators

1	Passini	Charlotte	4
2	Gallagher	Augusta, GA	1
3	Boucher/Feler	Memphis, TN	27
4	Dean	Winston-Salem	6
5	Kramer	Englewood, CO	10
6	Michie/Tipton	Cape Coral, FL	15
7	Newmark	Houston, TX	6
8	Schmitz/Young	Lexington, KY	12
9	Miller/Parks	Jackson, MS	10
10	Smith	St.Louis, MO	25
Total			116

A. Study Design

This was a double-blind, parallel-group, active control trial in patients requiring a loading dose of phenytoin to prevent or control seizures. Pts who met the inclusion/exclusion criteria were randomized in a 1:3 ratio to receive either parenteral Dilantin or Fosphenytoin.

The objectives of the study were 1) to evaluate the safety and tolerance of multiple IV doses of Fos for seizure prophylaxis in neurosurgery patients and 2) to obtain descriptive PK data for Fos in this patient population.

The study had 3 phases:

1. Screening phase
2. Treatment phase, Days 1-14
3. Follow-up phase for 2-4 days following the last IV dose

The treatment phase included a loading dose on Day 1 followed by daily IV maintenance infusions. "At the prestudy investigators meeting, the

minimum exposure requirement was defined as 72 hours, i.e. a loading dose followed by 2 days of maintenance dosing."

Pts at Center 5 had serial blood samples drawn over a 24 hour period beginning on the day of loading dose to determine total and free phenytoin concentrations in plasma.

Inclusion/exclusion criteria required that pts be 12 years of age or older. Patients were to require neurosurgery or were to have undergone neurosurgery. Pts were to be scheduled for neurosurgery within 14 days of entry into double-blind treatment.

To be excluded were pts with hypotension, bradycardia, and A-V block. Pts were excluded if they took any AED except benzodiazepines within 1 week prior to screen.

No medications were specifically excluded during the study. Any IV medications other than the study medication were to be administered at a site different from that used for study drug by using a second IV line.

By protocol, study drug could not be administered at rates greater than 50 mg/min either for loading or maintenance. The study drug could be administered either QD or BID as deemed appropriate by the investigator.

B. Subject Disposition and Baseline Comparison

The study was conducted between July 1992 and February 1993.

In general, patients were seriously ill neurosurgery patients who were suffering from head trauma or other neurological emergencies. With rare exceptions, patients underwent neurosurgical procedures on Study Day 1.

88 pts received IV Fos while 28 pts received IV Dilantin. The loading dose of Fos was given as a total dose between 7.3-22.4 mg/kg PE at infusion rates between 14-51 mg/min PE. Dilantin was given as a total dose between 7.8-19.8 mg/kg at infusion rates between 21-51 mg/min.

Maintenance doses of Fos were given as total doses of 1.2-23 mg/kg PE at infusion rates between 3.1-62.1 mg/min PE. Maintenance Dilantin was given as total doses of 1.3-18.4 mg/kg at infusion rates between 5.1-50

mg/min.

No patients received concurrent antiepileptic drugs during the screening phase of the study. Thus, patients should not have had baseline levels of phenytoin or any other AED. During the treatment phase, 4 pts received phenytoin in an unblinded fashion (3 Fos, 1 Dilantin), 3 pts received diazepam, and 2 pts received lorazepam.

Concurrent meds, other than AEDs, were in large part dictated by the individual's neurosurgery status. 108 pts actually had surgery during the study. 27/108 had surgery before beginning treatment with study drug. 79/108 had neurosurgery during the study. 2/108 had surgery after completing the study. Thus, 44% of pts were taking CNS agents at screen and this increased to 96% during double-blind treatment. The most common CNS agents were acetaminophen, fentanyl, codeine, and morphine.

To further complicate all this, we are told that small numbers of pts received BID maintenance dosing instead of QD, while similarly small numbers of pts received maintenance dosing as QD medication some days and BID medication other days.

14 pts withdrew from the study, 4 because of AEs and 10 for administrative reasons. Only 4 pts in each treatment group were treated for more than 7 days.

C. Results

Because the loading dose of Fos was not given at the bioequivalent rate of administration, this study cannot provide comparable safety data between an IV loading dose of Fos and an IV loading dose of Dilantin.

Comparable safety data between IV maintenance regimens of IV Fos and IV Dilantin is provided. One death occurred in each treatment group, unrelated to the treatment itself. One serious AE occurred in the Fos group and 2 serious AEs occurred in the Dilantin group; none were deemed related to the underlying treatment. Among AEs deemed associated with treatment, there was only 1 severe AE and this occurred in the Fos group: severe ataxia.

Among a listing of all AEs, the obvious discrepancies between treatment

groups occur for injection site reaction, injection site pain, and pruritus. The trend is for more local reactions with Dilantin and more generalized pruritus with Fos.

Seizures were so rare in both treatment groups that no meaningful statement about the anticonvulsant properties of either treatment can be made.

The sponsor (p 49 of the study report) presents changes in vital sign data between screening and 2 hours post loading dose for the 2 treatment groups. There are no obvious differences between treatment groups.

Changes seen in laboratory parameters during the study were felt to be most consistent with the population being studied, i.e. ill neurosurgery patients.

PK data was also accrued which demonstrates roughly equivalent trough levels of phenytoin with both the IV Fos and IV Dilantin regimens. During treatment, dose was adjusted by the investigators based on plasma phenytoin monitoring. The extrapolation of this might be that IV Fos can be used to achieve and maintain therapeutic plasma phenytoin concentrations *while monitoring trough plasma phenytoin levels.*

On page 65 of the study report, the sponsor summarizes changes in rates of infusion. Presumably, these changes pertain primarily to the loading doses administered. 17% of Fos pts and 36% of Dilantin pts required decreases in rates. Note, however, that the bioequivalent rate of Fos administration for IV loading was not given. Thus, a comparison of proportions of pts requiring dose reductions under the conditions of bioequivalence might have resulted in very different results.

The same problem in comparing groups arises when comparing groups for dose reductions due to injection site burning and itching. 5% of Fos pts required this while 18% of Dilantin pts required this.

TABLE 16. Most Frequent Adverse Events With IV Administration to Neurosurgical Patients (Study 982-015)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 88		Dilantin N = 28	
NERVOUS				
Nystagmus	12	(13.6)	4	(14.3)
Neuropathy	9	(10.2)	4	(14.3)
Reflexes Increased	7	(8.0)	0	(0.0)
Dizziness	6	(6.8)	3	(10.7)
Somnolence	6	(6.8)	3	(10.7)
Speech Disorder	5	(5.7)	1	(3.6)
BODY AS A WHOLE				
Fever	11	(12.5)	6	(21.4)
Face Edema	7	(8.0)	4	(14.3)
Injection-Site Reaction	6	(6.8)	5	(17.9)
Infection	6	(6.8)	2	(7.1)
DIGESTIVE				
Constipation	11	(12.5)	3	(10.7)
Nausea	9	(10.2)	4	(14.3)
Vomiting	6	(6.8)	5	(17.9)
CARDIOVASCULAR				
Tachycardia	7	(8.0)	2	(7.1)
Hypotension	6	(6.8)	2	(7.1)
SKIN AND APPENDAGES				
Pruritus	5	(5.7)	0	(0.0)
SURGERIES/PROCEDURES				
Surgeries/Procedures	9	(10.2)	3	(10.7)
RESPIRATORY				
Pneumonia	6	(6.8)	6	(21.4)
UROGENITAL				
Urinary Retention	7	(8.0)	3	(10.7)
MUSCULOSKELETAL				
Myasthenia	7	(8.0)	2	(7.1)
METABOLIC AND NUTRITIONAL				
Hypokalemia	8	(9.1)	2	(7.1)

Study 982-16: An Open-Label Safety and Tolerance Study of a Single IV Loading Dose of Fosphenytoin in Status Epilepticus

Investigators

1	Alldredge/Gelb	San Francisco	3
2	Allen/Runge	Charlotte, NC	18
4	Dean	Winston-Salem, NC	2
5	Turnbull et al	Chicago, IL	6
6	Kriel/Langendorf	Minneapolis	3
7	Lai/Allen	Kansas City, KS	0
8	Maria/Legarda	Gainesville, FL	9
9	Matsuo et al	Salt Lake City, UT	9
10	Parks/Carlton	Jackson, MS	1
11	Pellock	Richmond, VA	1
12	Unwin/Leroy	Dallas, TX	0
13	Uthman/Wilder	Gainesville, FL	2
Total			54

A. Study Design

This was an open-label, single dose study in status epilepticus.

The objectives of the study were to 1) establish the safety of two rates of IV Fos in pts with status and 2) obtain descriptive PK data.

By protocol, the first 10 patients would receive Fos up to a maximum rate of 100 mg PE/min. If that was well tolerated, subsequent patients would receive rates up to a maximum of 150 mg/min. On Feb 10, 1993, data from 14 patients who received Fos at 100 mg/min PE were reviewed by Parke-Davis in consultation with a panel of noncompany neurologists. The panel unanimously recommended that the rate of Fos administration could be increased to 150 mg/min PE as provided in the protocol.

Status was defined as 2 or more consecutive seizures without regaining consciousness or a single seizure of at least 10 minutes duration; patients with partial status or absence status were excluded.

Inclusion/exclusion criteria required that pts be 5 years of age or older. There were no restrictions on AED use prior to study entry. Likewise, there were no restrictions on concurrent medication to treat the episode of status.

The protocol required that "if two IV lines are available, study medication should be administered through one line and all other medications through the other. If only one line is available, it is important to clear the IV line with normal saline between the administration of other medications and study drug."

During administration, vital signs were to be recorded every 5 minutes. Continuous ECG recording was to be performed during infusion. If systolic blood pressure dropped by 20 mmHg, the investigator could slow the infusion rate. If the absolute SBP dropped below 70, the investigator was to stop the infusion; once the BP returned to an acceptable level, the infusion could be restarted at 50% the original rate.

The goal of the study was to enroll between 20-100 pts between July and December 1992.

B. Subject Disposition and Baseline Comparison

54 patients were enrolled at 10 centers by September 1, 1994. There were 32 males and 22 females, 23 whites and 23 blacks. The mean age was 39 years of age with a range of 15 years to 75 years.

26% of patients had status precipitated by AED withdrawal or noncompliance (i.e. had the potential to have low, but measurable levels of phenytoin already present **prior to IV loading**). The sponsor notes that only 43 pts had usable plasma drug-concentration data; of these, 16 had measurable phenytoin concentrations prior to Fos infusion. The mean level for these pts was 6 with a range from 0.12 up to 15.

Six pts (11%) had partial status or absence status in violation of the protocol. The other patients all had generalized status, either primary generalized or secondarily generalized.

In 42/54 (78%) of pts, benzodiazepines were given prior to administration of Fos.

35 patients received loading doses at rates of 100 mg/min. (Recall that 150 mg/min is the rate considered bioequivalent to standard Dilantin loading doses). 18 pts received loading doses at rates > 150 mg/min.

All but 4 pts received total loading doses of 10 mg/kg or greater.

C. Results

Unfortunately, safety data is presented for the entire group of 54 patients; it would be helpful to see a review of adverse events only for the 12 patients who were dosed as per the proposed labeling. On page 36 of the study report, the sponsor presents a brief review entitled "Adverse Events by Rate of Administration." Here the sponsor states that the 5 most frequent AEs appeared to occur at similar frequencies for pts at faster rates (41%) compared with slower rates (45%). In this section, the sponsor does not address the fact that the post hoc separation of pts into high rate/low rate groups does not control for baseline levels of AEDs, especially phenytoin.

No patients withdrew for AEs. 3 patients died after completing the study but all were considered unrelated to Fos. The 8 most frequent adverse events were nystagmus, ataxia, headache, agitation, dysarthria, somnolence, vomiting, and pruritus.

Of note in safety data accrued after the cutoff date for this report is the occurrence of two cases of postictal psychosis, both beginning 3 days after status was treated with Fos. One patient had a previous, less severe case of psychosis after status; the other patient had not experienced previous post-ictal psychosis. A sensation of itchiness followed the psychosis in one patients.

60% of patients had a > 20 mm Hg drop in systolic blood pressure; only 4% had a symptomatic drop in SBP. The sponsor states that, "While the magnitude of decreases in blood pressure were substantial in some patients, no changes in infusion rate or interventions (eg, Trendelenburg positioning, IV fluids, or medications) were required to treat any hypotensive symptoms."

Status continued beyond 30 minutes post infusion of Fos in only 3 patients. 2 of these had other explanations besides lack of efficacy i.e. subdural and anoxic brain insult post CPR. **Patient 8, Center 9 had a gradual decline in seizures over 45 minutes. The infusion rate for this patient was 90 mg/min PE; no plasma levels are available for this patient during the first 20 minutes of treatment raising the question whether a faster infusion rate would have been more effective.**

Study 982-21: A Single-Dose Study of the Tolerance and Safety of IV Fosphenytoin

Investigators

1	Wilder	Florida	21
2	Fischer	Illinois	23
3	So	Minnesota	8
Total			52

A. Study Design

This was a double-blind, parallel-group, active control trial in patients requiring a loading dose of phenytoin to prevent or control seizures. Pts who met the inclusion/exclusion criteria were randomized in a 1:3 ratio to receive either parenteral Dilantin or Fosphenytoin.

Inclusion/exclusion criteria required that pts be 12 years of age or older and require a loading dose of phenytoin. Pts whose condition was serious or life-threatening were not considered appropriate candidates for the study. In particular, patients in status epilepticus were excluded. Neurosurgery patients who required acute treatment were also excluded.

The inclusion criteria required that patients be able to evaluate the extent of pain, burning and itching experienced as a result of the infusion.

The anticipated enrollment was 60 patients, 20 from each of 3 centers.

During the infusion, vital signs were to be recorded every 5 minutes and ECG was to be monitored continuously. After the infusion, vital signs were to be recorded every 15 minutes for 2 hours.

The rate of infusion was not to exceed 50 mg/min PE. By protocol, the investigator was to consider slowing the rate if SBP dropped by 20 mmHg or greater. If SBP dropped to an absolute of 70mmHg, the infusion was to be stopped; once SBP was acceptable, the infusion could be restarted at half the previous rate.

By protocol amendment, the maximum rate was increased to 100mg/min PE for Fos patients.

B. Subject Disposition and Baseline Comparison

39 pts received IV Fos while 13 pts received IV Dilantin.

The majority of pts required a loading dose because of new onset seizures or because their baseline phenytoin levels had dropped below the therapeutic range due to noncompliance or prescribed dosage change.

Fos was given as a total dose between 480-1500 mg/kg PE at infusion rates between 40-103 mg/min PE. Dilantin was given as a total dose between 290-1000 mg/kg at infusion rates between 20-51 mg/min.

Because of the design of the study, a true comparison between randomized groups cannot be made. In addition to the variable of interest, Dilantin vs Fos, there were 4 additional variables that were not adequately controlled, to include:

1. total dose in PE
2. infusion rate (recall that the bioequivalent infusion rate for Fos is 3 X faster in PE than the rate for Dilantin)
3. presence or absence of measurable baseline levels of phenytoin
4. when present, the actual values for baseline phenytoin levels

10/13 Dilantin pts (77%) received 800-1000 mg PE while 23/39 Fos pts (50%) received 800-1000 mg PE or greater. The rate was about 50 mg/min PE for Dilantin, but only 18/39 (50%) of Fos pts received 100 mg/min or greater (100-150 mg/min is the bioequivalent rate when based on free phenytoin levels).

Therefore, at this point, the question would be, of the 23 pts who received 800 mg PE or greater, what percent of these received a rate of 100 mg/min or greater. One might guess that only 10-12 Fos pts are available to compare to the 10-12 Dilantin pts (certainly not *randomized* groups at this point); we have not even introduced the additional variable of background phenytoin levels at baseline.

To further complicate all this, we are told that 7/39 Fos pts (18%)

required changes in rate compared with 6/13 Dilantin pts (46%). The reason for the rate changes are as follows:

Fos	
Hypotension	2
Generalized burning or itching	4
Infusion pump problem	1
Dilantin	
Hypotension	1
Localized pain or burning at inj. site	5

C. Results

There were no deaths in either treatment group. Three withdrawals occurred, all in the Dilantin group. There was 1 withdrawal for AE; there were 2 withdrawals for "lost-to-f/u." No AEs in either treatment group were rated "serious."

Because of the multiple variables discussed above, any comparison between groups with regard to AEs is really inappropriate. Suffice it to say that the pattern of AEs seen in the Fos group raised only one unusual concern, the occurrence of pruritus in 30% of Fos pts vs 0% of Dilantin pts.

Looking only at Fos pts who received a total of 1000 mg PE at rates of 100 mg/min PE or greater, I identified 15 Fos pts in the category. Of these "high-dose, high-rate" pts, 3/15 or 1/5 had a rate change during the infusion because of an AE. One pt had hypotension, 1 had itching, and 1 had burning.

D. Clinical Labs

No clinically important differences are noted between groups and no clear trends toward abnormal values are evident.

E. Vital Signs

The sponsor's discussion of vital signs seems flawed since they have chosen to compare baseline to the 2-hour visit. (See Sponsor's Tables 20

and 21.) In fact, the vitals of interest are those at 5, 15, and perhaps 30 minutes.

Sponsor's Table 22 shows the incidence of decreases in systolic BP > 20 mm Hg: 7 Fos pts (18%) and 4 Dilantin pts (31%). However, the percentages are misleading because the true denominators for comparison are obscured by variable rates, total doses, and baseline phenytoin levels.

2 pts on Fos and 1 on Dilantin required rate changes due to hypotension. One of these Fos pts had a 26mmHg drop in SBP without symptoms. The other Fos pt had an 18mmHg drop with severe dizziness and moderate vertigo. The Dilantin pt had a 22mmHg drop with mild vertigo.

F. Infusion Sites

At the follow-up exam, investigators classified the overall appearance of the infusion sites. The majority of pts in both treatment groups tolerated the infusions, with no differences between groups noted.

Immediately after the infusion, 50% of Dilantin pts reported some pain and 83% reported some burning. By comparison, 2.6% of Fos pts reported some pain and 10% reported some burning. Except for 2 Fos pts who reported pain 2 hours after the infusion, both pain and burning had resolved for all pts in each treatment group by the end of double-blind treatment.

Investigators rated erythema, swelling, tenderness, necrosis, and bruising on a 4 point scale. Essentially no differences between treatment groups emerged.

F. Conclusions

Because the 2 drugs were mixed and administered the same way during this trial, nothing was learned about relative ease-of-use.

Rates were faster for Fos on average, but the sponsor's discussion avoids the issue that *where rate is important,* Fos must be given faster than it was in this study and may, under those conditions of use, be associated

with more AEs (both local and systemic) than were seen here. Rate is not important for maintenance loading and, in that clinical situation, the ability to administer a drug faster may not necessarily be an advantage.

This study provides some safety information in support of a subacute IV loading dose of Fos in non-emergent situations where the physician wishes to achieve therapeutic levels of phenytoin more rapidly than could be achieved by the oral route. Any comparison between the Fos loading and Dilantin loading was obscured by the study design as discussed above.

TABLE 15. Most Frequent Adverse Events With IV Administration to Patients With Epilepsy (Study 982-021)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 39		Dilantin N = 13	
NERVOUS				
Nystagmus	18	(46.2)	5	(38.5)
Dizziness	10	(25.6)	5	(38.5)
Ataxia	7	(17.9)	2	(15.4)
Vertigo	4	(10.3)	3	(23.1)
Paresthesia	4	(10.3)	0	(0.0)
Tremor	3	(7.7)	0	(0.0)
Neuropathy	3	(7.7)	0	(0.0)
Somnolence	2	(5.1)	1	(7.7)
Speech Disorder	2	(5.1)	2	(15.4)
BODY AS A WHOLE				
Headache	7	(17.9)	1	(7.7)
Pain	5	(12.8)	1	(7.7)
Reaction Unevaluable	4	(10.3)	1	(7.7)
Chills	2	(5.1)	0	(0.0)
Chest Pain	2	(5.1)	0	(0.0)
CARDIOVASCULAR				
Hypotension	3	(7.7)	1	(7.7)
SKIN AND APPENDAGES				
Pruritus	12	(30.8)	0	(0.0)
SPECIAL SENSES				
Amblyopia	4	(10.3)	3	(23.1)
Ear Disorder	2	(5.1)	0	(0.0)

Study 982-22: An Open-Label Study of the Safety and Tolerance of an IM Loading Dose of Fosphenytoin

Investigators

1	Leppik	Minneapolis, MN	5
2	Barkley	Detroit, MI	6
3	Ramsay	Miami, FL	28
4	Wilder	Gainesville, FL	14
5	Garnett/Pellock	Richmond, VA	7
Total			60

A. Study Design

The study was intended to be a safety study. The projected enrollment was 60 patients.

Patients were to require a loading dose of phenytoin for the treatment or prophylaxis of seizures. Open-label treatment was to consist of a single loading dose, minimum 10 mg/kg PE. This was followed by a 3-hour observation period. Patients were to return in 2-7 days for follow-up exams and procedures.

Inclusion/exclusion criteria dictated that patients be 12 years of age or older. Pts were not to be in serious or life-threatening condition. This excluded patients in status epilepticus from the study.

Not excluded were pts already being treated with phenytoin. Prior phenytoin usage was to be assessed when determining dosing requirements. If that information was unavailable, the investigator was to use clinical judgment to decide on a dose.

The dosing administration could be divided and given in separate locations on the buttock.

B. Subject Disposition and Baseline Comparison

The study was conducted between August 1992 and February 1993.

60 patients (34 male, 26 female) entered the study. 57 completed all the follow-up assessments. 32 pts were white; 24 were black; 1 was Asian. The mean age was 43 years with a range 16-80 years.

The reasons for loading dose were as follows:

Noncompliance	11
First treatment with phenytoin	18
Decreased phenytoin level (unknown reason)	13
Decreased phenytoin level (prescribed dose reduction)	9
Other reason	9

Therefore, IM loading in the face of absent plasma phenytoin occurred in about 27 patients. The other 33 patients had the potential to have low but measurable levels of phenytoin and might therefore have received downward adjusted doses (based on the clinical judgment of the investigator). AEDs taken within 3 days of study entry included phenytoin in 27 patients. Only 23 patients took no AEDs within 3 days of study entry.

A review of concurrent AEDs taken from day of Fos loading to follow-up follows:

None	10
Phenytoin	47
Carbamazepine	10
VPA	10
Lorazepam	5
Phenobarbital	2
Clorazepate	2
Methsuximide	1
Acetazolamide	1

This list reminds us that the follow-up assessments done after the day of Fos dosing will be obscured by the use of these other drugs and, in fact, might be more representative of these AEDs than the Fos itself.

The doses of Fos ranged from 350 to 1500mg (3.6 to 20.2 mg/kg) PE. 22

patients received a loading dose of 12 mg/kg or greater. An additional 25 pts received a loading dose between 10-12 mg/kg. The actual doses were between a gram and 1600 mg for 16 pts; 20 pts received between 800 to 1000 mg. Note that the 12 pts who received less than 10 mg/kg of Fos were actually in violation of the protocol requirement that pts receive at least 10 mg/kg.

Doses were given as a single injection for 28 pts. 28 pts had their doses divided into 2 injections. 4 pts received 3-4 injections.

C. Results

No patient died during the study. Withdrawals in the true sense of the word could not occur since the Fos was given as a loading dose.

Only one patient experienced serious AEs: arrhythmia, neuropathy, stupor, and tachycardia. This was also the only pt who experienced AEs that were graded severe in intensity. He was a 74 year old man with a history of a stroke with complex partial seizures. He received IM Fos on Day 1. On Day 4, he experienced an irregular pulse, deterioration in neurological status, stuporous condition, and tachycardia. None of these were considered related to study medication by the investigator. The pt had not yet recovered from these AEs by the end of the study.

66% of pts experienced some AEs. Most of these were considered associated with use of Fos. Almost all these AEs were considered mild in intensity.

Nystagmus was the most common AE, occurring in 47% of pts. Dizziness and ataxia occurred in 17% and 13% of pts respectively.

Evaluation of injection sites revealed that only 3 pts had mild injection site irritation 3 hours after IM dosing. 4 pts had mild irritation 2-7 days later at the follow-up visit. Only 1 pt had mild irritation at both time points. The sponsor states that no relationship was found between the dose or the number of injections and the tendency toward this mild irritation.

D. Conclusions

This study demonstrated no drug-related serious AEs, either systemically or locally at the injection site, when Fos was given IM at relatively high doses. 47 pts received 10 mg/kg or greater. However, only 28 pts received the entire loading dose at a single injection site and some of these may have received less than 10 mg/kg. Because of this last point, this study would probably best support the safety of IM Fos at comparable doses *with the total dose divided and given at two separate injection sites*.

Note that patients who required an emergent loading dose of phenytoin were excluded from this study. In particular, pts with status were excluded. Thus, this study would not support the efficacy of IM Fos in emergent situations. Likewise, there is no data that I am aware of to support use of IM Fos loading over PO Fos loading. In fact, IM Fos loading would probably only have a role in non-emergent settings where patients could not tolerate PO feedings. This might occur in patients chronically treated with AEDs (especially phenytoin) who develop transient gastrointestinal illnesses that preclude continued oral medication and result in dropping plasma AED levels.

At a minimum, although this study was designed to support the safety of IM **loading**, the data from this study can be used to support the safety of IM **maintenance** dosing. That is, if the higher doses given in this study were tolerated, the lower doses necessary for IM maintenance dosing should have a wider safety margin.

Pharmacologist Review

Review and Evaluation of Pharmacology and Toxicology Continuation of Review # 1

Drug: -9653-010

Category:

Anticonvulsant; prodrug for phenytoin.

Summary:

It was pointed out in our team meeting for this new drug that the in vivo hydrolysis o -9653 occurs in 2 steps, producing one mole of formaldehyde for each mole of prodrug. In the initial clinical Phase I trial, the top dose of 2250 mg would produce 5.5 mmoles of HCHO. The possible hazard from this burden will be discussed from several different veiwpoints below. All calculations are gross approximations, based on available information.

1. OSHA has adopted a permissible exposure level for toxic effects of formaldehyde other than cancer of 3 ppm as an 8 hour time weighted average, and 10 ppm maximum peak concentration for 30 minutes in an 8 hour period (Third Annual Report on Carcinogens, USDHHS Public Health Service, September, 1983, page 73). It has been reported that workers exposed to formaldehyde at a concentration of 7 mg/m^3 developed blood levels of 0.6 - 4.0 mg/l. The duration of exposure was not given (J.Piotrowski, Exposure Tests for Organic Compaounds in Industrial Toxicology, Gant Printing Office, DC, 1977, p.122). [1m^3 = 1000 l; wt. of air = 1.293 gms/l at 0°C + 760 mm Hg; therefore 7 mg/m^3 = 7 mg/1.293 kg = 5.4 mg/kg = 5.4 ppm in air]

   Since 5.4 ppm of HCHO → a maximum of 4 mg/l in blood, the 10 ppm maximum allowed by OSHA would → approximately 7.4 mg HCHO/liter or 0.25 meq HCHO/l in blood. This figure should more or less represent the maximal allowable blood level of HCHO according to OSHA. If we then assume that the 5.5 mmoles of HCHO that are split from the prodrug all appear in the circulation (ave. volume 5 liters) the concentration would be 33 mg/l or 1.1 meq/l, or approximately 4 fold higher than the OSHA level allowed. However, this is a very crude estimate since the data are not readily available for taking the time factor allowed under the OSHA limit into consideration.

2. There is a great deal of information in the literature that suggests that it is formic acid that is repsonsible for the ocular toxicity and acidosis seen following acute methanol poisoning (methanol → formaldehyde → formate). This toxicity would be of greater concern when dealing with a drug to be used acutely than would potential carcinogenicity. Although a role for HCHO has not been clearly ruled out, experiments in monkeys suggest that the resultant formate levels are of more concern.

In a model in rhesus monkeys for methanol ocular toxicity and metabolic acidosis, formate blood and CSF levels of 7 to 34 meq/l were associated with optic disc edema, morphological alterations in optic nerve and swelling of oligodendroglial cytoplasm (Martin - Amat, Hayreh, Baumtach et al, Arch Ophthalmol., 95, 1847-50, 1851-58, 1859-61; Martin-Amat, et.al., TAP, 45, 201-208, 1978). Pretreatment with folate increased the metabolism of formate and decreased the toxicity (McMartin et al, JPET, 201, 564-572, 1977). In the proposed clinical trial, if we assume the 5.5 meq of HCHO goes to 5.5 meq of formate, with a blood concentration of 1.1 meq/l, there is a minimum of a 7-fold safety factor before ocular toxicity occurred in the monkey (which is thought to metabolize HCHO like the human).

3. It has been reported that the mechanism for ocular toxicity caused by methanol is the inhibition of cytochrome oxidase by formate (Nicholls, BBRC, 67, 610-616, 1975). Since cytochrome oxidase activity is low in white matter, it has been suggested that its activity may be critical in that tissue. The Ki values determined for formate inhibition of cytachrome oxidase are between 5 and 30 m M (above reference plus Martin-Amat, Arch Ophthol., 95, 1847-50, 1977). Based on this data, blood levels of formate of 1.1 m M would be somewhat lower then those expected to produce toxicity.

4. In dogs and cats administered 35 mg/kg (1.2 meq/kg) of formaldehyde by i.v. infusion, a blood HCHO concentration of 25 mg/l (0.83 meq/l) was produced which declined to about 1 mg/l by 1 hour after the infusion. (4 x as much HCHO was in erythrocytes as in plasma). The peak plasma concentration of formate, however, was 144 mg/l (3.1 meq/l) at the end of the infusion, which declined with a $T_{1/2}$ of 1.5 hours. Toxicity was not addressed (G. Malorney et al, Naunyn - Schmiedebergs A.E.P.P., 250, 419-436, 1965). These data would suggest that peak levels of the possibly more toxic metabolite, formate, might be approximated as follows for top dose in the clinical trial:

   5.5 meq of HCHO (155 mg) = 3 mg/kg in a 50 kg person. If 35 mg/kg of i.v. HCHO → 144 mg/l of formate, 3 mg/kg or HCHO may result in peak blood levels of formate of 12 mg or 0.26 meq/l. (This is assuming comparable relative blood levles to body weight in humans and animals. Actually, dogs may have slightly larger blood volume/kg of body weight than humans, so the estimate for humans is possibly on the low side. The assumption for comparable metabolism is also made).

   This figure is considerably lower than the Ki for formate inhibition of cytochrome oxidase and it is about 25-30 fold lower than the lowest levels of formate associated with ocular toxicity in monkeys (see numbers 2 and 3 above). If instead, we examine the blood HCHO concentration using these data, an i.v. dose of prodrug that yields 5.5 mmoles of HCHO (0.11 mmoles/kg) would be expected to result in a peak blood concentration of HCHO of 0.08 mmoles/liter, or 1/3 of the maximal allowable HCHO exposure according to OSHA.

Evaluation and Recommendations:

The above approximations are extremely crude, but they do provide some data for evaluating the risk involved from a drug which will be used acutely that is metabolized to produce a mole of formaldehyde for every mole of drug.

Based on OSHA limits for exposure to formaldehyde, the guestimate is that the top dose of prodrug planned in the rising dose trial (2250 mg) would result in anywhere from 1/3 of 10 times the maximal allowable blood level of formaldehyde. If we assume that formate is responsible for the expected acute toxicty (occular and acidosis), there may be anywhere between a 7 fold and a 30 fold safety factor, based on toxicity observed in monkeys and blood levels of formate measured after i.v. administration of HCHO to dogs. If we believe that formate toxicity occurs through cytochrome oxidase inhibition, there is at least a small margin of safety based on the Ki.

In any case, it is a close call, and there are a couple of precautions that might be considered. Monitoring of blood formic acid, blood pH, bicarbonate and pCO_2 is recommended. Since folinic acid pretreatment hastens the elimination rate, a supplement of 2 mg, p.o., might be given the day before the trial. However, if it is considered that this is an appropriate time to determine whether or not formate levels in blood are detectable (since in practice there would not be time to give folinic acid) I would recommend careful monitoring for formate levels at all doses before proceeding to the next higher dose. SRD is May 4, so sponsor should be phoned.

Glenna G. Fitzgerald

Glenna G. Fitzgerald PhD, M.D.

cc: Orig.IND
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December 20, 1995

Review and Evaluation of Pharmacology and Toxicology

NDA: 20-450

Sponsor: Parke-Davis Pharmaceutical Research
Ann Arbor, MI 48105

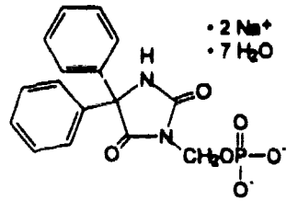
Drug: Cerebyx (fosphenytoin sodium)

Chemical Name: 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

Molecular Formula: $C_{16}H_{13}N_2O_6PNa_2$

Code name(s): ACC-9653; CI-982

Structure:



Mol. Wt.: 406.3

Category: Parenteral antiepileptic; prodrug of phenytoin for use in status epilepticus and neurosurgery

Related IND(s):

Table of Contents

All pivotal toxicology studies and all genetic and reproductive toxicity studies contain GLP statements. Studies were conducted by Parke-Davis,

Drug lot numbers are given with the individual studies.

I. PHARMACODYNAMICS

Anticonvulsant Activity

A) EFFECTS ON MES-INDUCED SEIZURES IN MICE (RR 740-02904, NDA Vol. 1.9).

1. After iv dosing with phenytoin (8 mg/kg) or fosphenytoin (11.9 mg/kg), no appreciable anticonvulsant activity was seen for either drug until 10 min, when 50% (4/8) of phenytoin-treated mice were protected from tonic hindlimb extension (THE) and 13% (1/8) of fosphenytoin-treated mice were protected (Table I.1).
2. Peak activity was reached for both compounds at 30 min when 63% (5/8) of phenytoin-treated and 88% of fosphenytoin-treated mice were protected (Table I.1). In addition to reducing the incidence of MES-induced THE, phenytoin and fosphenytoin reduced seizure duration.
3. When dose-response determinations were made at 10 and 30 min (Table I.2), both drugs exerted dose-dependent protection from MES-induced THE. The iv ED50 values (95% confidence limits) were 8.3 mg/kg (6.1-11.2) at 10 min and 6.6 mg/kg (5.1-8.0) at 30 min after dosing with phenytoin, compared to 10.8 mg/kg (8.4-17.5) at 10 min and 6.8 mg/kg (6.1-7.5) at 30 min after dosing with fosphenytoin (doses expressed as phenytoin equivalents). Neither vehicle was active. Based on statistical comparisons of the dose-response curves and potency ratios, the anticonvulsant potencies of fosphenytoin and phenytoin against MES-induced THE were not significantly different at either time point, although there were apparent differences in low dose activity and onset of action.
4. The ED50 values for iv phenytoin and fosphenytoin were in agreement with those reported in the literature for oral (9.0 and 12.8 mg/kg), sc (7.2 mg/kg), and ip (9.5 mg/kg) administration of phenytoin to mice and for oral (11.8 mg/kg PE) and ip (10.3 mg/kg PE) administration of the prodrug to mice.

Table I.1 TIME COURSE OF ANTI-CONVULSIVE ACTIVITY OF PHENYTOIN AND ACC-9653 IN MES-INDUCED THE-SEIZURES IN MICE

	MINUTES AFTER INJECTION									
	PHENYTOIN (8 mg/kg, IV)					ACC-9653 (11.9 mg/kg, IV)				
	5	10	30	60	120	5	10	30	60	120
Percent of mice proteced from THE-seizures	13	50	63	38	63	0	13	88	38	25
Duration of THE-seizures (seconds)	10.5* ± 1.0	12.3 ± 1.0	9.2* ± .2	9.2* ± 1.0	8.8 ± 2.0	10.9 ± .8	10.5 ± .9	10.8 –	10.2* ± .9	9.4* ± .5

Eighty mice were used in this study; eight at each time point with each drug. Duration values represent the mean ± S.E. of THE-seizure durations in unprotected animals.
* Indicates a significant difference from the corresponding value at the same time point in vehicle-treated mice (Table 1).

Table I.2 DOSE-REPONSE STUDY OF THE ANTI-CONVULSIVE ACTIVITY OF PHENYTOIN AND 9653 IN MES-INDUCED THE-SEIZURES IN MICE

PHENYTOIN			9653		
	Minutes After Dosing			Minutes After Dosing	
	10	30		10	30
Dose mg/kg IV	% Protected From THE-Seizures		Dose mg/kg IV	% Protected From THE-Seizures	
2	0	13	3	0	0
3	13	25	4.4	13	0
4.5	13	13	6.7	0	0
6.8	38	63	10.1	25	50
10.1	63	88	15.0	38	100
15.2	88	100	22.5	75	100

One hundred and twelve mice were used in this study; eight at each time point with each drug dose.

Cardiovascular effects

A) ANTIARRHYTHMIC ACTIVITY IN VITRO AND IN VIVO (RR 740-02905, Vol. 9).

In vitro, fosphenytoin had not antiarrhythmic effect in acetylstrophanthidin-treated guinea pig right atria at concentrations up to 400 uM, while phenytoin restored rhythmic beating in 4 of 7 atria at a mean EC50 of 20 uM. *In vivo*, fosphenytoin and phenytoin exerted similar antiarrhythmic activity, respectively converting oubain-induced tachycardia in 87 and 100 % of animals after an infusion time of 8.5 and 7 min, at administered doses of 24.3 and 14.1 mg/kg, and plasma levels of 18 and 29.5 ug/ml of phenytoin. This indicates that fosphenytoin has no direct antiarrhythmic action, but is similar to phenytoin under *in vivo* conditions, presumably due to enzymatic conversion to phenytoin.

B) HEMODYNAMIC EFFECTS IN ANESTHETIZED DOGS (RR 740-02906, Vol. 9).

1. Fosphenytoin (60 mg/kg) infused over 2 min (infusion rate of 20 mg/kg/min) produced marked reductions in systolic (50%) and diastolic (60%) blood pressure, heart rate (25%), and LvdP/dt (70%). The maximum effects were observed 10 min after termination of infusion and had returned toward normal by 60 min. After rapid infusion of an equimolar dose of phenytoin (40 mg/kg), changes in CV parameters were comparable to those seen after fosphenytoin (**Figures I.1 & I.2**). Effects on CV parameters appeared somewhat more pronounced after fosphenytoin (diastolic BP was significantly lower in fosphenytoin group at 4 min); however, 3 of the phenytoin animals died within 4 min from onset of infusion, while all 6 fosphenytoin dogs recovered.
2. Plasma levels of fosphenytoin were highest at the end of the infusion, while peak levels of formed phenytoin were seen at about 8 min after the end of infusion (**Figure I.3**). Peak plasma phenytoin levels (free levels not determined) were reached more rapidly after infusion of phenytoin than after fosphenytoin, although maximal levels achieved were similar.
3. Fosphenytoin (31 mg/kg) infused over 15, 20, or 30 min produced significant reductions in systolic (25%) and diastolic (35%) blood pressure, HR (10%), left ventricular contractility

(LvdP/dt, 20-45%), and cardiac output (20-40%) at all three infusion rates (**Figures I.4 and I.5**). The maximum effects were comparable at each infusion rate and the maximum effects were observed at the end of each infusion period. In each group, pressures had returned to normal by 60 min. There were no significant effects on systolic blood pressure, heart rate, left ventricular end diastolic pressure, or cardiac output. Comparable changes in CV parameters were seen when an equimolar dose of phenytoin (21 mg/kg) was infused over 30 min.

4. Analysis of plasma samples showed that maximum levels of fosphenytoin occurred at the end of the infusion period (**Figure I.6**). Peak fosphenytoin levels of 106, 82, and, 72 ug/ml were attained after infusion over 15, 20, and 30 min, respectively. The maximum levels of phenytoin were also observed at the end of the infusion period. Peak levels of phenytoin were 35, 29, and 31 ug/ml after infusion of fosphenytoin over 15, 20, and 30 min, respectively. Plasma levels declined rapidly thereafter. After infusion of phenytoin, plasma levels of phenytoin were maximal (33 ug/ml) at the end of infusion, and declined thereafter.

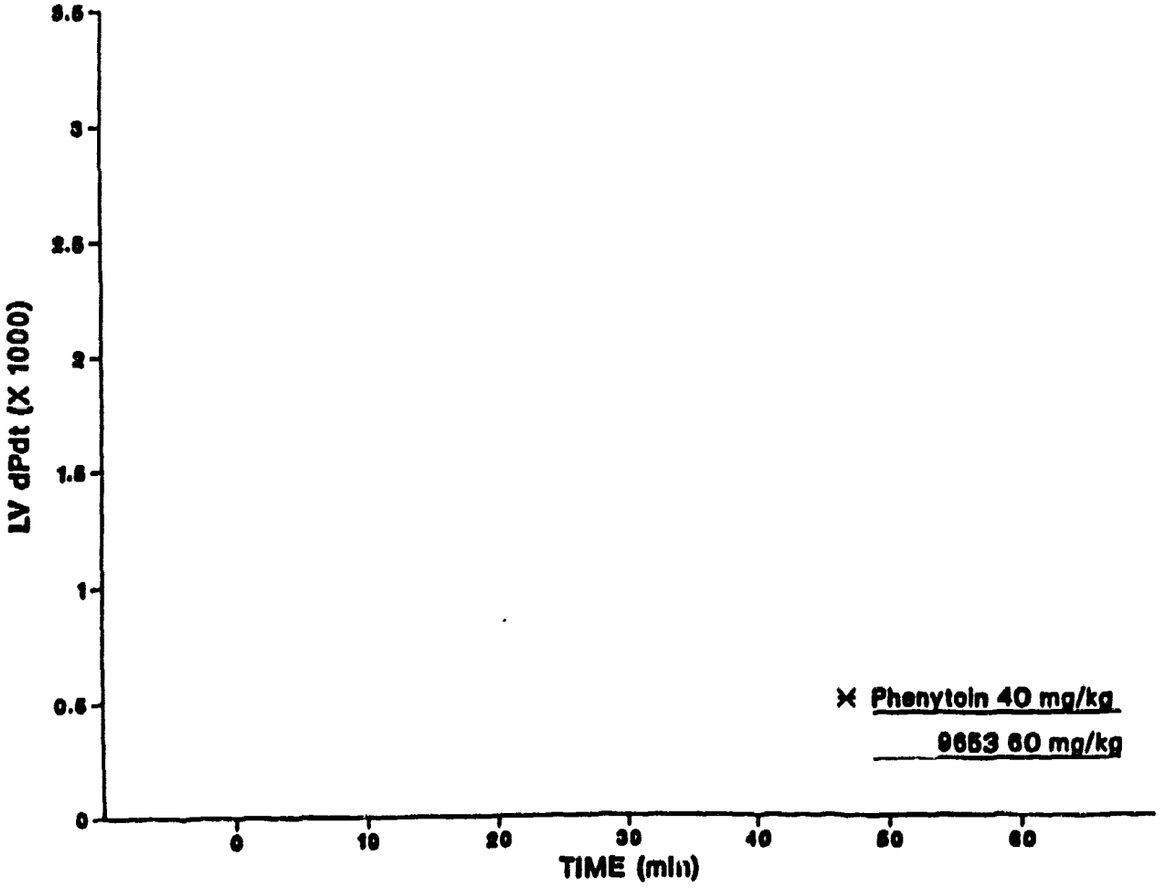


Figure I.1. Effect of fosphenytoin, 60 mg/kg, or phenytoin sodium, 40 mg/kg, infused iv over 2 min on LvdP/dt in anesthetized dogs. Values are the mean ± SEM (N=6).

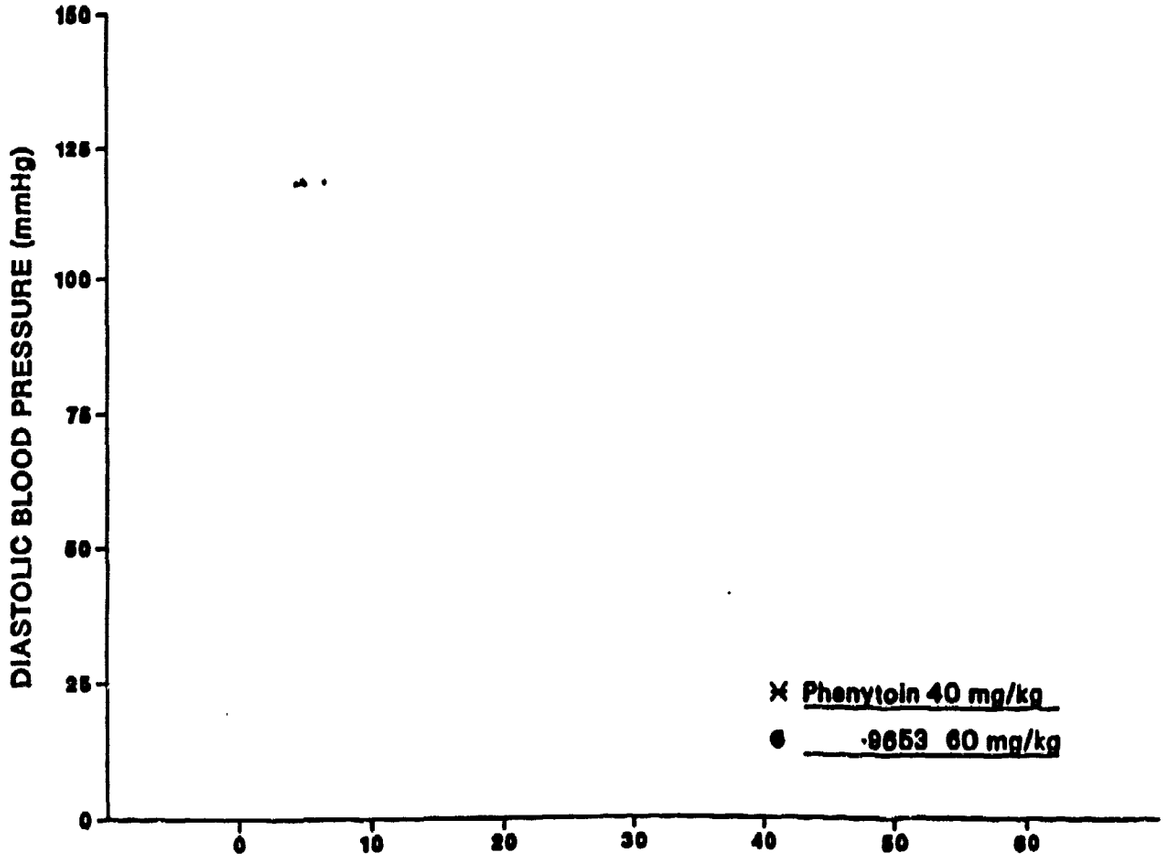


Figure I.2. Effect of fosphenytoin, 60 mg/kg, or phenytoin sodium, 40 mg/kg, infused iv over 2 min on diastolic blood pressure in anesthetized dogs. Values are the mean ± SEM (N=6).

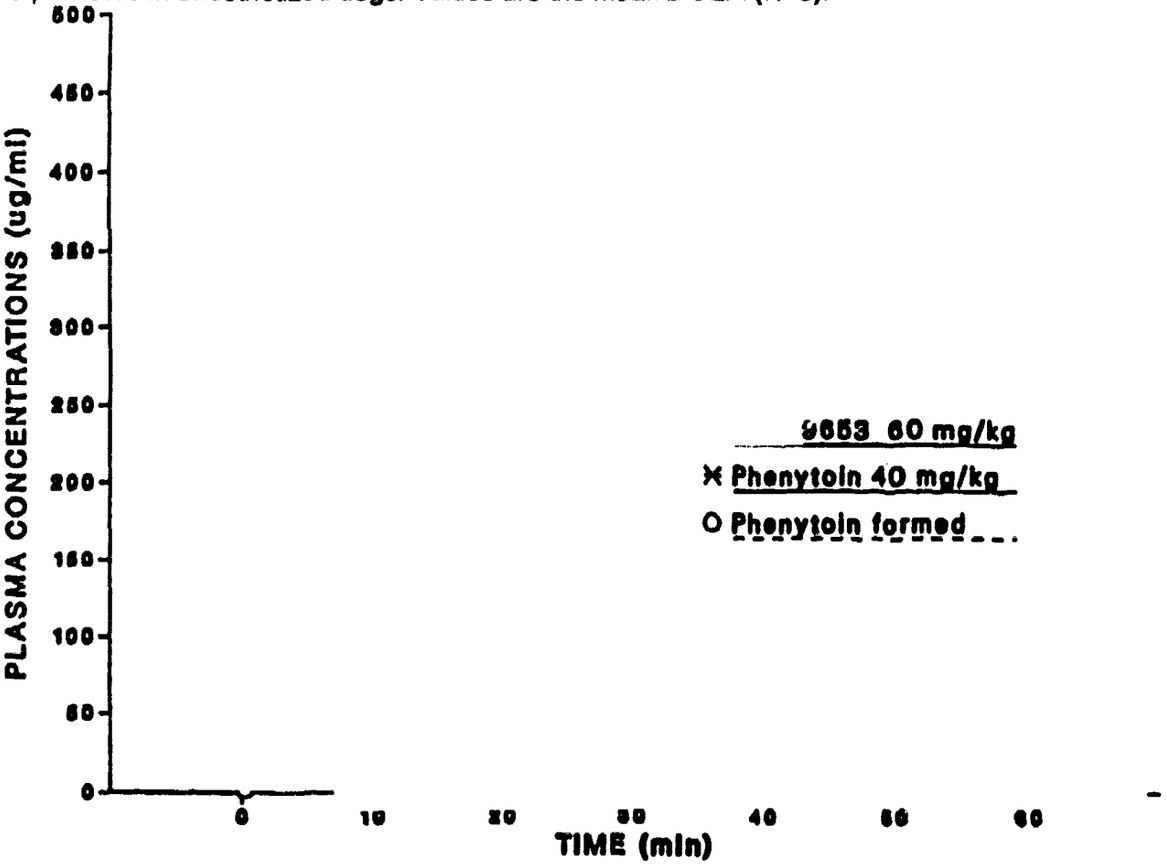


Figure I.3. Plasma levels of fosphenytoin or of the phenytoin formed following infusion of fosphenytoin, 60 mg/kg, infused iv over 2 min and of phenytoin following infusion in an equimolar amount of phenytoin sodium, 40 mg/kg, iv, over 2 min. Values are the mean of 6 determinations.

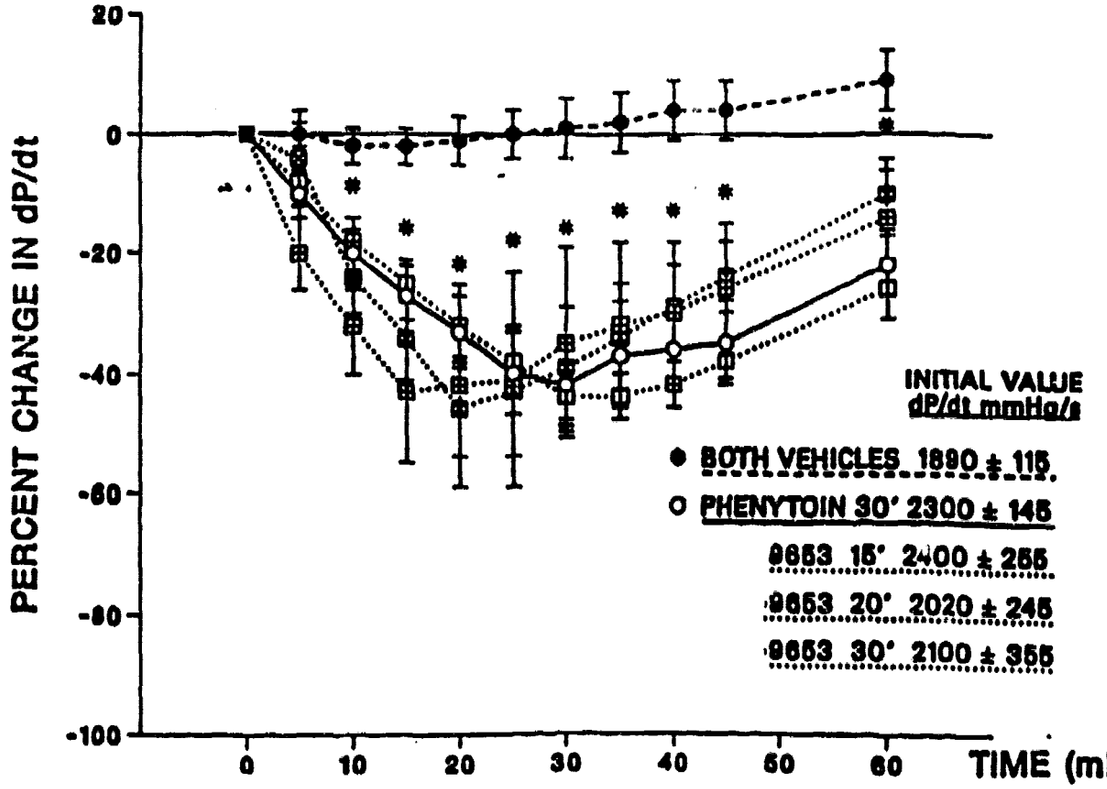


Figure I.4. Effects of fosphenytoin, 31 mg/kg, infused over 15, 20, or 30 min, of phenytoin sodium, 21 mg/kg, infused over 30 min, or of vehicles alone on LvdP/dt in anesthetized dogs. The vehicle data represent the combined mean data from the phenytoin vehicle (propylene glycol, alcohol; N=4) and the fosphenytoin vehicle (TRIS; N=3) treated animals. All values are mean ± SEM. Asterisks indicate values significantly different from comparable vehicle values, $p<0.05$.

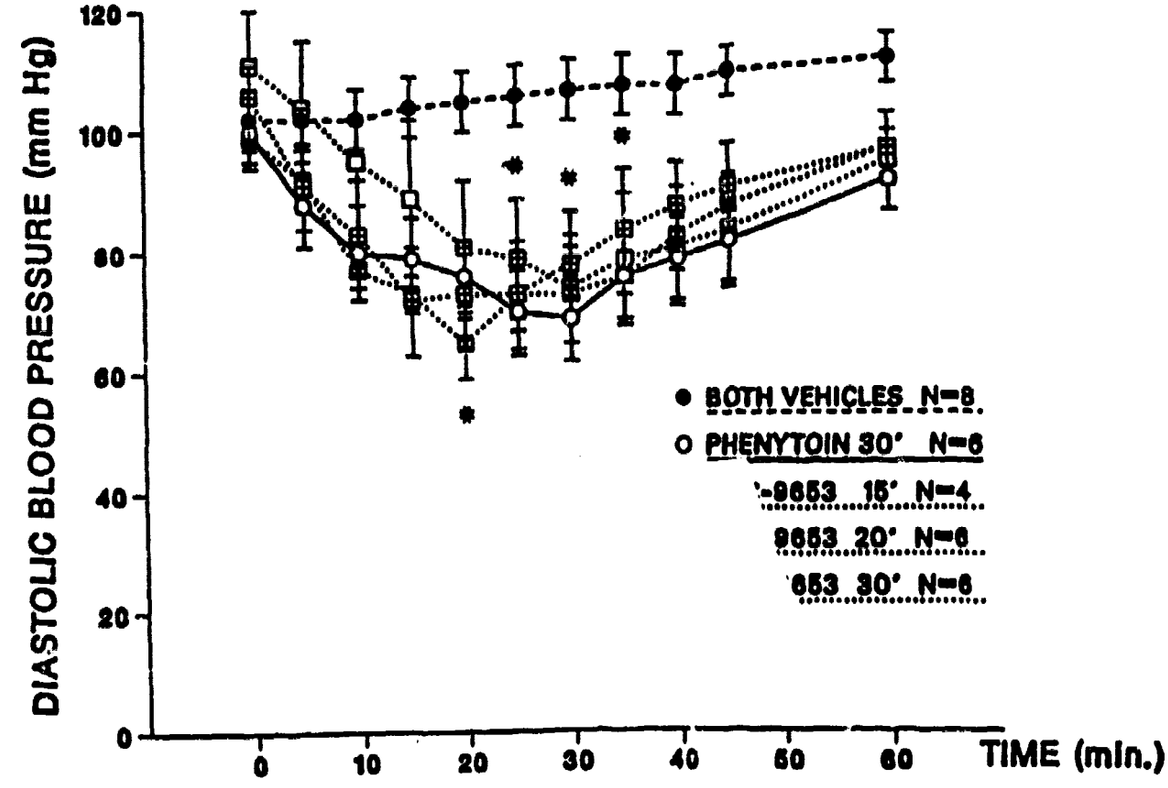


Figure I.5 Effects of fosphenytoin, 31 mg/kg, infused over 15, 20, or 30 min, of phenytoin sodium, 21 mg/kg, infused over 30 min, or of vehicles alone on diastolic blood pressure in anesthetized dogs. The vehicle data represent the combined mean data from the phenytoin vehicle (propylene glycol, alcohol; N=4) and the fosphenytoin vehicle (TRIS; N=3) treated animals. All values are mean ± SEM. Asterisks indicate values significantly different from comparable vehicle values, $p<0.05$.

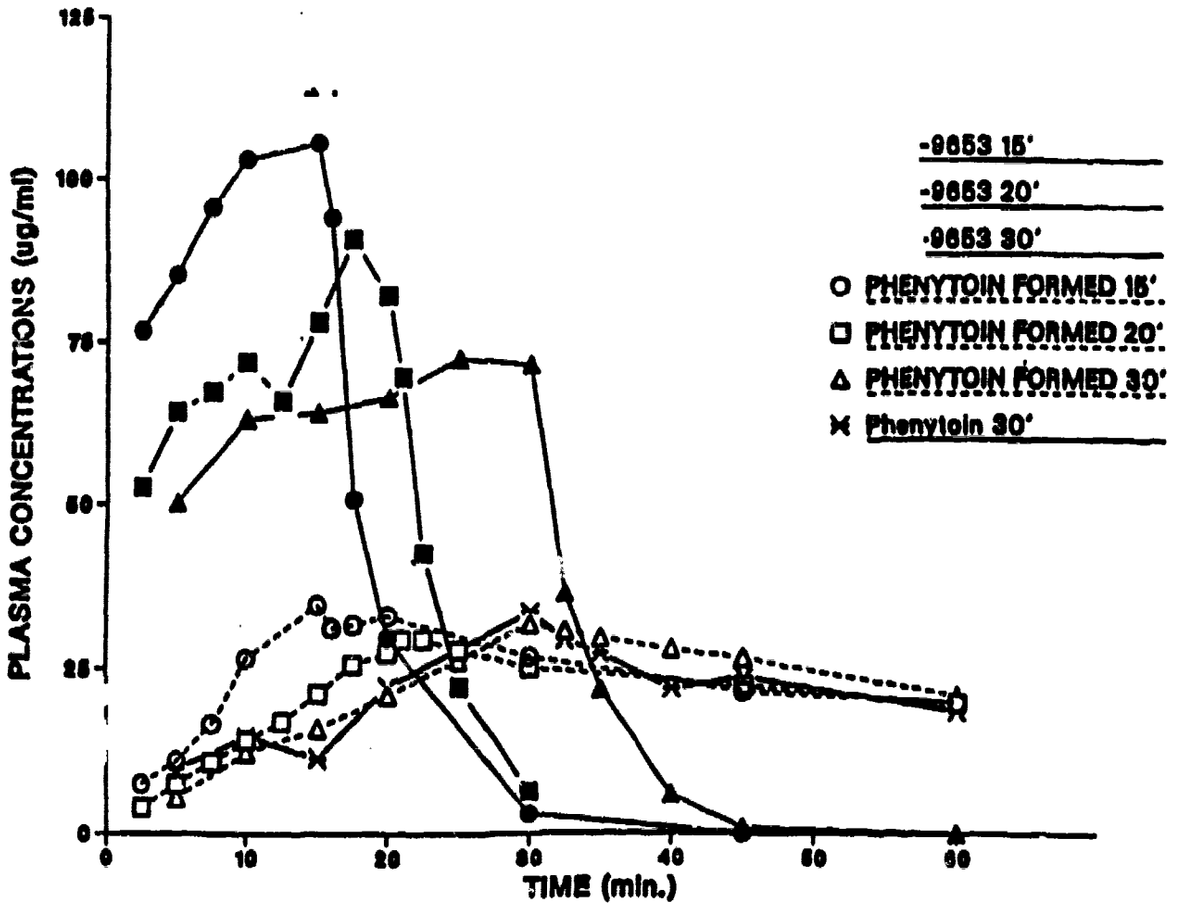


Figure I.6. Plasma levels of fosphenytoin and/or phenytoin following iv infusion of fosphenytoin, 31.5 mg/kg, over 15, 20, or 30 min or of phenytoin sodium, 21 mg/kg, iv over 30 min. All values are the mean ± SEM of 2- 6 samples.

C) EFFECTS ON GUINEA PIG ATRIA IN VITRO (RR 740-02907, Vol. 9).

1. Fosphenytoin and phenytoin both produced concentration-dependent decreases in the rate of spontaneous beating in right atrial preparations and both produced complete arrest.
2. Arrest occurred at a much lower concentration of phenytoin (100 uM) than of fosphenytoin (3000 uM). The EC50's for depression of spontaneous rate were 41 uM (11 ug/ml) for phenytoin and 535 uM (217 ug/ml) for fosphenytoin.
3. Both drugs produced similar concentration-dependent reductions in contractile force in electrically driven left atria (Figure I.7) . The EC50 for cardiodepression was similar for each: 98 uM (27 ug/ml) for phenytoin and 105 uM (43 ug/ml) for fosphenytoin. The vehicles depressed developed contractile force <20% at their highest concentrations.
4. This study indicated that under *in vitro* conditions in which less than 1% of phenytoin was present, fosphenytoin had a cardiac depressant effect similar to that of phenytoin in guinea pig left atrial preparations. The difference between effects on left and right atria is unexplained. Thus, the prodrug is a myocardial depressant under certain experimental conditions. The relevance of this finding to *in vivo* administration is unknown.

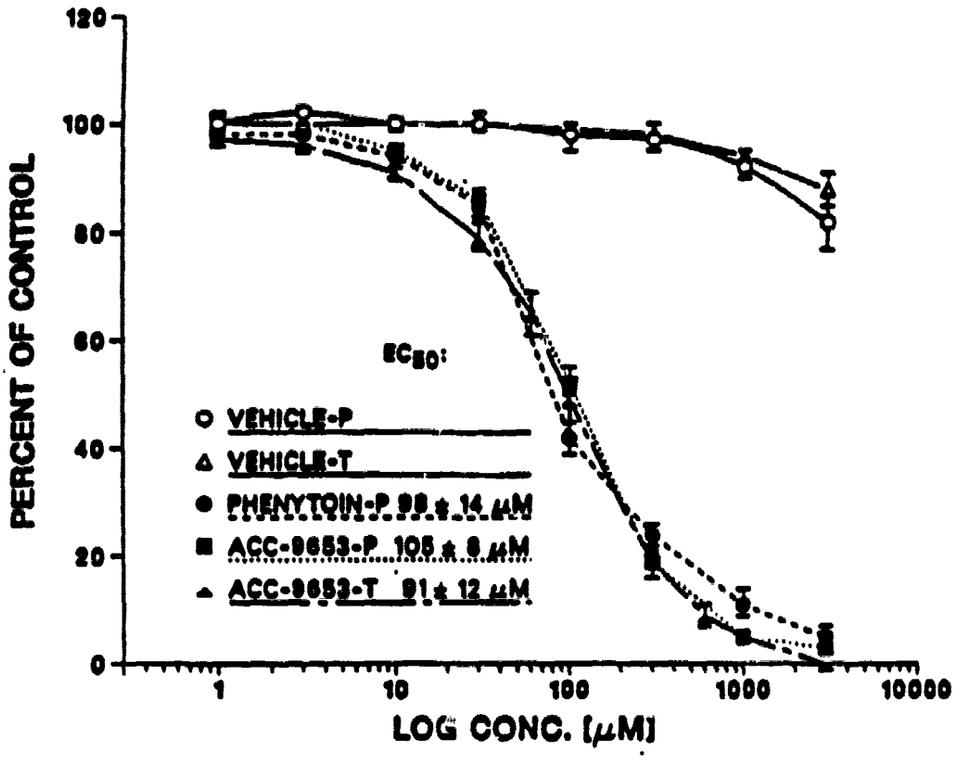


Figure I.7 Effects of ACC-9653 and phenytoin in guinea-pig left atria. The mean ± SE values of percent of initial developed force for N=4 (vehicles) or N=8 (each drug) atria are plotted versus the molar concentration of each drug or equivalent vehicle volume. ACC-9653 was examined after dissolution in vehicle-T and vehicle-P; the solid squares represent ACC-9653 in vehicle-P, while the solid triangles represent ACC-9653 in vehicle-T. Phenytoin is represented by solid circles whereas vehicle-P is represented by open circles; the open triangles represent vehicle-T and the values shown in the legend indicate the EC_{50} ± 99% confidence limits for causing cardiodepression for each drug.

II. ADME

Single-dose absorption and pharmacokinetics

A) BLOOD LEVELS AFTER IM ADMINISTRATION TO RATS (RR 764-01612, Vol. 1.10).

Groups of 4 male rats (CD-Sprague-Dawley) were given 115, 250, 370, or 500 mg/kg of fosphenytoin or 77, 169, 250, or 337 mg/kg of phenytoin (equimolar doses) by im injection. Blood samples were collected from each rat at 0.5, 1.5, 3, 6, and 24 hr post-dose. Analysis was by HPLC.

Peak blood concentrations of fosphenytoin were achieved at 30 min after im administration and averaged 9.6, 12.5, 21.4, and 19.6 ug/ml after doses of 115, 250, 370, and 500 mg/kg, respectively. Blood levels of fosphenytoin were still quantifiable at 6 hr in the 3 highest dose groups. Blood concentrations of phenytoin after im fosphenytoin peaked at 30 min and averaged 42.3, 112, 127, and 153 ug/ml at the respective doses. Corresponding peak levels after phenytoin administration were 14.9, 20.1, 31.2, and 33.2 ug/ml at 30 min after dosing. Thus, fosphenytoin administration resulted in phenytoin levels 5-6X higher than those produced by an equimolar dose of phenytoin, indicating greater bioavailability of phenytoin after im administration of fosphenytoin.

B) PHENYTOIN PHARMACOKINETICS AND BIOAVAILABILITY AFTER IV ADMINISTRATION OF EQUIMOLAR DOSES OF PHENYTOIN OR FOSPHENYTOIN TO DOGS (RR 764-01606, Vol. 10).

Five dogs were administered equimolar iv doses of phenytoin (10 mg/kg) or fosphenytoin (14.8 mg/kg) in a two-way crossover study designed to compare the pharmacokinetics and bioavailability of phenytoin after each drug (**Table II.1**). Analysis was by HPLC.

After iv administration of fosphenytoin, fosphenytoin t1/2, Vd, and AUC values averaged 2.6 min, 150 ml/kg, and 255 ug min/ml, respectively. The Cl of 40.2 ml/min/kg approximates the hepatic blood flow in dogs, which would be consistent with metabolism to phenytoin by phosphatases present in tissues such as kidney and liver. Conversion of fosphenytoin to phenytoin was rapid in dogs; the formation t1/2 averaged 0.42 min and the peak phenytoin levels (mean 6.98 ug/ml) were reached at 3.3 min . During the first 30 min after administration of phenytoin, phenytoin levels were higher than after administration of fosphenytoin, but levels were similar thereafter. The elimination t1/2, Cl, Vd, and AUC of phenytoin were not significantly different after iv administration of fosphenytoin and phenytoin sodium. The bioavailability of phenytoin after iv fosphenytoin administration averaged 97.7%.

Table II.1. Pharmacokinetic Parameters of Phenytoin in Dogs after IV Administration of 14.8 mg/kg of Fosphenytoin or an Equimolar Dose of Phenytoin Sodium

Phenytoin Parameters*	IV Fosphenytoin	IV Phenytoin
Formation t1/2(min)	0.42 ± 0.42	---
Elimination t1/2 (min)	137 ± 24.5	118 ± 15.2
Clearance (ml/min/kg)	7.35 ± 1.36	7.11 ± 1.09
Vd (ml/kg)	1409 ± 53.3	1197 ± 122
AUC (ug·min/ml)	1399 ± 255	1433 ± 223
Tmax (min)	3.28 ± 2.63	---
Cmax (ug/ml)	6.98 ± 0.27	---

* Data expressed as Mean ± SD of 5 dogs

Analysis of 48-hr urine samples collected after administration of phenytoin or fosphenytoin indicated similar metabolite elimination profiles. The glucuronide conjugate of 5-(m-hydroxyphenyl)-5-phenylhydantoin (m-HPPH) was the major metabolite identified in urine, accounting for 58.4 and 56.1% of the dose after fosphenytoin and phenytoin, respectively. Less than 5% of the dose was eliminated as phenytoin and 5-(p-hydroxyphenyl)-5-phenylhydantoin after administration of either compound, and fosphenytoin was not detected in 24 and 48-hr urine samples.

C) PHENYTOIN PHARMACOKINETICS AND RELATIVE BIOAVAILABILITY AFTER IM ADMINISTRATION OF PHENYTOIN OR FOSPHENYTOIN TO DOGS (RR 764-01601, Vol. 1.10).

Five dogs were administered equimolar im doses of phenytoin (10 mg/kg) or fosphenytoin (14.8 mg/kg) in a two-way crossover study to compare the pharmacokinetics and bioavailability of phenytoin after each (**Tables II.2 and II.3**). Samples were analyzed by HPLC.

After im administration, fosphenytoin levels reached a mean peak of 20.4 ug/ml at 9 min, then rapidly decreased such that fosphenytoin was not detectable in plasma after 120 min (**Table II.3**). The absorption and elimination t1/2 values averaged 3.2 and 17.4 min, respectively. The appearance of phenytoin in the plasma was fairly rapid after im administration of fosphenytoin. The formation t1/2, Cmax, and tmax were 24.7 min, 6.8 ug/ml, and 76.9 min, respectively (**Table II.2**). The corresponding values after im administration of an equimolar dose of phenytoin were 17.4 min, 2.16 ug/ml, and 68.1 min for the absorption t1/2, Cmax, and tmax, respectively. The elimination t1/2 and apparent volume of distribution of phenytoin after fosphenytoin administration averaged 164 min and 1058 ml/kg, respectively, which were significantly different than corresponding values of 369 min and 4086 ml/kg, respectively, obtained after im phenytoin. The differences probably reflect precipitation and deposition of phenytoin at the injection site.

The AUC values obtained after administration of phenytoin were substantially lower when compared to the phenytoin AUCs after fosphenytoin administration. From 0 to 720 min, the AUC values averaged 2091 and 960 ug.min/ml after fosphenytoin and phenytoin sodium, respectively. When extrapolated to infinity, the corresponding AUC values averaged 2236 and 1336 ug.min/ml, respectively. These findings show that the bioavailability of phenytoin administered as fosphenytoin was increased compared to im phenytoin sodium, and that the relative bioavailability was time dependent, again indicating that phenytoin was retained at the injection site and slowly released.

Table II.2. Pharmacokinetic Parameters of Phenytoin in Dogs after IM Administration of 14.8 mg/kg of Fosphenytoin or an Equimolar Dose of Phenytoin Sodium

Phenytoin Parameters*	IM Fosphenytoin	IM Phenytoin
Absorption/Formation t1/2(min)	24.7 ± 10.2	17.4 ± 18.7
Elimination t1/2 (min)	164 ± 46.7	369 ± 97.4
Clearance (ml/min/kg)	4.66 ± 0.94	8.2 ± 2.91
Vd (ml/kg)	1058 ± 127	4086 ± 626
$AUC_{0-\infty}$ (ug•min/ml)	2236 ± 557	1336 ± 419
Tmax (min)	76.9 ± 23.8	68.1 ± 57.5
Cmax (ug/ml)	6.83 ± 0.89	2.16 ± 0.38

* Data expressed as Mean ± SD of 5 dogs

Analysis of 48-hr urine samples collected after administration of phenytoin or fosphenytoin indicated similar metabolite elimination profiles. Approximately 58% of the dose was recovered in 48-hr cumulative urine after dosing with fosphenytoin and about 47.4% of the dose was recovered after phenytoin. The major metabolite was the glucuronide conjugate of 5-(m-hydroxyphenyl)-5-phenylhydantoin (m-HPPH), which accounted for 90% of the material recovered in urine in both cases.

D) FOSPHENYTOIN AND PHENYTOIN PHARMACOKINETICS AND BIOAVAILABILITY AFTER IV OR IM ADMINISTRATION OF FOSPHENYTOIN TO DOGS (RR 764-01609, Vol. 10).

Fosphenytoin (14.8 mg/kg) was administered iv to 5 dogs, and PK parameters (HPLC analysis) were compared to those determined in the previous im study (**Table II.3 and II.4**).

After iv administration, fosphenytoin levels averaged 220 ug/ml at 0.6 min after dosing, then rapidly declined in a biphasic manner. The distribution and elimination t1/2 averaged 1.8 and 9.5 min, respectively. The absorption t1/2, Cmax, and tmax after im administration were 3.2 min, 20.4 ug/ml, and 9.1 min, respectively. The elimination t1/2 and Vd were greater than the corresponding iv values. The bioavailability of im fosphenytoin was 100% based on AUCs.

Table II.3. Pharmacokinetic Parameters of Fosphenytoin in Dogs after an IM or IV Dose of 14.8 mg/kg

Fosphenytoin Parameters*	IM Fosphenytoin	IV Fosphenytoin
Absorption or Distribution t1/2(min)	3.22 ± 1.53	1.79 ± 0.16
Elimination t1/2 (min)	17.4 ± 6.22	9.52 ± 2.33
Clearance (ml/min/kg)	21.9 ± 3.21	22.10 ± 3.37
Vd (ml/kg)	544 ± 180	299 ± 82.5
AUC (ug·min/ml)	688 ± 100	685 ± 109
Tmax or T1 (min)	9.13 ± 2.79	0.63 ± 0.35
Cmax or C1 (ug/ml)	20.4 ± 8.52	220 ± 43.7

* Data expressed as Mean ± SD of 5 dogs

Conversion of fosphenytoin to phenytoin was rapid after iv administration. The formation t1/2 averaged 1.3 min, and peak phenytoin levels (mean 7.7 ug/ml) were seen at an average of 9 min after iv administration of fosphenytoin. Absorption of fosphenytoin and conversion to phenytoin was prolonged by im administration; the formation t1/2 averaged 24.7 min, and the peak phenytoin concentration of 6.8 ug/ml (comparable to iv Cmax) was reached after 77 min. The elimination t1/2, Vd, and Cl of phenytoin were similar for the two routes. Based on the AUCs, the bioavailability of phenytoin was 100% after im administration of fosphenytoin.

Table II.4. Pharmacokinetic Parameters of Phenytoin in Dogs after an IM or IV Dose of 14.8 mg/kg of Fosphenytoin

Phenytoin Parameters*	IM Fosphenytoin	IV Fosphenytoin
Formation t1/2 (min)	24.7 ± 10.2	1.25 ± 0.36
Elimination t1/2(min)	164 ± 46.7	194 ± 55.9
Clearance (ml/min/kg)	4.66 ± 0.94	4.75 ± 1.11
Vd (ml/kg)	1058 ± 127	1266 ± 102
AUC (ug·min/ml)	2236 ± 557	2220 ± 617
Tmax (min)	76.9 ± 23.8	9.01 ± 1.83
Cmax (ug/ml)	6.83 ± 0.89	7.67 ± 0.62

* Data expressed as Mean ± SD of 5 dogs

Distribution, Metabolism, and Elimination

A) TISSUE DISTRIBUTION IN RATS (RR 764-01600, Vol. 1.10).

The tissue distribution of 14C-fosphenytoin was examined in 36 male rats after a single iv bolus dose of 10 mg/kg. The distribution of total radioactivity into various tissues was very rapid. For blood, heart, kidneys, liver, lungs, and spleen, the highest amount of total radioactivity was seen within the first 5 min. The highest levels in brain, carcass, eyes, intestines, skin/hair, stomach, testes, and urinary bladder occurred at 20, 20, 30, 90, 30, 10, 60, and 60 min, respectively. The highest levels of radioactivity in the intestines, kidneys, liver, carcass, and skin/hair averaged 52.1, 1.9, 14.5, 32.6, and 22.1% of the dose, respectively. Only 0.2% of the dose was found in the brain at 5 and 60 min after dosing, and the amount of radioactivity declined rapidly thereafter.

Rapid elimination of total radioactivity was observed from blood and all tissues. At 24 hr the highest radioactivity was in the carcass and intestines (2.1 and 4.7% of the dose, respectively); the radioactivity in all other tissues including blood was less than 1% of the dose. At 48 hr after dosing, less than 1.4% of the dose remained in all tissues. The tissue/blood total radioactivity ratio was above 1 or close to 1 in the heart, intestines, kidneys, liver, lungs, and stomach over the entire study period. The highest tissue/blood ratios were in intestines> stomach> liver> urinary bladder> kidneys> lungs.

Radio-HPLC analysis of blood, intestines, kidney, and liver samples showed three radioactive peaks, which were identified as a mixture of p-HPPH glucuronide and an unknown metabolite, p-HPPH, and phenytoin, based on their retention times after beta-glucuronidase treatment. In brain, the radioactive peak corresponding to p-HPPH glucuronide was absent. m-HPPH was not detected in blood or any of the 4 tissues examined. The prodrug was rapidly converted to phenytoin. At 5 min after dosing, fosphenytoin was not detectable in brain, intestines, kidneys, and liver, and only a trace amount was detected in blood. The tissue/blood ratio for phenytoin was above one in liver, kidneys, and intestines, and was close to one in brain at several of the later time points after administration. Pharmacokinetic parameters were determined after the concentration-time profiles of phenytoin in blood, brain, intestines, kidneys and liver had been fitted to appropriate pharmacokinetic models. The elimination half-lives of phenytoin in blood, brain, intestines, kidneys, and liver were determined to be 72.8, 59.8, 52.6, 90.1, and 70.3 min, respectively. The elimination t1/2 for blood agrees very closely with published data (Varia and Stella).

B) MASS BALANCE AFTER IV ADMINISTRATION TO RATS (RR 764-01608, Vol. 1.10).

The metabolism and excretion of 14C-fosphenytoin were studied in 10 male rats following iv administration of 10 mg/kg. At 24 hr after dosing, 86.9% of the dose was recovered, with 46.7% in urine and 40.2% in feces. Cumulative urinary and fecal excretion of radioactivity over 72 hr averaged 51.7% and 47.7% of the dose, respectively. These results are consistent with what has been reported for DPH. In the 24 hr urine sample, a large fraction of the radioactivity was in the form of polar metabolites. In contrast, 24-hr fecal samples contained more non-polar metabolites. In the 24-48 and 48-72 hr urine and fecal samples, a larger percentage of the dose was eliminated as nonpolar metabolites. When separated by HPLC, the polar fraction was found not to contain any unchanged fosphenytoin. Three radioactive peaks were detected in this fraction; the major urinary metabolite was a glucuronide conjugate of p-HPPH. Two additional peaks were not identified. One major and two minor metabolites were detected in the nonpolar fraction of urine. The major metabolite was identified as p-HPPH, and one of the minor metabolites was phenytoin. One nonpolar metabolite remained unidentified. The nonpolar fraction of feces contained the same unknown minor metabolite detected in urine and a major metabolite identified to be p-HPPH. So, fosphenytoin was cleared entirely by metabolism; only a trace amount of phenytoin was recovered in urine;> 40% of the dose was recovered in urine and feces as the glucuronide conjugate of p-HPPH. Metabolism appears identical to that of phenytoin, ie, ring oxidation and glucuronidation, followed by renal and biliary excretion of the metabolites.

C) IN VITRO HYDROLYSIS IN HUMAN, DOG, AND RAT BLOOD AND TISSUES (RR 764-01597, Vol. 1.11).

In vitro conversion of fosphenytoin to phenytoin was examined in rat, dog, and human tissues and whole blood. Incubation of fosphenytoin with whole blood and various tissues from rats resulted in the rapid disappearance of prodrug with a concomitant appearance of equimolar amounts of phenytoin. Kidneys, small intestines, and liver exhibited the highest phosphatase activity. Dog and human blood hydrolyzed the drug much slowly. Mean *in vitro* half-lives of fosphenytoin in rat, dog, and human whole blood were 5.89, 89 minutes, respectively. Faster prodrug conversion was observed in dog tissue homogenates the small intestine, kidney, and liver again the most active in mediating hydrolysis of the prodrug. *In vitro* studies with partially purified alkaline phosphatase (bovine liver and dog intestines) and acid phosphatase (bovine) revealed that fosphenytoin was a better substrate for alkaline than for acid phosphatase.

D) PLASMA PROTEIN BINDING OF FOSPHENYTOIN (RR 764-01620, Vol. 1.11).

The protein binding of 14C-fosphenytoin to dog and human plasma was determined by the ultrafiltration method. Mean percentages of fosphenytoin (at a concentration of 20 ug/ml) bound to human and dog plasma proteins were 95.7 and 91.3%, respectively, indicating that the drug is highly protein bound at therapeutic concentrations. Albumin accounted for 88% of the fosphenytoin binding to human plasma proteins. Varying the concentrations of albumin from 25 to 50 mg/ml significantly increased the % fosphenytoin bound from 81 to 90.5. Binding of 20 ug/ml to human alpha-acid glycoprotein (0.2 to 2 mg/ml) was independent of protein concentration, with percent bound averaging 13.2%. Binding of fosphenytoin to human albumin, 40 mg/ml, decreased linearly from 81 to 67% when concentrations of fosphenytoin increased from 6 to 200 ug/ml.

The effect of fosphenytoin on the plasma protein binding of phenytoin was studied by coincubating DPH at various concentrations of fosphenytoin (7.5-500 ug/ml). Phenytoin binding decreased with increasing fosphenytoin concentrations. At a DPH concentration of 5 ug/ml, the free fraction of phenytoin increased from 4 to 18% when the fosphenytoin concentrations increased from 7.5 to 500 ug/ml. These results indicate that at high concentrations, fosphenytoin may enhance the pharmacological or toxicological effects of phenytoin by displacing DPH from its binding sites.

Drugs highly bound to albumin, such as phenylbutazone, sulfisoxazole, or warfarin, can displace fosphenytoin from binding sites on albumin. When toxic concentrations of AEDs such as PHB, DPH, or VPA were added to plasma, the drugs significantly increased (5-20%) the free fraction of fosphenytoin. Diazepam, phenytoin, and carbamazepine at a concentration of <10 ug/ml did not change the free fraction of fosphenytoin. Since fosphenytoin has little intrinsic pharmacological effect, the changes in free fraction should have no clinical significance. Addition of fosphenytoin at equimolar concentrations to carbamazepine, phenobarbital, or VPA resulted in small but significant displacement of these drugs from its plasma binding sites. The degree of displacement of diazepam or carbamazepine was not enhanced by increasing the concentration of fosphenytoin 30-80-fold. The slight increase in free fraction of these drugs caused by fosphenytoin is unlikely to have clinical significance.

Toxicokinetics

A) TOXICOKINETICS IN RATS FOLLOWING SINGLE IM OR IV DOSES (RR 764-02096, Vol. 1.11).

Plasma *phenytoin* concentrations were determined in serial blood samples collected for 32 hr after administration of single im or iv doses of 150 mg/kg fosphenytoin to Wistar rats (5/sex). While peak plasma levels were greater after iv administration, concentration-time profiles appeared similar between routes after Cmax was reached. Phenytoin mean Cmax values following im fosphenytoin were 50-60% lower than those after iv fosphenytoin (**Table II.5**). Mean tmax values were 10-15X greater after im administration. Elimination t1/2 averaged 2.4 (im) and 5.3 (iv) hr in males and (18 (im) and 21 (iv) hr in females. Mean AUC values were 331 (im) and 404 (iv) ug hr/ml in males and 649 (im) and 611 (iv) in females. Thus, sex differences in phenytoin pharmacokinetics were seen, peak phenytoin levels were reduced after im administration relative to iv administration, and total phenytoin exposure was similar following im or iv administration of the same dose.

Table II.5. Mean (%RSD) Pharmacokinetic Parameters of Phenytoin following IM or IV Bolus Administration of 150 mg/kg of Fosphenytoin to Male and Female Rats (N=5/sex)

Parameters	Male		Female	
	IM	IV	IM	IV
Cmax (ug/ml)	39.8 (15.9)	108 (8.3)	47.4 (18.6)	95.4 (4.9)
tmax (hr)	0.9 (20.8)	0.08 (0.0)	1.3 (46.7)	0.08 (0.0)
t1/2 (hr)	2.4 (27.5)	5.3 (35.8)	17.9 (117)	21.0 (64.2)
AUC (ug hr/ml)	331 (57.2)	404 (32.4)	649 (27.5)	611 (42.7)

B) TOXICOKINETICS IN DOGS FOLLOWING SINGLE IM AND IV DOSES (RR 764-02035, Vol. 1.11).

Phenytoin kinetics were determined after single im or iv doses of 50 mg/kg fosphenytoin to beagle dogs (**Table II.6**). Serial blood samples were collected for 32 hr after dosing. Mean Cmax and tmax values following im fosphenytoin were approximately 21% lower (21.3 ug/ml for im versus 26.8 for iv)

and 100% longer (1.2 hr for im versus 0.6 hr for iv) than those following iv fosphenytoin. Once Cmax was attained, plasma phenytoin concentration-time profiles were similar for both routes. Mean elimination t1/2 values were essentially the same following im (2.8 hr) and iv (3 hr) administration. Mean AUC values following im and iv administration were also comparable, averaging 159 and 163 ug hr/ml, respectively. There was no gender difference in pharmacokinetics in dogs.

Table II.6. Mean (%RSD) Pharmacokinetic Parameters of Phenytoin following IM or IV Bolus Administration of 50 mg/kg of Fosphenytoin to Beagle Dogs (N=3/sex)

Parameters	IM	IV
Cmax (ug/ml)	21.3 (12.8)	26.8 (18.4)
tmax (hr)	1.2 (34.9)	0.6 (125)
t1/2 (hr)	2.8 (19.1)	3.0 (16.9)
$AUC_{0-\infty}$ (ug•hr/ml)	159 (28.9)	163 (27.0)

III. TOXICOLOGY

A) ACUTE IV TOXICITY IN MICE, RATS, RABBITS, AND DOGS (RR's 745-01722, 745-01726, 745-01727, 745-01725, 745-01721, 745-01728, 745-01729; Vol. 1.12)

Results of acute iv toxicity studies comparing fosphenytoin to phenytoin in mice (5/sex/group), rats (5/sex/group), rabbits (6/sex), and dogs (2/sex) are presented in **Table III.1**. Rodents were administered a single dose, while non-rodents received rising doses, allowing one or more days for recovery between doses. Doses were administered either as an iv injection or a 30 min iv infusion.

The acute toxicity of fosphenytoin was similar to that of equimolar doses of phenytoin when both drugs were administered by iv infusion. However, when administered by bolus injection phenytoin was more potent than fosphenytoin, probably because of the more gradual rise in peak phenytoin levels with the later compound. Clinical signs were similar for both and included ataxia, prostration, convulsions, and hypokinesia in both rodent and non-rodent species. Tremors and dyspnea were commonly observed in rodents, while struggling, salivation, and vomiting/retching were seen in dogs. When administered to rats by 30 min infusion, both drugs produced rigid hindlimbs, while only fosphenytoin produced this finding after rapid iv bolus injection. In general the times of onset and recovery of toxic effects were similar for both compounds except following rapid iv injection to rats. Under these conditions, toxic effects were observed immediately after dosing with phenytoin but only after mean lag times of 4 to 14 min with fosphenytoin. Necropsies of rats, rabbits and dogs revealed no macroscopic pathology which could be attributed to drug treatment.

Since phenytoin is commonly administered to children, the acute toxicities of fosphenytoin and phenytoin were compared in weanling (4 week old) and neonatal (7 days) rats. When administered by 30 min iv infusion to weanlings, the compounds produced similar toxic signs, which included ataxia, prostration, hypokinesia, sedation, piloerection, dyspnea, hypopnea, tremors, and convulsions (few fosphenytoin rats only). The phenytoin and fosphenytoin MLD's in weanling rats were similar to those obtained in adult rats. Because iv injections could not be made in neonates, both neonatal and weanling rats were administered fosphenytoin or phenytoin ip. It was concluded from this study that the acute toxicities of the two drugs were similar following ip administration, but that both were more toxic (lethal) in neonates.

B) ACUTE IM TOXICITY IN RATS AND DOGS (RR 745-01738, RR 745-01742; Vol. 1.12)

The acute toxicities of fosphenytoin and phenytoin were also compared after im administration to rats (3/sex/dose) and dogs (3/sex). Clinical signs were noted in rats within 40 to 60 min postdose with both compounds. Ataxia and prostration were observed in rats with fosphenytoin doses 1/2 and 1/3 lower, respectively, on a molar basis, than those phenytoin doses producing the same signs. Deaths occurred between 3 and 19 hr postdose with fosphenytoin doses $\geq$ 247 mg/kg (phenytoin equivalents), while no deaths occurred with phenytoin doses up to 337 mg/kg (**Table III.2**). In dogs, sedation and emesis occurred with both compounds, while prostration, ataxia, and convulsion were seen only with fosphenytoin. Struggling during dosing, presumably resulting from pain, was seen only with phenytoin. No deaths occurred in dogs at doses of up to 50 mg/kg of either compound. In a separate PK study in rats, whole blood phenytoin concentrations were consistently 5 to 6 times higher after administration of fosphenytoin than with equimolar doses of phenytoin (see PK section, above). Thus, the greater solubility and resultant higher blood levels presumably accounted for the increased systemic toxicity of fosphenytoin seen in both rats and dogs. In both species, phenytoin caused injection site necrosis while no necrosis was observed with fosphenytoin.

Table III.1. Summary of Acute IV Toxicity Studies of Fosphenytoin and Phenytoin

Species	Route	Drug	Results (mg/kg phenytoin equivalents)		
			NOAEL	MTD	MLD
Mouse	IV infusion	Fosphenytoin	33.3	63.3	156
		Phenytoin	<33	63	192
Rat	IV bolus	Fosphenytoin	50	153	213
		Phenytoin	<45	45	90.4
Rat	IV infusion	Fosphenytoin	<50	153	242
		Phenytoin	<45	210	275
Rat (weanling)	IV infusion	Fosphenytoin	33.3	120	258
		Phenytoin	33	120	297
Rat (weanling)	IP	Fosphenytoin	60	ND	352
		Phenytoin	60	ND	339
Rat (neonate)	IP	Fosphenytoin	100	ND	160
		Phenytoin	102	ND	224
Rabbit	IV infusion	Fosphenytoin	40	40	ND
		Phenytoin	27	40.5	ND
Dog	IV bolus	Fosphenytoin	13.3	26.7	ND
		Phenytoin	6	24	ND
Dog	IV infusion	Fosphenytoin	13.3	26.7	ND
		Phenytoin	12	24	ND

Table III.2. Comparison of Acute IM Toxicity of Fosphenytoin and Phenytoin in Rats and Dogs

Species	Route	Drug	Results (mg/kg phenytoin equivalents)		
			NOAEL	MTD	MLD
Rat	IM	Fosphenytoin	33.3	167	278
		Phenytoin	34	337	>337
Dog	IM	Fosphenytoin	33.3	33.3	ND
		Phenytoin	6.7	> 50	ND

C) FOUR-WEEK IV TOXICITY IN RATS (RP 250-01648, Vol. 1.14).

1. Treatment

Four groups of 18 Wistar rats/sex were given daily iv (bolus) doses of vehicle or fosphenytoin (30, 60, and 150 mg/kg) for 4 weeks. Ten rats/sex/grp were euthanized at the completion of dosing, and 5/sex/group were sacrificed after a 4 week recovery period (week 8). Three rats/sex/group were sacrificed 15 min postdose during week 3 for determination of whole blood and plasma phenytoin concentrations. All animals were observed daily for signs of toxicity. Body weight and food consumption were determined weekly. Detailed physical and ophthalmoscopic exams were performed pretest and at termination (week 4 or 8). Samples for hematology, biochemistry, and urinalysis were obtained prior to termination. Selected organs were weighed, and tissues from control and HD groups and liver and injection sites from all groups were examined microscopically. Liver from selected control and HD animals were evaluated by EM.

Drug lot #: CM 345120

2. Clinical Signs and Mortality

a) Ataxia or hypoactivity were observed infrequently in 1 and 2 MD males, respectively. Ataxia and hypoactivity were seen throughout the treatment phase in all HD animals. Salivation was noted in 3 MD and 14 HD rats. Urinary staining and dyspnea occurred in both sexes at the HD. The incidence of injection-related skin sores was similar in treated and control groups.
b) No animals died during the study.

3. Body weight and food consumption

a) BW was decreased 18% in HD males, with a 32% reduction in weight gain during the dosing period. In the recovery period, BW gain was higher in HD males and there were no statistically significant differences at week 8.
b) Food consumption was 14% lower in HD males and 10% higher in HD females compared to controls.

4. Physical and Ophthalmoscopic exams

No significant treatment-related effects.

5. Hematology

Small decreases in RBCs, HGB, and HCT and an increase in MCHC were seen in HD females at week 4 compared to controls (not considered toxicologically significant).

6. Clinical Chemistry

a) Increases (30-60%) in alanine aminotransferase and alkaline phosphatase activities were observed in HD males and females.
b) A 48% decrease in triglyceride concentration was seen in HD males at 4 weeks.
c) Urea was slightly decreased in all treatment group males at 4 weeks (15% at HD).

7. Urinalysis

No TR effects.

8. Organ weights

Statistically significant increases in absolute and relative liver weight were noted at 4 weeks in treated females at all doses. Relative liver weights were also increased in HD males, but absolute weights were lower than controls. Relative liver to BW ratios were increased at 8 weeks in HD males and females, but there were no differences in absolute liver weig

9. Gross Pathology

Treatment-related changes in the skin at the tail injection sites were noted in HD rats at 4 weeks and 8 weeks.

10. Histopathology

Changes in the liver and injection sites were seen in treated males and females at week 4.

a) Liver -The incidence of periportal cytoplasmic vacuolization of hepatocytes was increased in treated males (minimal to mild) and females (mild to moderate). No liver abnormalities were observed in the recovery groups. 4 week liver tissue from selected control and HD group animals exhibited no evidence of hepatocellular injury by EM; however, glycogen deposition was increased in treated animals, particularly in a females having the greatest periportal vacuolization.

b) Skin - Cutaneous necrosis and inflammation were increased at the injection sites of treated males and females at 4 weeks. No changes were noted at 8 weeks.

11. Plasma concentrations

Phenytoin concentrations at 15 min postdosing were proportional to dose and similar in plasma and whole blood of males and females (**Table III.3**).

Table III.3. Plasma and Whole Blood Phenytoin Concentrations in Rats Given Fosphenytoin IV for 4 Weeks

Fosphenytoin Dose (mg/kg)	Plasma Concentration (ug/ml)*			
	Plasma		Whole Blood	
	Male	Female	Male	Female
30	7.34 ± 0.85	10.9 ± 1.75	7.85 ± 0.24	10.7 ± 0.79
60	18.4 ± 4.24	21.2 ± 0.91	19.0 ± 3.67	22.4 ± 1.27
150	54.6 ± 1.10	51.0 ± 0.91	55.1 ± 2.12	55.5 ± 1.04

* Samples obtained 15 min postdose from 3 animals/sex/group during week 3; values are mean ± standard.

D) 13 WEEK IM TOXICITY IN RATS (RR 745-01744, conducted by IRDC, Vol. 1.15).

1. Treatment

Fifteen Sprague Dawley (Charles River CD) rats/sex/group were randomly assigned to each of five treatment groups, to receive either normal saline (controls), phenytoin sodium (positive control; 100 mg/kg in 40% propylene glycol and 10% ETOH), or fosphenytoin (30, 60, or 150 mg/kg in 0.1 M TRIS buffer) by intramuscular injection, once daily, for 13 weeks. Ten rats/sex/group were designated as main study animals and the remaining 5/sex/group were used for pharmacokinetic studies. The phenytoin and HD fosphenytoin groups received approximately equimolar doses. Because of excessive mortality, the phenytoin group was terminated during week 9, and all tests scheduled for termination were carried out at that time.

Drug lot #: Z86-7-10

2. Observed signs

Decreased activity, leaning to one side, excessive salivation, and dilated pupils were observed in HD fosphenytoin animals. Only excessive salivation was observed in the MD group. The phenytoin group exhibited decreased activity, excessive salivation, swollen hindlimbs, and autocanibalism of hind limbs.

3. Mortality

In the phenytoin group, 8/15 male and 10/15 female rats died by week 8. In the fosphenytoin groups, deaths occurred in 1/15 LD females, 1/15 MD females, 2/15 HD males and 1/15 HD females. One saline control female died. Only the phenytoin group and HD fosphenytoin group deaths were considered treatment-related; the others were thought to be related to the blood collection procedure.

4. Body Weights and Food Consumption

a) BWs for males and females in both the HD fosphenytoin group and the phenytoin group were lower than those in the saline control group throughout the treatment period.

b) Food consumption (g/animal) for HD fosphenytoin group males was consistently lower than saline controls. However, when calculated relative to BW, food consumption values (g/kg) for both male and female HD animals were generally higher than those for the control group. Food consumption in the LD and MD fosphenytoin groups was slightly (<10%) lower than controls. In the phenytoin group, both absolute and relative consumption were reduced compared to controls.

5. Hematology (routine hematology, serum chemistry and urinalysis tests were conducted on all main study rats during week 6 and at termination)

No treatment-related effects on hematology were observed among any of the fosphenytoin-treated groups. Significant decreases in RBCs, HGB and HCT, and increases in WBCs observed in phenytoin-treated rats were attributed to hemorrhage and infection secondary to autocannibalism induced by the local irritation of im phenytoin.

6. Clinical Chemistry

a) Aspartate and alanine aminotransferase and alkaline phosphatase levels were

elevated in the HD fosphenytoin group (≈ about 2-fold for all 3 in M & F). Only slight increases in alkaline phosphatase levels were noted in the phenytoin group.

b) Non-fasted glucose concentrations (from samples collected 2 hr after dosing) were significantly elevated (4-fold compared to saline) in the HD fosphenytoin group. Phenytoin had previously been shown to induce hyperglycemia, presumably by inhibiting insulin release, and glucose was elevated about 2-fold in the phenytoin group at 9 weeks in the current study. A hyperglycemic effect has also been previously shown for fosphenytoin. The hyperglycemia was no longer evident by the time routine blood samples were collected 24 hr later.

7. Urinalysis

Glucosuria was observed in both the phenytoin and HD fosphenytoin groups.

8. Organ Weights

a) Absolute and relative liver weights were elevated in MD and HD fosphenytoin groups, primarily in females (70-80% in HD females). In contrast, absolute and relative (to brain) liver weights were decreased in the phenytoin group.

b) Relative adrenal weights were increased in phenytoin group animals, and absolute adrenal weights were increased in the HD fosphenytoin group.

c) Thymus weights were significantly decreased in HD fosphenytoin males and females, while relative thymus weights were significantly decreased in phenytoin group females.

9. Gross Pathology

Macroscopic evidence of tissue irritation at injection sites was observed in the phenytoin- and fosphenytoin-treated groups. Changes in the phenytoin group consisted of pockets of fibrous material, nodules, necrosis, thickened tissue, and abscesses. The lesions were bilateral and the intensity was moderate to severe. Also, 10/15 males and 8/15 females in this group had missing toes or foot parts from their rear limbs. In fosphenytoin groups, changes included necrosis, hemorrhage or discolored areas, and pale, firm areas. The lesions were unilateral or bilateral, focal, and varied from mild to severe. The changes in the fosphenytoin groups were dose-related, and no signs of autocannibalism were seen.

10. Microscopic Pathology

a) Injection site - Microscopic evidence of injection site irritation, consisting of hemorrhage, inflammation, necrosis, mineralization, and thrombosis, was seen in both the phenytoin and fosphenytoin groups. The response was dose-dependent in the fosphenytoin groups, and the changes were reportedly somewhat less severe than in the phenytoin group.

b) Liver - Increased intracytoplasmic vacuolization of hepatocytes was observed in HD fosphenytoin animals (8/10 males, 9/10 females). This was thought to be due to glycogen accumulation. Single cell hepatocyte necrosis was observed in the phenytoin group animals (3/10 males, 3/10 females).

c) Thymus - Thymuses of rats in the phenytoin and HD fosphenytoin groups showed trace to moderate lymphoid depletion (correlated with decreases in thymus weights; considered stress-related).

d) A few animals in the phenytoin and HD fosphenytoin groups had cortical cell vacuolization or hypertrophy of the adrenals. This was also considered stress-related.

11. Plasma Drug Concentrations

Blood samples were collected from rats designated for blood level studies immediately prior to, and at 30, 60, and 120 min after dosing on study days 1, 42, and at termination (**Table III.4**).

At equimolar doses, peak phenytoin levels were about 3-4 times higher following fosphenytoin administration than after phenytoin injection. Absorption of phenytoin was apparently prolonged, since significant levels were measured in this group prior to dosing on day 42.

Table III.4. Plasma Fosphenytoin and Phenytoin Concentrations in Rats Given Fosphenytoin or Phenytoin IM for 13 Weeks

Fosphenytoin Dose (mg/kg phenytoin equivalents)	Plasma Concentration (ug/ml)*			
	Fosphenytoin		Phenytoin	
	Male	Female	Male	Female
20	< 0.1	< 0.1	8.42 ± 1.40	7.53 ± 1.22
40	0.782 ± 0.85	0.319 ± 0.65	14.3 ± 4.88	18.0 ± 4.87
100	2.10 ± 1.25	3.19 ± 2.38	46.7 ± 16.5	48.9 ± 6.64
Phenytoin 100 mg/kg	NM	NM	15.2 ± 10.2	23.8 ± 1.36

* Samples obtained 30 min postdose from 5 animals/sex/group, on day 91 (week 13) from animals given fosphenytoin and on day 42 (week 6) from animals given phenytoin; values are mean ± standard.
NM = not measured

E) FOUR-WEEK IV TOXICITY IN DOGS (RR 745-01970, Vol. 1.18)

1. Treatment

Four groups of beagle dogs (4/sex/group) were given daily iv bolus doses of fosphenytoin at 0 (vehicle-0.1 M Tris buffer, pH 8.8), 15, 30, or 50 mg/kg for 4 weeks. Three animals in each group were sacrificed after 4 weeks; the remaining dog in each group was sacrificed after a 4 week recovery period. Animals were observed daily for signs of toxicity and systemic effects. Body weights were recorded pretest, weekly, and at termination. Food consumption was assessed daily by visual inspection. Physical and ophthalmoscopic exams were performed pretest and at weeks 4 and 8. Blood pressure measurements and ECG were performed pretest, before and 60 min after dosing on day 1 and during week 4, and at 8 weeks. Hematological, clinical chemistry and urinalysis determinations were made pretest and at weeks 4 and 8. Blood samples for determination of phenytoin concentrations were collected 30 min after dosing during week 2. Complete necropsies were performed on all animals at termination after 4 or 8 weeks.

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2. Clinical Signs and Mortality

a) Salivation, emesis, mucoid feces were observed in all treatment groups (D-R).
b) Erythema of the gums and/or muzzle after dosing was seen in MD and HD dogs.
c) All HD males and 2 HD females exhibited ataxia, and hypoactivity and tremors occurred sporadically in HD animals.
d) No significant signs were observed during the recovery period.
e) No unscheduled deaths occurred.

3. Body Weight and Food Consumption

There were no significant drug-related effects on body weights or food consumption.

4. Physical and Ophthalmoscopic exams

No significant treatment-related effects.

5. Blood Pressure and ECG

There were no significant treatment-related changes.

6. Hematology and Bone Marrow

No drug-related alterations in hematologic parameters or bone marrow data were observed.

7. Clinical Chemistry

A D-R increase in serum alkaline phosphatase (≈ 2.5-3X C at HD) was seen in treated dogs compared to pretest and control values. These returned toward normal during the recovery period, but were still elevated at 8 weeks.

8. Urinalysis

No treatment-related changes.

9. Organ Weights

a) D-R increases in liver weights occurred in treated dogs (absolute ≥+25-30% at HD).
b) Mandibular salivary gland weights were increased in HD males and MD and HD females.
c) Small (10%) increases in absolute and relative heart weights were seen in MD and HD males.

10. Gross Pathology

No TR changes were noted.

11. Histopathology

a) Two HD males had minimal diffuse hypertrophy of mandibular and parotid salivary gland acini which correlated with salivation noted clinically and increased salivary gland weights. These changes were not seen in females.
b) No differences in the incidence or severity of injection site alterations were noted between vehicle controls and treated groups.

12. Plasma concentrations

Mean plasma and whole blood phenytoin concentrations increased proportionately with dose. Plasma and whole blood phenytoin concentrations were similar and were equivalent between sexes at each dose (**Table III.5**).

Table III.5. Plasma and Whole Blood Phenytoin Concentrations in Dogs Given Fosphenytoin IV for 4 Weeks

Fosphenytoin Dose (mg/kg)	Plasma Concentration (ug/ml)*			
	Plasma		Whole Blood	
	Male	Female	Male	Female
15	6.43 ± 0.33	6.76 ± 0.41	6.54 ± 0.31	6.95 ± 0.07
30	13.4 ± 0.99	13.2 ± 0.19	13.7 ± 0.30	13.8 ± 0.40
50	22.2 ± 1.47	24.0 ± 2.90	23.5 ± 0.69	23.8 ± 2.46

* Samples obtained 30 min postdose from 4 animals/sex/group during week 2; values are mean ± standard.

F) 13 WEEK IM TOXICITY IN DOGS (RR 745-01740, conducted by IRDC, Vol. 1.19).

1. Treatment

Fosphenytoin was administered im to beagle dogs at dose levels of 15, 30, and 60 mg/kg/day for 13 weeks. A negative control group was administered saline, and a positive control group received phenytoin sodium on the same regimen. The phenytoin dose was 40 mg/kg, which was equimolar to the high fosphenytoin dose. All groups contained 4 males and 4 female dogs.

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2. Clinical Signs

Ataxia, decreased activity, and mucoid diarrhea were observed in the HD fosphenytoin group. Emesis and ptyalism were seen in all fosphenytoin-treated dogs in a dose-related manner. Ataxia, emesis, and diarrhea were observed in the phenytoin group, with incidences intermediate between that seen in the MD and HD fosphenytoin groups. Other observations made in phenytoin-treated dogs include the inability to bend rear legs, thinness, swollen legs, and loss of appetite. Dogs in this group also struggled and vocalized during dosing. Both phenytoin and fosphenytoin groups exhibited swelling at the injection sites.

3. Mortality

All study animals survived until termination.

4. Body Weight and Food Consumption

BW gain was increased in male fosphenytoin group dogs (1.5X saline controls at HD) and slightly decreased in phenytoin group males and females compared to saline controls. Food consumption was decreased in HD females and in phenytoin group males and females.

5. Ophthalmoscopic Examination

No treatment-related ophthalmoscopic abnormalities were detected.

6. Physical Examination

Signs of injection site irritation were noted in the phenytoin group only.

7. Cardiovascular Examination

No cardiovascular abnormalities were detected at one month or at the end of the study.

8. Hematology (pre-study and at 1, 2, and 3 months)

No changes in hematologic values were noted in the analysis of blood samples. However, one HD fosphenytoin female had an elevated myeloid/erythroid ratio (M/E = 6.1) in the bone marrow smear performed post mortem, indicative of depressed erythrogenesis. All other hematologic parameters were normal for this dog, however.

9. Clinical Chemistry (pre-study and at 1, 2, and 3 months)

Alkaline phosphatase levels were elevated in the phenytoin group males and females (≈ 2-3-

fold C), in HD fosphenytoin group males and females (2-3X C), and in MD fosphenytoin females (+60% compared to C). Creatine phosphokinase (CPK) values were elevated in MD and HD fosphenytoin males (2X C), in HD fosphenytoin group females (2X C), and in phenytoin group females (2-3X C). AST and ALT were increased in phenytoin group females (2 X). BUN was decreased in phenytoin group males and females (-30-40%).

10. Urinalysis (pre-study and at 1, 2, and 3 months)

The urinalysis values for all groups were normal.

11. Organ Weights

A dose-related increase in liver weights occurred in fosphenytoin group males (≥+35% at HD) and females (+28% at HD). Liver weight was also increased in the PC group (+28% M, 14% F).

12. Macroscopic Pathology

Injection site changes were observed in dogs from the phenytoin group and from the MD and HD fosphenytoin groups. These were more extensive and severe in the phenytoin group and consisted of abscesses, fibrous tissue masses, and multiple hemorrhages. Only 2 females in the MD fosphenytoin group and 2 males and 2 females in the HD group had tissue changes consisting of discolored fat and muscle, edema between muscles, and petechial hemorrhage.

13. Microscopic Pathology

a) Injection site - Microscopic changes were observed at the injection site in the phenytoin group and in the HD and MD fosphenytoin groups. Abnormalities seen at the injection site in phenytoin treated dogs included hemorrhage, inflammation, necrosis, thrombosis, mineralization and abscess formation. Injection site changes in the fosphenytoin groups were reportedly much less severe.

b) Livers of 1 male and 1 female from the phenytoin group and of all females from the HD fosphenytoin group showed diffuse increases in intracytoplasmic vacuolization of hepatocytes.

14. Plasma Drug Levels

Blood samples were collected from each animal 30 min before and at intervals up to 3 hr after dosing on days 1, 42 and at termination (**Table III.6**). Peak fosphenytoin levels were seen 10-15 min after administration. Rapid conversion to phenytoin was demonstrated by the appearance of phenytoin levels by 5 min after dosing. Phenytoin levels peaked at approximately 60 min after prodrug administration. Peak phenytoin levels in the phenytoin group were consistently about 3 times lower than those in the equimolar fosphenytoin group.

Table III.6. Plasma Fosphenytoin and Phenytoin Concentrations in Dogs Given Fosphenytoin or Phenytoin IM for 13 Weeks

Fosphenytoin Dose (mg/kg phenytoin equivalents)	Plasma Concentration (ug/ml)			
	Fosphenytoin*		Phenytoin**	
	Male	Female	Male	Female
10	13.7 ± 5.91	20.2 ± 10.9	6.24 ± 0.59	6.34 ± 0.81
20	28.1 ± 12.9	21.7 ± 8.09	12.1 ± 0.90	11.2 ± 1.32
40	60.6 ± 7.18	51.4 ± 12.8	27.5 ± 3.47	28.7 ± 11.0
Phenytoin 40 mg/kg	NM	NM	6.67 ± 1.57	9.97 ± 1.65

* Samples obtained 10 min postdose from 4 animals/sex/group on day 91 (week 13); values are mean ± standard.
**Samples obtained 60 min postdose from 4 animals/sex/group on day 91 (week 13); values are mean ± standard.
NM = not measured

IV. SPECIAL TOXICITY

A) VENOUS AND PERIVASCULAR IRRITATION IN RABBITS (RR 745-10724, Vol. 1.20).

When administered as a 30-min iv infusion (0.05 ml/min) into the right ear or as a 0.1 ml perivascular injection into the left ear, fosphenytoin at concentrations of 10, 25, or 50 mg/ml was no more irritating than the saline control at either site. A concentration of 75 mg/ml resulted in higher (50%) irritation scores than the saline control at both sites. Phenytoin concentrations of 16.9, 33.7, and 50 mg/ml produced significantly greater microscopic irritation than did the saline control at the venous site and concentrations of 33.7 and 50 mg/ml produced significantly greater irritation at the perivascular site. The three highest doses of phenytoin were only slightly more irritating than their undiluted vehicle (40% propylene glycol, 10% alcohol, water - pH adjusted to 12 with NaOH). The irritation produced by phenytoin and its vehicle included a high incidence of thrombosis, which was not seen in the fosphenytoin groups.

B) LOCAL IRRITATION AFTER ACUTE IM INJECTION OF RABBITS (RR 745-01737, Vol. 1.20).

Microscopic irritation scores (slight to moderate) were not different among injections sites for saline, phenytoin vehicle, and phenytoin (50 mg/ml). Irritation scores (minimal to mild) at fosphenytoin vehicle (0.1 M Tris buffer, pH adjusted to 8.8 with HCl) or fosphenytoin (25, 50, 75, or 100 mg/ml) sites were statistically lower than those for saline control and phenytoin.

C) LOCAL IRRITATION AFTER DAILY IM INJECTION OF RABBITS FOR FIVE CONSECUTIVE DAYS (RR 745-01741, Vol. 1.20).

When a 1 ml volume was injected im into the hindlimb of rabbits daily for 5 consecutive days, fosphenytoin concentrations of 50, 75 and 100 mg/ml produced concentration-dependent irritation compared to saline controls (increased serum creatine kinase and irritation scores). Based on macroscopic scores and effects on serum CK, phenytoin at 50 mg/ml was more irritating than equimolar concentrations of fosphenytoin. Irritation produced by the undiluted phenytoin vehicle was comparable in severity to that seen with formulated phenytoin at a concentration of 50 mg/ml.

D) HYPERGLYCEMIC EFFECTS IN RATS (RR 745-01734, Vol. 1.20).

Fosphenytoin (150 mg/kg) or phenytoin (100 mg/kg) were administered by 30 min infusions to 10 rats/group, and multiple blood and urine samples were collected over a 48 hr period. Serum glucose concentrations in the fosphenytoin and phenytoin groups were elevated by 30 min after dosing and peaked at about 400 mg/dL at 1 hr. Levels were significantly increased for 4-6 hr after dosing. Glucose levels in both groups had returned to normal by 24 hr. Urine glucose levels increased during the first 12 hr after dosing in both groups compared to saline controls and returned to normal during the second 12 hr. Effects on glucose were comparable for the two drugs.

E) CNS TOXICITY IN MICE (RR 745-01736, vol. 1.20).

6 mice/group received single ip injections of equimolar doses of fosphenytoin or phenytoin sodium solution. Saline and vehicle controls were included. Fosphenytoin at 50 mg/kg or phenytoin at 33 mg/kg produced no effects. Dose-related CNS toxicity, including decreased respiration, prostration, piloerection, tremors, ataxia, sedation, decreased pupil response, reduced righting reflex, decreased grip strength, decreased body temperature, and death (at 2 highest doses), were observed after doses of 100, 200, 500, or 1000 mg/kg of fosphenytoin or 69, 134, 337, or 675 of phenytoin. Responses to equimolar doses of fosphenytoin and phenytoin were similar, but there was a suggestion of quantitatively greater effects with fosphenytoin. These differences may have been due to differences in absorption after ip administration.

F) CARDIOVASCULAR TOXICITY IN DOGS (RR 745-01735, Vol. 1.20).

The cardiovascular effects of fosphenytoin, phenytoin, and their respective vehicles (0.1 M Tris buffer, pH 8.8 and 40% propylene glycol, 10% alcohol, pH 12) were compared following iv bolus (3 sec) injection to anesthetized female dogs (4/group). A saline control was also included. The phenytoin dosage (18 mg/kg) used in the study was considered to represent a clinically effective dose for treatment of status epilepticus, which would normally be infused over 20-30 min. The fosphenytoin dose (27 mg/kg) was equimolar. Heart rate, left ventricular dP/dt at 40 mmHg (LVdP/dt), left ventricular end diastolic pressure (LVEDP), mean arterial pressure (MAP), and Lead II electrocardiograms were recorded at frequent intervals for 1 hour after dosing. Blood samples for determination of drug concentrations were collected at each interval.

Since there were no differences in CV parameters among the three control groups, data from these were pooled. Lead II ECG recordings were similar among groups. A slight increase in QT interval was seen in both treated groups, but this effect was not considered biologically significant. Intravenous phenytoin resulted in decreases in heart rate (80% of baseline), LvdP/dt (max -55% compared to C), and MAP (-40% compared to C) and a significant increase in LVEDP (2-3-fold). Effects on LVdp/dt and LVEDP lasted 3-5 min, while changes in MAP gradually returned toward baseline over the 60-min observation period and HR remained low up to 1 hr (**Figures IV. 1 and IV.2**). Peak phenytoin levels in blood occurred at 30 sec after dosing (49 ug/ml) and gradually decreased to 14 ug/kg at 60 min (**Table IV.1**). Fosphenytoin resulted in more gradual decreases in HR (80% of baseline), LvdP/dt (max -36% compared to C), and MAP (-40% compared to C and baseline). These changes peaked at 2-3 min and then slowly returned toward baseline (HR remained low at 1 hr). Effects on LVEDP were variable and did not appear to be as pronounced as those produced by phenytoin administration. Phenytoin blood levels rose more slowly after fosphenytoin administration, peaking at 5 min after dosing (22 ug/ml). Effects on CV parameters appeared to correlate with phenytoin blood levels in both cases. The major difference between drugs was in effects on LVEDP. The less pronounced effects seen after fosphenytoin presumably reflect the lower peak blood level of phenytoin resulting from its administration.

Table IV.1

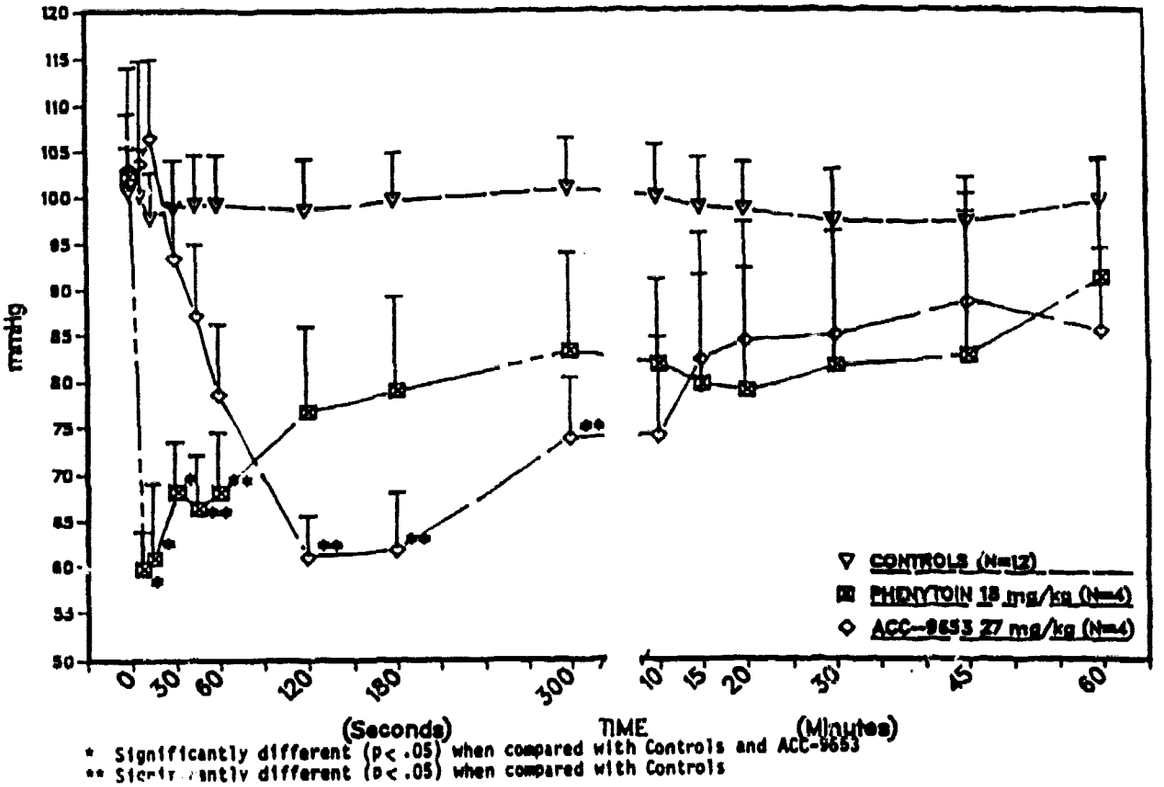
Mean 9853 and Phenytoin Blood Levels (µg/mL)

Time	Phenytoin 18 mg/kg Mean	SD	N	9853 27 mg/kg -9853 Mean	SD	N	Phenytoin Mean	SD	N
Baseline	BQL[a]	-	4	BQL[a]	-	4	BQL[a]	-	4
5 Seconds	41.6	54.3	3	194	68.9	4	0.5	0.4	4
15 Seconds	47.8	30.1	3	258	68.2	4	2.5	1.6	4
30 Seconds	49.4	17.3	4	241	28.0	4	5.5	1.3	4
45 Seconds	39.9	12.5	4	179	31.1	4	8.9	2.2	4
60 Seconds	34.2	8.3	4	168	13.9	4	10.4	1.0	4
2 Minutes	41.3	4.6	4	104	16.2	4	16.3	2.0	4
3 Minutes	37.7	3.8	4	66.7	9.0	4	19.5	1.5	4
5 Minutes	33.2	2.2	4	35.9	6.0	4	22.1	1.9	4
10 Minutes	28.1	3.1	4	11.1	2.5	4	20.5	1.5	4
15 Minutes	21.9	1.5	4	4.1	1.2	4	17.0	1.9	4
20 Minutes	20.9	2.1	4	1.5	0.8	4	15.8	0.8	4
30 Minutes	17.9	1.3	4	0.4	0.2	4	14.5	2.6	4
45 Minutes	14.9	2.6	4	0.2	0.1	4	10.7	2.1	4
60 Minutes	13.8	3.5	4	0.1	0.2	4	10.5	2.1	4

[a] BQL=Below Quantifiable Limit (0.1 µg/mL)

Figure IV.1

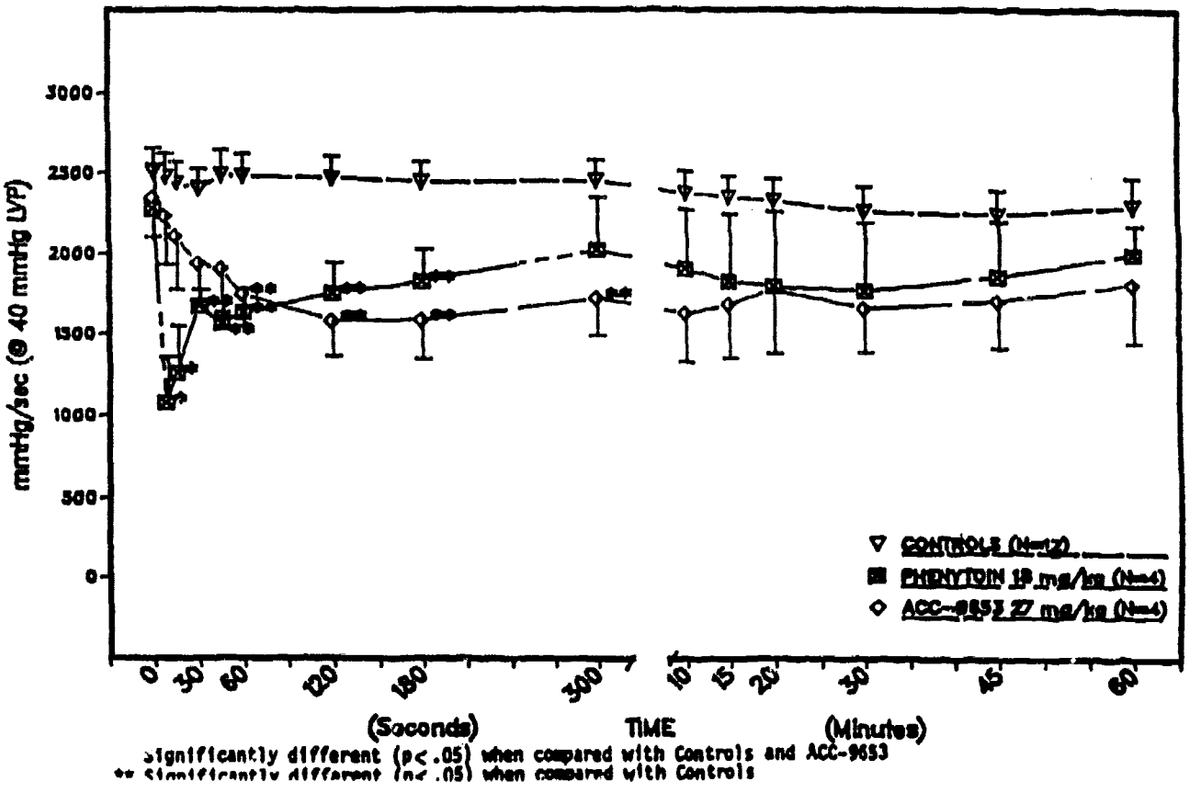
CARDIOVASCULAR TOXICITY EVALUATION
OF -9653 AND PHENYTOIN
MAP Means ± S.E.M.



* Significantly different ($p < .05$) when compared with Controls and ACC-9653
** Significantly different ($p < .05$) when compared with Controls

Figure IV.2

CARDIOVASCULAR TOXICITY EVALUATION
OF 9653 AND PHENYTOIN
LV dP/dT Means ± S.E.M.



* Significantly different ($p < .05$) when compared with Controls and ACC-9653
** Significantly different ($p < .05$) when compared with Controls

G) IN VITRO EFFECTS ON HUMAN BLOOD (RR 745-01746, Vol. 1.20).

Washed cell and plasma from blood collected from 4 human donors were mixed with various concentrations of fosphenytoin and phenytoin and compared to positive controls for hemolysis and plasma protein flocculation by measuring hemoglobin concentration or optical density. Fosphenytoin produced little hemolysis (<0.7%) at any of the concentrations tested (0.15 - 75 mg/ml). Phenytoin produced only slight hemolysis (<3.6%) at concentrations up to 5 mg/kg, but essentially complete hemolysis was seen at 10, 20, and 50 mg/ml. Fosphenytoin produced no plasma protein flocculation at any concentration tested. Phenytoin produced mild flocculation at 20 mg/ml but none at lower or higher concentrations, indicating that this may have been an anomalous result. No explanation for the difference in hemolytic effects was provided.

H) POTENTIAL RISK ASSOCIATED WITH SYSTEMIC FORMALDEHYDE (RR-MEMO 745-01786, Vol. 1.31)

Formaldehyde is generated during the conversion of fosphenytoin to phenytoin by tissue phosphatases (t1/2 approximately 3 min in humans). The theoretical maximum dose of formaldehyde, assuming complete, instantaneous conversion after an iv dose of 2100 mg fosphenytoin (said to be maximum human iv dose), and based on a 1:1 molar ratio, would be 155.3 mg (5.17 mmol) or 3.1 mg/kg (50 kg BW). The theoretical maximal rate of exposure to formaldehyde was calculated as 0.22 mg/kg/min, based on a fosphenytoin infusion rate of 150 mg/min. (The proposed maximum dose and rate are now 30 mg/kg and 225 mg/min, respectively.)

The pharmacokinetics of formaldehyde and its major metabolite formate were modeled using data from a published report (McMartin et al., Biochem Pharmacol 28:645-649, 1979) in which formaldehyde (30 mg/kg) was administered iv to monkeys. Using this model, peak formaldehyde and formate concentrations resulting from first order input of 3 mg/kg formaldehyde, with a formation half-life of 8 min, were simulated (**Figures IV. 3** and **IV.4**). Peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 min. Maximal formate levels were predicted to be 0.08 mmol/L, which is below the baseline levels measured in 2 monkeys in the same published study (0.18 and 0.27 mmol/L). These are worst case simulations analogous to a bolus dose of 2100 mg of fosphenytoin. Background levels of formate in humans have been reported in the literature to be 3 to 19 mg/L (0.07 to 0.4 mM). Elevations in formate levels were expected to be transient, since an elimination t1/2 of about 11 min was predicted. Metabolic acidosis and other characteristics of methanol poisoning reported in 2 monkeys following administration of a high dose of methanol (3 g/kg) were associated with plasma formate levels of 6.4 and 10.5 mmol/L (McMartin et al., above). Plasma formate levels measured in 4 healthy volunteers following administration of 1200 mg of fosphenytoin by iv infusion over 30 min were not significantly different from those observed in a placebo group (N=5) or from baseline levels, which averaged about 25 mg/L. It is thought that endogenous production of formaldehyde during normal metabolism in humans amounts to about 36 g/day in a 50 kg person; thus, the estimated maximal amount of formaldehyde added as a result of fosphenytoin administration (3.1 mg/kg) represents about 0.5% of the daily body burden due to metabolism.

Since the theoretical maximum dose of formaldehyde represents only a fraction of the total body burden from normal metabolism, and since the PK simulations indicated that formaldehyde concentrations would exceed background levels for a relatively short time, the sponsor considers the potential risks associated with formaldehyde exposure as a result of fosphenytoin administration to be negligible.

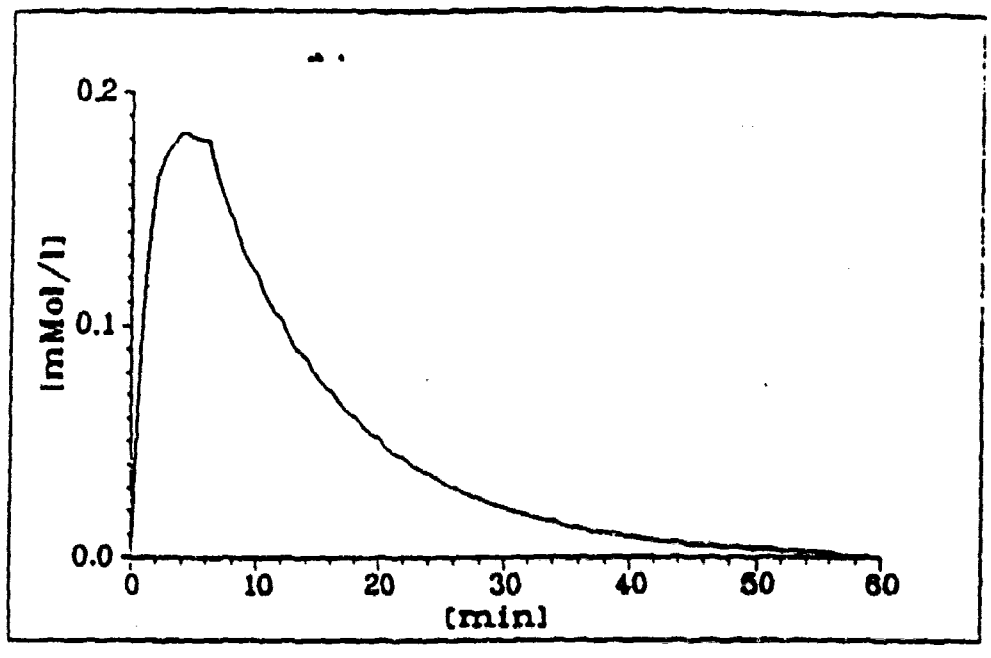


Figure IV.3 Simulated blood formaldehyde concentrations following a 3-mg/kg (0.1 mM/kg) dose of formaldehyde generated by a first order process (formation half-life = 8 minutes). This simulation would be analogous to a bolus intravenous dose of 2100 mg fosphenytoin in a 50-kg human.

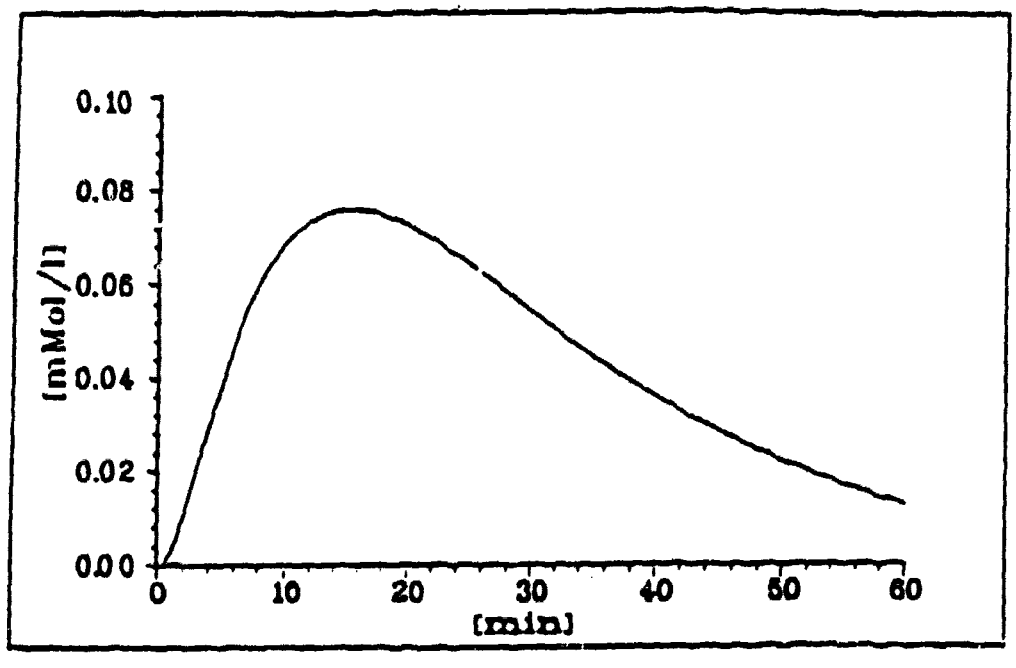


Figure IV.4 Simulated blood formate concentrations following a 3-mg/kg (0.1 mM/kg) dose of formaldehyde generated by a first order process (formation half-life = 8 minutes). This simulation would be analogous to a bolus intravenous dose of 2100 mg fosphenytoin in a 50-kg human.

V. GENETIC TOXICOLOGY (Vol. 1.31)

A) AMES TEST (RR 745-01958)

Fosphenytoin was tested with Salmonella strains TA-98, TA-100, TA-1535, TA-1537, and TA-1538, both with and without metabolic activation. In initial rangefinding tests, no toxicity to the background lawn occurred, by either plate incorporation or preincubation methods, over concentrations ranging from 0.5 to 5000 ug/plate. No increase in revertants occurred for any strain in these tests. Confirmatory tests were performed by the plate incorporation method in triplicate with concentrations ranging from 312.5 to 5000 ug/plate. The positive controls produced appropriate increases in revertant frequency with each strain, and all background frequencies were within historical ranges. No toxicity to the background lawns occurred. Statistically significant trends were seen in TA-100, with and without activation, and with TA-98 without activation; however, the increases were relatively small and not considered biologically significant. The sponsor pointed out that greater (statistically significant) increases in revertant frequency were seen with placebo (Tris buffer vehicle) in both of these strains. The maximum response with TA-100 was 1.4-fold the background level at 5000 ug/plate without activation, while the maximum increase with TA-98 was 1.7X the background at 625 and 1250 ug/plate without activation.

Drug lot: CM 344120

B) MUTATION ASSAY IN V79 CHINESE HAMSTER LUNG CELLS (RR 745-01935)

V79 Chinese hamster lung cell cultures were exposed to fosphenytoin for 3 hr in the presence and absence of S9. The concentrations ranged from 100 to 4000 ug/ml in both studies. In dose range-finding for cytotoxicity, the high concentration produced no effect on cell survival in the absence of S9, but in the presence of S9 there was a 89% reduction in cell survival at 4000 ug/ml.

In the 2 nonactivated mutation (HGPRT locus) assay trials, the presence of fosphenytoin did not produce an increase in mutant frequency. The positive control (ethyl methanesulfonate) produced appropriate increases in both trials (>4X background), but the magnitude of the response differed markedly between trials (68.2 and 836.4 mutants/10^6). All background frequencies were within the acceptable range (0-15 mutants/10^6).

In both activation trials, the positive control (benzo(a)pyrene) produced appropriate increases in mutant frequency, and background frequencies were within the acceptable range. Cell viability was reduced by about 40-50% (relative to vehicle controls) at the maximum fosphenytoin concentration in both trials. In trial 1, there was a significant quadratic trend due to an increase in mutation frequency at two intermediate drug concentrations (23 and 24 mutants/10^6 at 1000 and 2000 ug/ml, respectively, versus 11 mutants/10^6 in vehicle controls). Although not significant by linear dose trend analysis, the effect met other criteria for a positive assay, ie, mutant frequency at least 2X vehicle control at two or more contiguous drug concentrations and exceeding 20 mutants per 10^6 viable cells with at least one concentration. In trial 2, however, no effect on mutation frequency was seen in fosphenytoin exposed cultures.

Drug lot: CM 344120

C) CHROMOSOME ABERRATION IN V79 CHINESE HAMSTER LUNG CELLS (RR 745-02101)

Fosphenytoin, at concentrations up to 4000 ug/ml (high concentration arbitrarily chosen in the absence of cytotoxicity or insolubility), was tested for its ability to induce structural chromosome aberrations (SCA) in cultured V79 Chinese hamster lung cells.

In assays performed without S9 activation, with fosphenytoin concentrations from 500 to 4000 ug/ml, there was a statistically significant increase in the percentage of cells with aberrations at the 12 hr harvest time after exposure to 4000 ug/ml (8.5% vs 2.5% in vehicle control; 14 and 15% after 1 and 1.25 ug/ml mitomycin C). Because this finding did not satisfy the pre-established criteria of statistically significant increases at 2 consecutive concentrations, with at least one response exceeding the historical control range (0-5% with S9, 0-6.3% without S9), it was not considered to be biologically significant.

Fosphenytoin was tested in the presence of S9 in 3 separate trials. In the first trial, the positive control (cyclophosphamide) did not significantly increase SCA at either concentration, so the trial was considered invalid (data not submitted). In the second trial (**Table V.1**), with concentrations ranging from 1000-4000 ug/ml, the percentage of cells with aberrations and the mean number of aberrations per cell were both significantly increased at all concentrations and at both harvest times (18 & 24 hr). In many cases, these values were higher than those in the positive control groups, which were also significantly increased. In a third trial (**Table V.2**), with lower concentrations of fosphenytoin (125-2000 ug/ml), no significant increase in chromosomal aberrations was observed at any dose or harvest time. However, the positive control significantly increased SCA only at the highest concentration and only at 1 of the 2 harvest times (18 hr) in this trial (met sponsors minimum criteria for valid assay).

The sponsor postulated that the clastogenic effect was due to the generation of formaldehyde in vitro. Phenytoin was reportedly not clastogenic in previous studies with CHO cells (literature references), while formaldehyde has been reported to induce chromosomal aberrations in vitro in CHO cells at concentrations as low as 5 ug/ml (literature reference). However, attempts to measure formaldehyde in cultures in the present study were unsuccessful. Addition of formaldehyde dehydrogenase to the S9 would have been an alternate approach. The degradation product diphenylhydantoic acid, which was said to be present at 1.5 to 2% of total drug in these studies (prior to metabolic activation), was considered unlikely to be involved, but this possibility was not investigated.

Drug lot: CM 344120

D) MOUSE MICRONUCLEUS (RR 745-01898)

Micronucleus formation in bone marrow polychromatic erythrocytes (PCEs) was determined in groups of male and female mice (5/sex/group/time) after administration of single iv doses of fosphenytoin (50, 100, or 200 mg/kg). The doses were chosen on the basis of a previous acute iv infusion study showing 50 mg/kg to be a no-effect dose and 234 mg/kg to be the combined sex LD50. In the present study, clinical signs were seen at the MD and HD, but no deaths occurred. Significant decreases in PCE/total erythrocyte ratios were seen in HD groups, indicating bone marrow toxicity. Small, but statistically significant (by trend but not pair-wise analysis) increases in micronucleated PCEs (MNPCEs) were observed at 24 and 48 hr sacrifice times in HD animals when sexes were combined. The elevation in MNPCE frequency was less than twice the placebo control rate and was within the historical control range. No significant differences were detected in the analysis of individual sex MNPCE data. The positive control (cyclophosphamide) produced a significant increase (about 12X) in mean MNPCE values at 12 hr compared to vehicle (saline) and placebo (Tris buffer) controls.

Table V.1 Summary of CI-982 in Vitro Chromosome Aberrations With Metabolic Activation (S9+, Trial 2)

Fixation Time	Conc'n (ug/mL)	Total Gaps	Chromatid Breaks	Chromatid Exchanges	Chromosome Breaks	Chromosome Exchanges	Total Abs (-G)	Abs/ Cell (-G)	% Cells w/Abs (-G)
18-HOUR									
VEHICLE	0	0	1	2	3	0	6	0.0300	3.00
EMEM	0	3	2	0	3	0	5	0.0250	2.50
CI-982	1000	16	13	2	13	1	29	0.1450	12.50
	2000	16	11	2	5	0	18	0.0900	8.00
	3000	32	15	5	20	0	40	0.2000	16.50
	3500	35	15	5	17	1	38	0.1900	16.50
	4000	27	9	6	11	0	26	0.1300	11.00
CP	4	13	7	2	22	0	31	0.1550	12.50
	6	29	19	1	27	0	47	0.2350	19.00
24-HOUR									
VEHICLE	0	4	4	0	0	0	4	0.0200	2.00
EMEM	0	2	1	0	2	0	3	0.0150	1.50
CI-982	1000	5	5	1	2	1	10	0.0500	5.00
	2000	14	6	1	11	0	18	0.0900	7.00
	3000	13	12	9	6	2	31	0.1550	13.00
	3500	22	13	10	6	3	32	0.1600	15.50
	4000	29	19	6	20	2	47	0.2350	19.00
CP	4	13	2	1	11	0	14	0.0700	6.50
	6	9	3	2	17	0	22	0.1100	9.50

CP = Cyclophosphamide
-G = Without Gaps
Abs = Aberrations
N = 200 cells
EMEM = Eagle's minimum essential medium (untreated control)

Table V.2 Summary of CI-982 in Vitro Chromosome Aberrations With Metabolic Activation (S9+, Trial 3)

Fixation Time	Conc'n (ug/mL)	Total Gaps	Chromatid Breaks	Chromatid Exchanges	Chromosome Breaks	Chromosome Exchanges	Total Abs (-G)	Abs/ Cell (-G)	% Cells w/Abs (-G)
18-HOUR									
VEHICLE	0	4	2	1	0	0	3	0.0150	1.50
EMEM	0	5	4	1	4	0	9	0.0450	3.50
CI-982	125	4	2	0	0	0	2	0.0100	0.50
	250	3	4	0	0	0	4	0.0200	2.00
	500	7	8	0	3	0	11	0.0550	5.00
	750	7	3	0	2	0	5	0.0250	2.00
	1000	22	1	0	2	0	3	0.0150	1.50
	1500	8	3	0	6	0	9	0.0450	4.00
	2000	11	6	0	0	0	6	0.0300	3.00
CP	4	11	8	0	1	0	9	0.0450	4.50
	6	29	18	4	7	0	29	0.1450	11.00
24-HOUR									
VEHICLE	0	6	6	0	0	1	7	0.0350	3.50
EMEM	0	7	1	0	1	0	2	0.0100	1.00
CI-982	125	4	0	0	0	0	0	0.0000	0.00
	250	4	4	0	2	0	6	0.0300	3.00
	500	3	3	0	0	0	3	0.0150	1.50
	750	4	0	0	0	0	0	0.0000	0.00
	1000	1	1	0	1	1	3	0.0150	1.50
	1500	4	2	0	0	0	2	0.0100	1.00
	2000	6	5	0	2	0	7	0.0350	3.50
CP	4	2	5	0	0	0	5	0.0250	2.50
	6	6	6	0	5	0	11	0.0550	5.00

CP = Cyclophosphamide
-G = Without Gaps
Abs = Aberrations
N = 200 cells
EMEM = Eagle's minimum essential medium (untreated control)

VII) REPRODUCTIVE TOXICITY

A) SEGMENT I STUDY IN MALE RATS (RR 745-02042, Vol 1.21)

1. Treatment

Male rats (40/grp) were dosed with 0, 25, 75, or 150 mg/kg, im, for 75 days prior to mating and throughout mating with untreated females (1:1 cohabitation, 10 day maximum), then sacrificed. An additional group remained untreated. Females were either sacrificed on Day 21 of gestation (½) or allowed to deliver and wean their offspring.

Strain: Sprague Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 344120

2. Fo Data

a) Treatment-related clinical signs included injection site skin lesions and salivation in MD and HD males, and chromodacryorrhea, corneal opacity, ataxia, hypoactivity, and prostration in HD males. Convulsions were seen in 1 HD animal on the first day of treatment. Mechanical injuries, ie, damaged incisors, damage or swollen nose, palatine lesion, occurred only in HD rats, and were thus considered indirectly T-R.

b) Two HD animals died during treatment, on Days 11 and 12. In addition, 2 HD males were sacrificed after sustaining mechanical injuries.

c) T-R decreases in BW (10 and 30% in MD and HD, respectively), BW gain (26 and 92% in MD and HD, respectively), and food consumption were observed in MD and HD groups during the premating period.

d) Mean plasma phenytoin concentrations on Day 0 were 4.7, 18.6, and 37.3 ug/ml in LD, MD, and HD males, respectively. On Day 73, levels were 6.6, 20.9, and 44.9 ug/ml in the same respective groups.

f) All groups had lower than expected fertility indices, but there were no apparent relationship to treatment.

g) Histopathologic evaluation of the right testis on Day 91 revealed no drug-induced testicular changes. There were no significant group differences in testicular or accessory organ weights, epididymal sperm count or spermatid head count, percent motile sperm, or percent normal sperm morphology. Hemorrhage at the injection site was increased in all treatment groups relative to controls.

3. Term Sacrifice Parameters

a) A small increase in preimplantation loss was seen in HD group litters. The mean value (12.5%) was within the historical control range, however.

b) The incidence of stunted fetuses was increased in HD group litters. There were 7 fetuses (6 male) weighing <4 g in 4 HD litters vs 1 stunted fetus in both controls. The HD incidence of stunted fetuses was said to be within the historical control range, and group mean BWs were not different. In addition, 4 of the HD stunted fetuses were in 1 litter with 8 resorptions.

c) A statistically significant difference in fetal sex ratio occurred at the MD and HD compared to VC, and was outside the historical control range. However, the VC ratio was outside the range in the other direction. The ratio of males to females was 47:53, 56:44, 53:48, 43:57, and 44:56 for UC, VC, LD, MD, and HD groups, respectively. There were no other group differences in fetal developmental parameters.

4. Delivery and Offspring Developmental Parameters

a) There were no treatment-related effects on reproductive parameters in dams allowed to deliver (gestation length, uterine implants on Day 21 of lactation, viable pups). There were no group differences in offspring sex ratios at birth.

b) Offspring BWs during the lactation period were comparable among groups. Maturation (PN Weeks 3-13) BW was slightly decreased in HD group male offspring.

c) There were no other group differences in various measures of offspring development, including acquisition of developmental landmarks, rotorod performance, locomotor activity, emotionality, acoustic startle response, and shuttle box avoidance behavior.

B) SEGMENT I STUDY IN FEMALE RATS (RR 745-02092, Vol. 1.23)

1. Treatment

Female rats (40/grp) were dosed with 0 (vehicle), 25, 75, or 150 mg/kg, im, for 15 days prior to mating with untreated males, and throughout mating, gestation, and lactation. Half of females underwent C-section on Day 21 of gestation, while the remainder were allowed to deliver and wean their offspring.

Strain: Sprague-Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 344120

2. Fo Data

a) T-R clinical signs included hypoactivity, ataxia, prostration, salivation, chewing, alopecia, swelling of paw or nose, chromodacryorrhea, hypothermia, dyspnea, and eye changes, seen primarily in MD and HD animals. All HD animals exhibited signs of neurotoxicity.

b) Two HD females died and 3 were sacrificed moribund during the premating treatment period. One MD female was sacrificed moribund on Day 23 of gestation with treatment related dystocia.

c) BW and BW gain during the premating period were decreased in MD and HD females. Statistically significant weight loss of 15.5 g occurred in the HD rats compared to a mean gain of 12.6 g in VC. Most of the weight loss in both MD and HD animals occurred during the first 6 days of treatment. During the gestation period, BW gain was significantly decreased by 7 and 45% in the MD and HD groups, respectively. During lactation, weight gain in the HD females was 48% greater than in VC animals (NS).

d) Plasma phenytoin concentrations on Day 7 of gestation are shown in Table VI.1.

e) There was a D-R increase in the number of females with prolonged diestrus in the MD and HD groups, and an increase in the number of females with prolonged estrus (>2 consecutive days) at the HD. Five HD females were in constant diestrus during the treatment period and 13 were in diestrus on 15 of 16 days of treatment. All HD females had abnormal estrous cycles consisting of prolonged estrus, prolonged diestrus, or an estrous cycle length of 7 days. There was also a D-R decrease in the number of estrous cycles completed in MD and HD groups.

f) There were no effects of treatment on mating or fertility indices, but number of days to mating was increased (statistically significant) in the HD group (Table VI.2).

g) There was an increase in gross pathology findings of small thymus, injection site lesions, alopecia, and ocular abnormalities (chromodacryorrhea, enlargement, opacity, and/or lens prolapse) in F0 females at necropsy.

Table VI.1. Plasma Phenytoin Concentrations

Fosphenytoin Dose (mg/kg)	Cmax (ug/ml)	tmax (hr)	AUC (0-6, (ug*hr/ml)
25	5.80	1.0	17.6
75	18.7	1.0	64.5
150	38.0	1.0	189

Table VI.2. Fertility Data

	Female Fosphenytoin Dose (mg/kg)				
	0 (untreated)	0 (vehicle)	25	75	150
Mating Index (%)[1]	95.0	90.0	95.0	92.6	94.3
Fertility Index (%)[2]	94.7	88.9	92.1	91.9	90.9
No. days to mating	2.2 ± 0.18	2.4 ± 0.23	2.3 ± 0.22	2.6 ± 0.23	3.6 ± 0.37

[1] Mating Index = $\frac{\text{Number Copulated}}{\text{Total Cohabited}} \times 100$

[2] Fertility Index = $\frac{\text{Number Pregnant}}{\text{Number Copulated}} \times 100$

3. C-Section Data

a) Corpora lutea, implants, litter size, and live fetuses were decreased and % pre- and postimplantation loss were increased in the HD group (all but corpora lutea and preimplantation loss statistically significant compared to VC; Table VI.3). Fetal BWs were significantly decreased in MD (7% below VC) and HD (50% below VC) litters.

b) The overall malformation incidence and incidences of external/visceral malformations, external/visceral variations, and skeletal variations were increased in HD fetuses (Tables VI.4a and VI.4b). The percent of fetuses per litter and percent of litters with external/visceral malformations was 5-10 times those of concurrent and historical controls. These malformations included brain (missing occipital lobe and missing portion of temporal lobe, histologically decreased cerebral cortex size), cardiovascular, limb (ectrodactyly), and reproductive tract (hermaphrodite) defects. One LD fetus also had a brain malformation (microcephaly with dilated fourth ventricle and missing telencephalon). The effect on external/visceral variations was due to an increase in stunted fetuses; 100% of HD fetuses were stunted (BW <4.0 g). The number of stunted fetuses was also increased at the MD. Increased incidences rudimentary ribs and of hypoplastic and unossified bones in the skull, pelvis, and vertebral column were seen in HD

litters. In addition, misshapen, bifid, and dumbbell-shaped centra occurred more frequently in the MD and HD groups. Significantly decreased ossification was seen in MD and HD fetuses.

4. Delivery Data

a) Parturition was significantly delayed in the HD group. Five HD females delivered live litters on Day 24 of gestation and a sixth delivered 1 cannibalized pup on Day 24. Three HD and 1 VC females were sacrificed after failing to deliver by Day 24, and live pups were found in utero. One additional HD dam sacrificed on Day 24 had total litter resorption. One MD dam was sacrificed moribund during parturition, and 1 LD dam had retained placenta and fetuses at necropsy on Day 4 of lactation.

b) Implants, litter size, and number of live pups were significantly decreased and postimplantation loss significantly increased at the HD (Table VI.6).

c) Pup birth weights were decreased in HD litters. Postnatal BW gain through week 4 was decreased in MD and HD offspring.

d) Postnatal survival was decreased in HD offspring, especially in the neonatal period (survival 63% vs 96% in controls).

e) Clinical observations of chromodacryorrhea (9 pups in 5 litters) and circling (1 pup) were made only in HD offspring. Eye opening was significantly delayed in HD offspring. There were no group differences in external or visceral malformations among F1 neonates.

Table VI.3. Caesarean Section Data (group mean ± SE)

	Fosphenytoin Dose (mg/kg)				
	0 (untreated)	0 (vehicle)	25	75	150
Number of Litters	17	16	17	17	16
Corpora Lutea (no.)	16.6 ± 0.47	15.8 ± 0.46	16.1 ± 0.44	16.8 ± 0.62	14.8 ± 0.73
Uterine Implants	14.8 ± 0.88	14.6 ± 0.83	15.6 ± 0.43	15.4 ± 0.60	12.8 ± 0.79
Live Fetuses	13.7 ± 0.91	13.6 ± 0.88	14.6 ± 0.48	14.0 ± 0.76	10.0 ± 1.12
Resorption	1.1 ± 0.21	0.9 ± 0.27	1.0 ± 0.23	1.4 ± 0.41	2.8 ± 0.71
Litter Size	13.7 ± 0.91	13.6 ± 0.88	14.6 ± 0.48	14.0 ± 0.76	10.0 ± 1.12
Preimplantation Loss (%)	5.6 ± 1.58	8.8 ± 4.02	3.2 ± 1.12	8.2 ± 2.63	13.7 ± 3.58
Postimplantation Loss	12.1 ± 5.34	6.8 ± 2.14	6.5 ± 1.49	9.5 ± 2.64	23.5 ± 6.05
Fetal Body Weight (g)					
Male	5.1 ± 0.06	5.1 ± 0.08	5.1 ± 0.09	4.8 ± 0.11	2.6 ± 0.21
Female	4.8 ± 0.06	4.9 ± 0.08	4.9 ± 0.07	4.5 ± 0.12	2.4 ± 0.22

Table VI.4a. External and Visceral Findings in F1 Fetuses

	Dose (mg/kg)				
	untreated	vehicle	25	75	150
No. of fetuses examined	247	218	248	243	155
No. of litters examined	17	16	17	17	16
Malformed fetuses (litters)	1 (1)	1 (1)	3 (3)	0 (0)	6 (5)
Malformations					
Anophthalmia	1 (1)	-	-	-	-
Brain - malformed	-	-	1 (1)	-	1 (1)
Aortic arch - stenosis	-	-	1 (1)	-	-
- interrupted	-	-	-	-	1 (1)
- retroesophageal	-	-	-	-	1 (1)
Interventricular septal defect	-	-	-	-	1 (1)
Ectrodactyly	-	-	-	-	2 (1)
Hermaphrodite	-	-	-	-	1 (1)
Situs inversus	-	1 (1)	-	-	-
Tail - thread-like	-	-	1 (1)	-	-
Variations					
Brain - dilated ventricles, slight	1 (1)	-	-	-	-
Hematoma - ventral aspect	1 (1)	-	-	-	-
Kidney - dilated pelvis	2 (2)	2 (2)	11 (6)	5 (3)	-
- reduced papilla & dilated pelvis	1 (1)	7 (3)	4 (2)	2 (1)	1 (1)
Liver - lobulated lobe	-	1 (1)	-	-	-
Stunted (<4.0 g)	7 (6)	2 (2)	5 (3)	25 (6)	155 (16)
Ureter - dilated	5 (5)	8 (4)	19 (7)	7 (3)	4 (3)

Table VI.4b. Skeletal Findings in F1 Fetuses

	Dose (mg/kg)				
	untreated	vehicle	25	75	150
No. of fetuses examined	171	149	173	152	105
No. of litters examined	17	16	17	16	15
Malformed fetuses (litters)	3 (2)	0 (0)	1 (1)	1 (1)	3 (2)
Malformations					
Digits					
- ectrodactyly	-	-	-	-	2 (1)
Ribs					
- malformed	-	-	-	1 (1)	-
- agenesis	-	-	-	-	1 (1)
Vertebral column					
- 1 less presacral vertebrae	3 (2)	-	1 (1)	-	2 (2)
- agenesis	-	-	1 (1)	-	-
- malformed	-	-	1 (1)	-	-
Variations					
Limbs					
- calcaneus ossified	7 (4)	2 (1)	6 (3)	-	-
Pelvic girdle					
- unossified	-	-	-	-	20 (7)
- hypoplastic	-	-	-	-	9 (4)
Ribs					
- wavy	-	1 (1)	-	-	-
- short last	3 (2)	4 (4)	5 (2)	8 (4)	5 (4)
- extra rudimentary	3 (1)	2 (1)	6 (3)	3 (3)	12 (5)
- extra cervical	2 (2)	3 (3)	5 (2)	1 (1)	1 (1)
Skull					
- hypoplastic	-	2 (1)	1 (1)	-	24 (7)
- unossified	2 (2)	-	-	-	10 (5)
Sternum					
- asymmetric	-	1 (1)	1 (1)	-	-
Vertebral column					
- extra presacral vertebrae	1 (1)	-	-	1 (1)	1 (1)
- misshapen centra	2 (2)	3 (2)	3 (3)	13 (9)	8 (4)
- bifid centra	2 (2)	2 (2)	2 (1)	8 (4)	12 (6)
- hypoplastic arches	-	-	-	-	20 (6)
- figure 8-shaped centra	-	2 (2)	1 (1)	4 (3)	4 (4)
- unossified ventral tubercle	29 (12)	22 (10)	16 (6)	25 (6)	63 (14)
- caudal/sacral vertebrae unossified	-	-	-	-	27 (7)

Table VI.5: F0 Dam Delivery - Maternal and Litter Parameters[a]

Treatment	Untreated	Vehicle	Fosphenytoin (mg/kg)		
Dose	—	0	25	75	150
Gestation duration (days)	22.2 ± 0.10	22.1 ± 0.07	22.1 ± 0.06	22.3 ± 0.11	23.6 ± 0.22
No. females in subgroup	20	20	20	20	18
No. gravid	18	16	18	17	14
No. nongravid	2	4	2	3	4
No. w/ total resorption	0	0	0	0	1
No. sacrificed GD 24	0	1	0	0	3
No. sacrificed moribund	0	0	0	1	0
No. w/ viable litters	18	15	17[b]	16	10
Liveborn	14.4 ± 0.54	14.1 ± 0.67	14.0 ± 0.36	12.8 ± 0.92	8.9 ± 1.51
Stillborn/dead Day 0	0.4 ± 0.14	0.3 ± 0.15	0.2 ± 0.13	0.4 ± 0.18	0.5 ± 0.27
Litter size	14.8 ± 0.51	14.4 ± 0.67	14.2 ± 0.38	14.1 ± 0.97	9.4 ± 1.51
Implant sites	16.3 ± 0.57	15.0 ± 0.73	15.6 ± 0.29	15.0 ± 0.98	11.9 ± 1.35
Postimplantation loss (%)	11.3 ± 2.77	5.3 ± 1.82	9.5 ± 1.85	7.8 ± 1.65	28.6 ± 9.22

[a] Group mean ± SE, where applicable.
[b] Excludes 1 animal that delivered live pups and retained fetuses in utero.

C) INTRAVENOUS TERATOLOGY STUDY OF FOSPHENYTOIN IN RATS (RR 745-01973, Vols. 1.25-26).

1. Treatment

Pregnant rats (40/group) were treated with 0 (vehicle), 10, 50, or 100 mg/kg, iv, on gestation Days 7 through 17. An untreated control group (N=40) was evaluated concurrently. C-sections were performed on 25/group on Day 21; the remaining 15/group were allowed to deliver and rear offspring. At weaning, 1/sex//litter were retained for behavioral evaluation, and 1/sex/litter were retained for evaluation of reproductive performance.

Strain: Sprague Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 344120

2. F0 Effects:

a) T-R clinical signs, including salivation, chewing motions, hypoactivity, ataxia, and limb rigidity, were noted in HD dams. Salivation was also seen in MD dams.
b) Four HD dams died during treatment (2 dosing accidents, 2 possibly T-R) and another was euthanized due to broken limbs.
c) Gestational BW gain was decreased during (38%) and following (18%) treatment in the HD group.

3. Maternal plasma levels

Mean plasma phenytoin concentrations measured 1 hr postdose (ie, not peak) on gestation Day 17 increased approximately dose-proportionally (Table VI.6). One sample from a vehicle control had measurable phenytoin levels, for unknown reasons.

Table VI.6: Maternal Plasma Drug Levels

Treatment	Vehicle	Fosphenytoin		
Dose (mg/kg)	0	10	50	100
No. Dams	5	5	4	5
Phenytoin concentration (ug/ml)*	0.26 ± 0.55	4.10 ± 0.56	24.0 ± 1.62	43.3 ± 6.27

*Mean ± SE; samples taken about 1 hr postdose on gestation Day 17

4. C-Section Data

Term fetuses were examined for external and palatine abnormalities. All fetuses were then examined by fresh dissection for visceral abnormalities, and skeletal examinations were performed on 2/3 of the fetuses from each litter. The heads of the other 1/3 were fixed and examined for abnormalities.

a) Postimplantation loss was increased about 2-fold in HD dams compared to concurrent and historical controls.
b) Mean fetal BW was decreased (30% below VC) in the HD group.
c) Increased incidences of skeletal malformations (slight; primarily hemicentra), external/visceral variations, and skeletal variations were seen in HD litters (Table VI.7). The increase in variations was due to a marked increase in growth retarded fetuses in HD litters; 60% of HD fetuses were stunted (BW <4 g).

5. Delivery Data

a) The duration of gestation was significantly increased in the HD group.
b) Postimplantation loss was slightly increased at the MD and HD (Table VI.8).
c) Birth weights were significantly decreased (10%) in HD males and females. Weight gain was comparable among groups during lactation, but weight gain from week 3 through 13 and mean weights at week 13 were decreased in all treated male offspring (5, 6, and 15% less than VC, all statistically significant) and in HD female offspring (7%, NS).
d) Vaginal opening was delayed in MD and HD female pups.
e) Two littermates in the HD group exhibited abnormal circling behavior, and 27 pups from 8 HD litters and 1 MD pup had chromodacryorrhea. Both have previously been associated with prenatal phenytoin exposure. One of the HD circlers later died (P 23).
f) Locomotor activity was increased in HD males on P 42; however, this was due to the increased activity of a single HD pup. No group differences were found in acoustic startle parameters on P 43 or in shuttle avoidance parameters during week 9.
g) Reproductive parameters were comparable among F1 groups.

Table VI.7: Incidence of Fetal Malformations and Variations

Treatment	Untreated	Vehicle	Fosphenytoin		
Dose (mg/kg)	---	0	10	50	100
No. fetuses/litters examined	326/24	298/23	323/25	337/24	244/20
No. fetuses/litters with malformations	2/2	2/2	1/1	3/3	6/5
Percent fetuses per litter with:[a]					
Ext/visc malformations	0.6 ± 0.43	0.6 ± 0.40	0.3 ± 0.31	0.3 ± 0.30	0.7 ± 0.50
Skeletal malformations	0.9 ± 0.61	0.9 ± 0.60	0	0.8 ± 0.55	2.9 ± 1.39
Ext/visc variations	6.3 ± 1.85	10.7 ± 3.13	5.4 ± 1.74	3.7 ± 1.18	68.8 ± 7.79
Skeletal variations	29.0 ± 5.86	21.0 ± 4.02	24.5 ± 3.44	24.0 ± 4.28	54.2 ± 7.25
Percent litters with:[b]					
Ext/visc malformations	8.3	8.7	4.0	4.2	10.0
Skeletal malformations	8.3	8.7	0	8.3	20.0
Ext/visc variations	41.7	52.2	44.0	37.5	90.0
Skeletal variations	70.8	69.6	88.0	91.7	95.0

[a] Mean ± SE
[b] Group mean

Table VI.8: F0 Dam Delivery - Maternal and Litter Parameters[a]

Treatment	Untreated	Vehicle	Fosphenytoin		
Dose	---	0	10	50	100
No. delivered:					
Day 20	0	1	0	0	0
Day 21	2	0	2	0	0
Day 22	12	12	12	13	8
Day 23	0	0	0	1	6
Gestation duration	21.9 ± 0.10	21.8 ± 0.15	21.9 ± 0.10	22.1 ± 0.07	22.4±0.14
No. females in subgroup	15	15	15	15	15
No. gravid	14	15	15	14	15[b]
No. nongravid	1	0	0	1	0
No. w/ implants only	0	1	1	0	0
No. w/ viable litters	14	13[c]	14	14[d]	14[d]
Liveborn	13.8 ± 0.35	13.4 ± 0.21	13.9 ± 0.42	12.1 ± 0.94	12.4±0.66
Stillborn/dead Day 0	0.1 ± 0.07	0.2 ± 0.12	0.4 ± 0.14	0.6 ± 0.29	0.5±0.23
Litter size	13.9 ± 0.35	13.6 ± 0.27	14.3 ± 0.45	12.7 ± 0.93	12.9±0.70
Implant sites	15.1 ± 0.32	13.9 ± 0.97	14.2 ± 1.03	14.4 ± 0.98	14.1±0.69
Postimplantation loss (%)	8.4 ± 1.89	9.0 ± 1.51	8.3 ± 1.56	13.8 ± 4.50	13.0±2.50

[a] Mean ± SE, where applicable
[b] Includes 1 animal that died during treatment
[c] Excludes 1 dam unable to deliver, sacrificed on Day 24; 1 fetus in uterus
[d] Includes 1 dam with litter size <8; excluded from group mean calculations

D) INTRAVENOUS TERATOLOGY STUDY IN RABBITS (RR 745-01931, Vol. 1.27).

1. Treatment

Pregnant rabbits (20/group) were treated with 0 (vehicle), 10, 25, or 50 mg/kg, iv, on gestation Days 6 through 18. An untreated control group (N=20) was evaluated concurrently. C-sections were performed on Day 30 of gestation.

Strain: New Zealand White
Drug lot #: CM 345120

2. FO Effects:

a) Chewing signs during or after dosing were observed in MD and HD animals. Additional signs that occurred daily during treatment in 1 or 2 HD does included ataxia, limb rigidity, and shallow rapid breathing.
b) None of the treated or control animals died during the study.
c) D-R suppression of food consumption and BW gain was evident during the treatment period in MD and HD does (statistically significant at HD). BW gain was significantly increased in HD does during the postdosing period.
d) Mean plasma phenytoin concentrations measured 1 hr postdose on gestation day 18 increased approximately dose-proportionally (Table VI.9). HD levels were 1.5-3.5 times the generally accepted range of therapeutic concentrations (10-20 ug/ml).

Table VI.9: Maternal Plasma Drug Levels

Treatment	Vehicle	Fosphenytoin		
Dose (mg/kg)	0	10	25	50
No. pregnant animals	5	5	4	4
Phenytoin concentration (ug/ml)*	0	7.1 ± 1.3	17.5 ± 1.3	35.0 ± 1.5
No. nonpregnant	0	0	1	1
Phenytoin concentration (ug/ml)	0	0	22.1	39.2

* Mean ± SE; samples taken about 1 hr postdose on gestation Day 18

3. Reproductive and Fetal Parameters

a) None of the animals aborted, delivered early, or had total resorption.
b) The numbers of corpora lutea, implantation sites, live, dead, and resorbed fetuses were comparable across groups. Pre- and postimplantation loss were not affected by treatment.
c) Fetal weights were slightly decreased at the HD.

4. Fetal Evaluation

There were no group differences for external, visceral, and skeletal malformations or variations.

E) PERINATAL-POSTNATAL STUDY IN RATS (RR 745-02071, Vol. 1.28).

1. Treatment

Female rats (25/group) were treated with 0 (vehicle), 25, 50, or 100 mg/kg, iv, from Day 15 of pregnancy through Day 20 postpartum. An untreated control group was also included. The dams were allowed to deliver and rear offspring. F1 offspring were evaluated for survival, clinical appearance, growth, behavior, and reproductive performance.

Strain: Sprague Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 345120

2. F0 Effects:

a) Clinical signs observed with increased frequency in treated females (primarily at HD) included excessive chewing motion, salivation, hypoactivity, ataxia, and prostration
b) One MD and 9 HD dams died or were sacrificed moribund during dosing, all apparently as a result of treatment. One VC dam died of unknown causes.
c) Maternal BW gain during the gestational treatment period was significantly decreased (-19%) by the HD. Weight gain during the first 2 weeks of lactation was also suppressed at the HD (-20-30%), but overall lactational weight gain was comparable among groups. Food consumption was decreased during the entire treatment period in HD dams.
d) Mean plasma phenytoin concentration determined 1 hr after dosing on the last day of treatment (PND 20) were 6.67, 12.7, and 29.2 ug/ml in LD, MD, and HD groups, respectively.

3. Parturition (Table VI.10)

a) One MD and 5 HD dams died around the time of parturition (GD 22-23). All were found to have fetuses in utero, and all dead HD dams had resorptions.
b) A statistically significant increase in the duration of gestation was seen in the MD and HD groups compared to vehicle controls.
c) The number of stillborn pups or pups that died on postnatal Day 0 and the percent postimplantation loss were increased in all treatment groups relative to VC; the increase in stillbirth was statistically significant at the HD. At the LD, this finding was due to 1 litter with 17 dead pups.

Table VI.10: F0 Dam Delivery : Maternal and Litter Parameters[a]

Treatment	Untreated	Vehicle	Fosphenytoin		
Dose	---	0	10	50	100
No. delivered:					
Day 21	2	0	1	0	0
Day 22	15	21	15	12	3
Day 23	5	1	6	10	15
Day 24	0	0	0	0	1
Gestation duration[a]	22.1 ± 0.12	22.0 ± 0.05	22.2 ± 0.11	22.5 ± 0.11	22.9 ± 0.11
No. mated females	25	25	25	25	25
No. gravid	22	24	22	23	24
No. nongravid	3	1	3	2	1
No. dying/sacrificed prior to delivery	0	1	0	1	5
No. dying postpartum	0	0	0	0	4
No. of viable litters	22	22	22	22	19
No. with total dead litters	0	0	1	0	0
No. with total resorption	0	1	1	0	0
Liveborn[a]	14.2 ± 0.65	15.3 ± 0.41	13.6 ± 0.87	14.6 ± 0.62	13.8 ± 0.92
Stillborn/dead Day 0	0.2 ± 0.15	0.2 ± 0.08	1.0 ± 0.78	1.0 ± 0.48	1.4 ± 0.72
Litter size	14.5 ± 0.65	15.5 ± 0.41	14.5 ± 0.59	15.5 ± 0.43	15.2 ± 0.59
Implant sites	15.6 ± 0.70	16.7 ± 0.38	15.6 ± 0.56	17.2 ± 0.28	16.4 ± 0.62
Postimplantation loss (%)	8.6 ± 1.55	9.0 ± 1.62	12.6 ± 4.55	14.3 ± 3.38	15.8 ± 4.55

[a] Mean ± SE

4 F1 Neonatal and Weanling Parameters

a) Survival at birth was decreased in all treatment groups, and was statistically significant at the HD. Subsequent survival was not affected by treatment.

b) Offspring BW at birth and postnatal weight gain through weaning were decreased (10% compared to VC; statistically significant) in HD males and females. This effect on pup BW at the HD persisted into the maturation period (below).

c) Several developmental landmarks (pinnae detachment, lower incisor eruption, and testes descent) appeared significantly earlier in treatment groups than in controls. This can be attributed to their increased time of in utero development. There were no group differences for eye opening and vaginal opening. All pups responded positively to the visual placement test on PND 21.

d) In external and visceral examinations performed on stillborn, dead, and pups sacrificed at weaning, malformation were found in 1 untreated control pup (patent ductus arteriosus) and 2 HD pups (unilateral forepaw brachydactyly; microphthalmia, microstomia, short tail, and malformed nose).

e) Structural variations of the ureter and kidney were increased in MD and HD litters compared to C. At the MD, almost all observations came from 1 litter. In the HD group, findings were primarily from 2 litters. All kidney/ureter variations were observed in pups from dams that died during late gestation.

5. F1 Offspring Behavior

a) Rotorod performance was comparable among groups.

b) Treated male offspring were different (NS) from controls on several measures of activity on PND 42: total distance traveled during minute 2 was increased by 13% in LD and MD males and by 41% in HD males and was elevated by 21%, 27%, and 32% during minute 3 in the LD, MD, and HD groups, respectively; average speed was elevated 14-20% at the HD for minutes 2-4, relative to VC; vertical movements during minute 3 were increased 29, 19, and 40% in LD, MD, and HD males, respectively; vertical time was increased 33 and 70% during minute 2 in MD and HD males, respectively, and during minute 3 was elevated 41, 39, and 52% in LD, MD, and HD males, respectively; and the amount of time spent in the center of the open field was 38% less in HD males. Increased activity has been reported previously in rats prenatally exposed to phenytoin.

c) Results of acoustic startle testing on PND 43 indicated no T-R differences in startle response.

d) Increases (NS) in shuttle box avoidance responding, recall testing, and number of crossing were observed in MD and HD males relative to VC during postnatal Week 9, presumably secondary to hyperactivity.

6. F1 Offspring Maturation Parameters

a) Weight gain over PN weeks 3-13 and BW at 13 weeks were decreased (5-10%) in HD males (significant) and females (NS).

b) Reproductive performance of F1 animals was comparable among groups. Although corpora lutea were slightly decreased in HD females at term, the value was within the historical control range. An increased incidence of stunted fetuses was found in litters born to HD group F1 females at term sacrifice, but the number of affected litters was the same as in the control group.

VII. SUMMARY

PHARMACODYNAMICS

In the initial pharmacological evaluation by NINDS fosphenytoin showed good anticonvulsant activity in the MES test but, as expected, was not active in the scMET test. Activity against MES-induced seizures was equivalent to that of phenytoin after ip and oral administration (Table I.1). Fosphenytoin displayed slightly greater toxicity (Rotorod TD50) after ip administration, possibly due to more rapid absorption. The anticonvulsant potency of fosphenytoin against MES-induced seizures in mice was not significantly different than that of phenytoin either 10 or 30 minutes after iv dosing, and the time courses of anticonvulsant action were comparable for the two drugs (Tables I.1 and I.2).

The ability of fosphenytoin to reverse cardiac glycoside-induced arrhythmias in intact dogs was similar to that of phenytoin when the two drugs were administered intravenously, although phenytoin restored normal rhythm marginally faster. In an *in vitro* preparation, it was determined that the prodrug had no inherent antiarrhythmic effect.

In a study comparing the hemodynamic effects of iv infusion of equimolar amounts of fosphenytoin or phenytoin to anesthetized dogs, both drugs produced marked reductions in blood pressure, heart rate, and left ventricular contractility. When equimolar doses of the two drugs were rapidly infused (40 mg/kg PE over 2 min), changes in CV parameters were similar but somewhat more pronounced after fosphenytoin than after phenytoin. The onset of action was slightly delayed by fosphenytoin administration, and CV effects appeared to correlate with plasma phenytoin levels (Figures I.1-3). When lower equimolar doses (21 mg/kg PE) of fosphenytoin or phenytoin were infused over 15-30 min, the maximum effects (reductions in diastolic BP and contractility) were comparable and were observed at similar plasma levels of phenytoin (Figures I.4-6). The maximum effects of fosphenytoin appeared to be primarily determined by the total dose rather than the rate of administration. At times when plasma levels of both fosphenytoin and phenytoin (formed from fosphenytoin) were high, effects were not greater than those seen at comparable levels of phenytoin alone; therefore, it did not appear that fosphenytoin had any significant hemodynamic effects of its own *in vivo* under the conditions of this study. However, under *in vitro* conditions in which less than 1% of phenytoin was present, fosphenytoin (EC50=43 ug/ml) had a cardiac depressant effect similar to that of phenytoin (EC50=27 ug/ml) in guinea pig left atrial preparations (Figure I.7). No such intrinsic activity of fosphenytoin was seen in guinea pig right atria.

Fosphenytoin was shown to reduce brain damage in several models of ischemic stroke, but did not protect against NMDA-induced brain damage.

ADME

Absorption and Pharmacokinetics

Single-dose studies were performed in rats and dogs to compare fosphenytoin and phenytoin pharmacokinetics following im and iv administration. Peak blood levels of phenytoin were greater (5-fold) following im administration of fosphenytoin (115-500 mg/kg) to rats than after im administration of phenytoin (equimolar), indicating that prodrug administration significantly enhanced phenytoin bioavailability.

After an iv dose of 14.8 mg/kg of fosphenytoin (equivalent to 10 mg/kg of phenytoin) to dogs, fosphenytoin t1/2, Vd, and AUC values averaged 2.6 min, 150 ml/kg, and 255 ug·min/ml, respectively. The Cl of 40.2 ml/min/kg approximated hepatic blood flow, which would be consistent with metabolism to phenytoin by phosphatases in kidney and liver. Fosphenytoin was not detected in blood at 30 min postdose. Peak phenytoin levels (mean 6.98 ug/ml) were reached at 3.3 min, with the formation t1/2 averaging 0.42 min. During the first 30 min after administration of phenytoin, phenytoin levels were higher than after administration of fosphenytoin, but thereafter, levels were similar. The elimination t1/2, Cl, Vd, and AUC of phenytoin were not significantly different after iv administration of fosphenytoin or phenytoin sodium (Table II.1). The bioavailability of phenytoin after iv fosphenytoin administration averaged 97%. The metabolic elimination pattern was not

different after iv prodrug, with the m-HPPH glucuronide constituting the major urinary metabolite and accounting for approximately the same % of the dose (55%) after administration of either drug.

After im administration of fosphenytoin (14.8 mg/kg), fosphenytoin levels reached a mean peak of 20.4 ug/ml at 10 min (Table II.3), then rapidly decreased such that fosphenytoin was not detectable in plasma after 120 min. The absorption and elimination t1/2 values averaged 3.2 and 17.4 min, respectively. The appearance of phenytoin in the plasma was fairly rapid after im administration of fosphenytoin. The formation t1/2, Cmax, and tmax for were 24.7 min, 6.8 ug/ml, and 76.9 min, respectively (Table II.2). The corresponding values after im administration of an equimolar dose of phenytoin were 17.4 min, 2.16 ug/ml, and 68.1 min for the absorption t1/2, Cmax, and tmax, respectively. The elimination t1/2 and apparent volume of distribution of phenytoin after fosphenytoin administration averaged 164 min and 1058 ml/kg, respectively, which were significantly different than corresponding values of 369 min and 4086 ml/kg, respectively, obtained after im phenytoin. These results are consistent with precipitation of phenytoin at the injection site, with slow release into the circulation. The AUC values obtained after administration of phenytoin were substantially lower than phenytoin AUCs after fosphenytoin, indicating that the bioavailability of phenytoin administered as fosphenytoin was increased compared to phenytoin sodium after im administration. Fosphenytoin was completely absorbed after im administration of a dose of 14.8 mg/kg (10 mg/kg PE) to dogs (Table II.3).

The exposure to phenytoin following im administration of fosphenytoin (14.8 mg/kg) to dogs was essentially the same as that after iv administration of the prodrug (Table II.4). Although the rate of conversion to phenytoin was slower after im than iv fosphenytoin, and time to peak plasma phenytoin level was longer, other phenytoin parameters (Cmax, elimination t1/2, Vd, Cl, and AUC) were equivalent.

Protein Binding

In vitro binding of [14C]-fosphenytoin to dog and human plasma proteins was assessed by ultrafiltration. Binding of 20 ug/ml to dog and human plasma proteins averaged 91.3% and 95.7%, respectively. Albumin accounted for 88% of the fosphenytoin binding to human plasma proteins. Phenytoin binding decreased with increasing fosphenytoin concentrations. At a DPH concentration of 5 ug/ml, the free fraction of phenytoin increased from 4 to 18% when the fosphenytoin concentrations increased from 7.5 to 500 ug/ml. These results indicate that at high concentrations, fosphenytoin may enhance the pharmacological or toxicological effects of phenytoin by displacing DPH from its binding sites.

Drugs highly bound to albumin, such as phenylbutazone, sulfisoxazole, or warfarin, can displace fosphenytoin from binding sites on albumin. When toxic concentrations of AEDs such as PHB, DPH, or VPA were added to plasma, the drugs significantly increased (5-20%) the free fraction of fosphenytoin. Diazepam, phenytoin, and carbamazepine at a concentration of <10 ug/ml did not change the free fraction of fosphenytoin. Since fosphenytoin has little intrinsic pharmacological effect, the changes in free fraction should have no clinical significance. Addition of fosphenytoin at equimolar concentrations to carbamazepine, phenobarbital, or VPA resulted in small but significant displacement of these drugs from its plasma binding sites. The degree of displacement of diazepam or carbamazepine was not enhanced by increasing the concentration of fosphenytoin 30-60-fold. The slight increase in free fraction of these drugs caused by fosphenytoin is unlikely to have clinical significance.

In Vitro Hydrolysis

The *in vitro* hydrolysis of fosphenytoin to phenytoin was examined in tissues and whole blood from rats and dogs and in human whole blood. Rat whole blood and tissue hydrolyzed fosphenytoin rapidly, with kidneys, small intestine, and liver exhibiting the highest phosphatase activity. Dog and human whole blood hydrolyzed the drug much more slowly. Mean *in vitro* half-lives of fosphenytoin in rat, dog, and human whole blood were 5.69, 321, and 189 minutes, respectively. Faster prodrug conversion was observed in dog tissue homogenates, with the small intestine, kidney, and liver again the most active in mediating hydrolysis of the prodrug. Studies with partially purified enzymes revealed that fosphenytoin was a better substrate for alkaline phosphatase than for acid phosphatase. Despite the presence of alkaline phosphatase activity in plasma, in

vitro hydrolysis of fosphenytoin was slow in dog and human blood compared to in vivo conversion. There was no explanation for the discrepancy between *in vitro* and *in vivo* fosphenytoin conversion times.

IM Injection Site Accumulation

Potential accumulation of phenytoin in dog hindlimb muscles was assessed following single- and multiple-dose (BID) im administration of 14C-fosphenytoin (10 mg/kg) and 3H-phenytoin (10 mg/kg). At 8 hr following simultaneous single-dose administration, phenytoin concentrations at the injection site were 150-fold greater in the hindlimb injected with phenytoin compared to the limb injected with fosphenytoin. The difference increased to 2500-fold following repeated administration, indicating increased accumulation of precipitated phenytoin at the injection site. Although im phenytoin consistently resulted in edematous swelling at the injection site, im fosphenytoin did not precipitate or cause tissue damage following single or multiple-dose administration.

Distribution, Metabolism, and Elimination

Following iv bolus administration of 14C-fosphenytoin (10 mg/kg; label on hydantoin ring), both tissue distribution and elimination were rapid. Highest levels of radioactivity in blood, heart, kidneys, liver, lung, and spleen were measured within 5 min postdose. Highest brain levels (0.2% of dose) occurred at 10-60 min. Three radioactive peaks were identified as p-HPPH glucuronide, p-HPPH, and phenytoin. Elimination t1/2's for phenytoin ranged from 50-90 min in blood and various tissues. At 48 hr postdose, >98% of the administered radioactivity was eliminated, demonstrating that fosphenytoin and/or its metabolites were not retained.

After administration of 14C-fosphenytoin to rats, recovery of radioactivity from urine and feces over 72 hr averaged 52 and 48%, respectively. Mean cumulative urinary and fecal recovery was 99%. p-HPPH glucuronide accounted for >40% of dose recovered from urine and feces over the 0- to 24-hr collection interval.

Urine and feces (rat only) were collected for metabolite profiling following administration of 14C-fosphenytoin to rats and unlabeled fosphenytoin and phenytoin to dogs. Phenytoin, p-HPPH, and p-HPPH glucuronide were urinary metabolites common to both species. p-HPPH glucuronide (33.9%) was the major metabolite in rat urine, whereas m-HPPH glucuronide (51-58%) was the major metabolite in dog urine. Rodent fecal samples contained only p-HPPH (21.6%), p-HPPH glucuronide (8.3%), and an unidentified metabolite (10.2%). The metabolism and excretion profiles of fosphenytoin and phenytoin were the same following iv administration to dogs.

Toxicokinetics

Toxicokinetic studies in rats showed that the rate of phenytoin appearance in plasma was decreased following im administration relative to iv administration of a single 150 mg/kg dose of fosphenytoin (tmax values 10-15X greater), peak phenytoin levels were reduced (50-60%) after im administration, there was a sex differences in phenytoin clearance (elimination t1/2 4-7.5-fold longer in females), and total phenytoin exposure (AUC) was similar within sex following im or iv administration of the same dose (Table II.6). Fosphenytoin levels were not determined.

Phenytoin kinetics determined after single im or iv doses of 50 mg/kg fosphenytoin to dogs (Table II.6) were fairly comparable. Although tmax values following im fosphenytoin were longer than those following iv fosphenytoin (1.2 hr for im versus 0.6 hr for iv), Cmax values (21.3 ug/ml for im versus 26.8 for iv) and plasma phenytoin concentration-time profiles (im and iv AUC values of 159 and 163 ug hr/ml, respectively) were similar for both routes. Mean elimination t1/2 values were essentially the same following im (2.8 hr) and iv (3 hr) administration. There was no sex difference in pharmacokinetics in dogs. Fosphenytoin levels were not determined.

Thus, rate of phenytoin appearance in plasma was decreased following im fosphenytoin administration relative to iv administration, but total phenytoin exposures as determined by AUC data were similar in rats and dogs following im and iv fosphenytoin. Relative fosphenytoin exposures were not determined.

TOXICOLOGY

Acute toxicity

Acute iv toxicity studies were conducted in mice, rats, rabbits, and dogs (**Table III.1**). The median lethal doses of fosphenytoin and phenytoin in mice and rats were essentially equivalent when both drugs were administered by iv infusion, with values ranging from approximately 150-350 mg/kg. Phenytoin was more potent than fosphenytoin when the drugs were administered as an iv bolus, probably due to a more gradual rise in peak phenytoin levels with the prodrug. Similar CNS-related signs were observed after iv injection of fosphenytoin or phenytoin in both rodents and non-rodents and included ataxia, hypoactivity, prostration, and convulsions. In addition, salivation and vomiting were seen in dogs, and tremors and dyspnea occurred in rodents. The MLD's of iv fosphenytoin and phenytoin in weanling rats were the same as in adults; however, neonatal rats were more sensitive to the toxic effects of both drugs than weanling rats following ip administration. After im administration, fosphenytoin induced clinical signs, convulsions, and/or deaths in rats and dogs at lower doses than phenytoin due to increased absorption and higher blood concentrations achieved by this route (**Table III.2**). Gross pathologic changes were not observed in acute studies with fosphenytoin, while tissue necrosis at im injection sites in rats and dogs was observed with phenytoin.

Multidose toxicity

Rat

A 4-week rat study (10/sex/group main study, 5/sex/group recovery, 3/sex/group PK) was conduced with iv (bolus) doses of 0 (vehicle), 30, 60, and 150 mg/kg of fosphenytoin. T-R clinical signs were seen primarily in MD and HD animals and consisted of ataxia, hypoactivity, salivation, and dyspnea. BW gain during the dosing period was decreased (32%) in HD males compared to controls. Erythrocyte parameters (RBC, HGB, HCT) were slightly decreased and MCHC was increased in HD females compared to controls. ALT and ALP were increased by about 50% in HD males and females at week 4. Liver weights were increased in females at all doses, and periportal vacuolization was observed microscopically in HD males and females. Liver changes were not seen following a 4 week recovery period. The increased liver weights and enzyme activities presumably reflected the induction of hepatic microsomal drug metabolizing enzymes, which is a well recognized effect of phenytoin in animals and humans. The increased periportal vacuolization in HD rats was shown by EM to be mainly due to the presence of larger areas of glycogen deposition than in controls. Reversible injection site irritation was seen at all doses (D-R). Plasma phenytoin levels 15 min after dosing during week 2 were proportional to dose and similar in males and females; mean concentrations ranged from 9.1 at the LD to 52.8 ug/ml in the HD group (**Table III.3**).

A 13 week rat study (10/sex/group main study, 5/sex/group PK) was conducted with im doses of 0 (saline), 30, 60, or 150 mg/kg of fosphenytoin. A group receiving phenytoin (100 mg/kg, equimolar to HD) served as a positive control (PC). Hypoactivity, ataxia, and salivation were observed in both the HD and PC groups. In addition, autocanibalism of the hindlimbs was seen in phenytoin-treated rats. T-R deaths occurred only in the HD (2/15 M, 1/15 F) and PC groups (8/15 M, 10/15 F). There were no hematologic effects related to fosphenytoin treatment. AST, ALT, and ALP levels were elevated in HD males and females, while only slight increases in ALP were seen in the PC group. Increased plasma glucose levels (2 hr after dosing) and glucosuria were observed in the HD and PC groups. Liver weights were increased in the MD (females) and HD groups, and thymus weights were decreased in HD animals. Injection site lesions were observed in fosphenytoin- and phenytoin-treated animals (D-R in fosphenytoin groups). Intracytoplasmic hepatocyte vacuolization was seen in the HD group (8/10 M, 9/10 F) and single cell hepatocyte necrosis was observed in PC animals (3/10 M, 3/10 F). Decreases in thymus weights in HD animals correlated with histologic evidence of lymphoid depletion. Plasma phenytoin levels were 3-4 times higher following HD fosphenytoin

administration than after phenytoin injection by the im route; concentrations ranged from 46.7 to 48.9 ug/ml after the HD of fosphenytoin and from 15.2 to 23.8 ug/ml after an equimolar dose of phenytoin (**Table III.4**).

Dogs

Four groups of dogs (3/sex/group main study, 1/sex/group recovery) were given iv bolus doses of fosphenytoin at 0 (vehicle), 15, 30, or 60 mg/kg for 4 weeks. Clinical signs were observed with a D-R incidence in treated dogs and consisted of emesis, diarrhea, salivation, erythema of the gums, hypoactivity, ataxia, mydriasis, and tremors (HD only). No deaths occurred. There were no significant T-R effects on weight gain or food consumption. Hematological parameters were comparable among groups. Serum ALP was elevated about 2-fold in HD dogs compared to C at 4 weeks and after a 4-week recovery period. Increased salivary gland weights and hypertrophy of mandibular and parotid salivary gland acini were noted in HD dogs. There was a trend toward increased liver weights in MD and HD animals, but no apparent histological correlate. Small (10%) increases in absolute and relative heart weights were seen in MD and HD males, but no pathology was seen upon microscopic examination. No differences in the incidence or severity of injection site alterations were noted between vehicle controls and treated groups. Plasma phenytoin levels 30 after dosing during week 2 increased approximately dose-proportionately and were similar between sexes; mean concentrations ranged from 6.6 at the LD to 23.7 ug/ml in the HD group (**Table III.5**).

Fosphenytoin was administered im to 5 groups of dogs (4/sex/group) at dose levels of 15, 30, and 60 mg/kg/day for 13 weeks. A negative control group was administered saline, and a positive control group received phenytoin sodium (40 mg/kg, equimolar to HD). Ataxia, decreased activity, and mucoid diarrhea were observed in the HD group, and emesis and ptyalism were seen in all fosphenytoin-treated dogs in a dose-related manner. Ataxia, emesis, and diarrhea were observed in the phenytoin group, with incidences intermediate between that seen in the MD and HD fosphenytoin groups. Both phenytoin and fosphenytoin groups exhibited swelling at the injection sites. All animals survived to termination. BW gain was increased in male fosphenytoin-treated dogs and decreased in phenytoin group males and females compared to saline controls. No changes in hematologic values were noted in the analysis of blood samples. However, one HD fosphenytoin female had an elevated myeloid/erythroid ratio (M/E = 6.1) in the bone marrow smear performed post mortem, indicating depressed erythrogenesis. Alkaline phosphatase and creatine phosphokinase levels were moderately elevated in MD, HD and PC groups. The former was probably related to hepatic enzyme induction and the latter may have been related to muscle tissue injury. A dose-related increase in liver weights occurred in fosphenytoin-treated males (+35% at HD) and females (+28% at HD). Liver weight was also increased in the PC group (+28% M, 14% F). Livers of 1 male and 1 female from the phenytoin group and of all females from the HD fosphenytoin group showed diffuse increases in intracytoplasmic vacuolization of hepatocytes. Injection site changes were observed in dogs from the phenytoin group and from the MD and HD fosphenytoin groups, but were reportedly more extensive and severe in the phenytoin group. Phenytoin levels peaked at approximately 60 min after prodrug administration (**Table III.6**), averaging 25.5, 23.3, and 28 ug/ml on days 1, 42 and 91, respectively, in the HD group (there was no apparent effect of repeated dosing). Peak phenytoin levels in the phenytoin group were consistently about 1/3 times those in the equimolar fosphenytoin group, averaging 8.6, 7.8, and 8.1 ug/ml on days 1, 42, and 91 (also comparable over time). In the phenytoin group, measurable phenytoin levels were still present in samples collected just prior to dosing, indicating slow absorption after im injection. No phenytoin was measured in predose samples from fosphenytoin groups.

SPECIAL TOXICITY

Local irritation

Fosphenytoin produced significantly less venous and perivascular irritation (based on microscopic irritation scores) than phenytoin at equimolar concentrations. Local irritation after im injection of fosphenytoin to rabbits was significantly lower than after im phenytoin. When injected im into the hindlimb of rabbits daily for 5 consecutive days, phenytoin was more irritating than equimolar concentrations of fosphenytoin.

Cardiovascular effects

The cardiovascular effects of equimolar doses of phenytoin (18 mg/kg) and fosphenytoin (27 mg/kg) were comparable following iv bolus (3 sec) injection to anesthetized female dogs (4/group). Intravenous phenytoin resulted in decreases in heart rate (80% of baseline), LvdP/dt (max -55% compared to C), and MAP (-40% compared to C) and significantly increased LVEDP (2-3-fold). Fosphenytoin resulted in more gradual decreases in HR (80% of baseline), LvdP/dt (max -36% compared to C), and MAP (-40% compared to C and baseline). Effects on LVEDP were variable and did not appear to be as pronounced as those produced by phenytoin administration. Effects on CV parameters appeared to correlate with phenytoin blood levels in both cases. The major difference between drugs was in effects on LVEDP. The less pronounced effects seen after fosphenytoin presumably reflect the lower peak blood level of phenytoin resulting from its administration (22 ug/ml vs 49 ug/ml after phenytoin administration). (**Figures IV. 1 & IV.2 and Table IV.1**).

Formaldehyde formation

The theoretical maximum dose of formaldehyde (assuming complete, instantaneous conversion) after an iv dose of 2100 mg fosphenytoin (30 mg/kg is given as maximum dose in proposed labeling) would be 5.17 mmol or about 0.1 mmol/kg (3 mg/kg) for a 50 kg person. The pharmacokinetics of formaldehyde and its major metabolite, formate, were modeled using data from a published report in which formaldehyde (30 mg/kg) was administered iv to monkeys. Based this model, peak formaldehyde and formate concentrations resulting from first order input of 3 mg/kg formaldehyde (formation half-life = 8 min) were simulated (**Figures IV. 3 and IV.4**). These simulations were analogous to bolus administration of a fosphenytoin dose of 2100 mg. Peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 min. Maximal formate levels were predicted to be 0.08 mmol/L, which is below the baseline levels measured in 2 monkeys in a published study (0.18 and 0.27 mmol/L). Background levels of formate in humans have been reported in the literature to be 0.07 to 0.4 mmol/L.

Since the theoretical maximum dose of formaldehyde represents only a fraction of the total body burden from normal metabolism (36 g/day in a 50 kg person), and since the PK simulations indicated that formaldehyde concentrations would exceed background levels for a relatively short time, the sponsor considers the potential risks associated with formaldehyde exposure as a result of fosphenytoin administration to be negligible. Plasma formate levels measured in 4 healthy volunteers following administration of 1200 mg of fosphenytoin by iv infusion over 30 min were not significantly different from those observed in a placebo group or from baseline levels (25 mg/L). (The dose and infusion rate used in this study were considerably lower than the maximum values in the proposed dosing recommendations, ie, 30 mg/kg and 225 mg/min, respectively; and the sample was very small.)

GENETIC TOXICITY

No biologically significant effects on revertant frequencies were seen with fosphenytoin in the Ames test. Fosphenytoin was negative for effects on mutation frequency at the HGPRT locus in V79 Chinese hamster lung cells were evaluated after exposure to fosphenytoin concentrations up to 4000 ug/ml in the absence or presence of metabolic activation. Structural chromosome aberration frequency in V79 Chinese hamster lung cells was increased by exposure to fosphenytoin concentrations ≥ 1000 ug/ml in the presence of metabolic activation (**Table V.1 & V.2**). In mice given single iv doses of up to 200 mg/kg (iv LD50 = 234 mg/kg), no biologically significant differences in micronucleus formation were detected.

REPRODUCTIVE TOXICITY

Segment I (male)

Male rats (40/grp) were dosed with 0, 25, 75, or 150 mg/kg, im, for 75 days prior to mating and throughout

mating with untreated females (1:1 cohabitation, 10 day maximum), then sacrificed. Females were either sacrificed on Day 21 of gestation (1/2) or allowed to deliver and wean their offspring. Paternal toxicity, characterized by clinical signs (injection site lesions, neurotoxicity) and suppression of BW gain, occurred at the MD and HD. Two HD males died and 2 were sacrificed moribund. Mean plasma phenytoin concentrations ranged from about 5 (LD) to 45 ug/ml (HD) and did not appear to accumulate during treatment. No T-R effects were apparent for male reproductive parameters, including semen evaluation. F0 fertility indices were decreased compared to historical data, but both control and treated males were affected. No biologically significant effects on female reproductive or fetal parameters were observed at C-section. There was a slight increase in stunted fetuses (<4 g) at the HD, but the value was within the historical control range. In litters from females allowed to deliver, there were no T-R effects on reproductive parameters or on neonatal growth, survival, and acquisition of developmental landmarks. In addition, no group differences were found in several postweaning tests of neurobehavioral function, and there were no treatment effects on F1 reproductive parameters.

Segment I (female)

Female rats (40/grp) were dosed with 0 (vehicle), 25, 75, or 150 mg/kg, im, for 15 days prior to mating with untreated males, and throughout mating, gestation, and lactation. C-sections were performed on 1/2 of the females on Day 21 of gestation; remaining females were allowed to deliver and wean their offspring. A high incidence of neurotoxicity (hypoactivity, ataxia, and prostration) was observed in HD females, which is consistent with the blood levels achieved at this dose (33-38 ug/ml). Similar CNS signs have been reported at plasma phenytoin levels >25-30 ug/ml, in rats and humans. BW gain was decreased in MD and HD females during the premating and gestation periods. Estrous cycles were altered at the MD and HD, but mating and fertility indices were unaffected. Parturition was significantly delayed at the HD, and disturbed at all doses. Fosphenytoin produced developmental toxicity primarily at the HD (decreased growth, increased intrauterine and postnatal death, malformations, functional effects; **Tables VI.3-5**), although there were effects on growth at the MD. The MD and HD produced peak maternal plasma phenytoin concentrations of approximately 20 and 40 ug/ml, respectively (10-20 ug/ml considered therapeutic). Teratogenicity (cardiac, digit, brain anomalies) was significant at the HD; however, the occurrence of a brain malformation in a single LD fetus may have been drug-induced, since brain malformations are rare and have been previously reported after prenatal phenytoin exposure. Chromodacryorrhea and circling were seen in HD offspring; these have been previously reported after prenatal phenytoin exposure.

Segment II (rat)

Pregnant rats (40/group) were treated with 0 (vehicle), 10, 50, or 100 mg/kg, iv, on gestation Days 7 through 17. C-sections were performed on 25/group on Day 21; the remaining 15/group were allowed to deliver and rear offspring. Maternal toxicity occurred primarily in HD dams and consisted of death (4 HD dams), clinical signs (salivation, chewing, ataxia, hypoactivity, and limb rigidity), and suppression of BW gain. Mean maternal plasma phenytoin levels at 1 hr postdosing (approximate Cmax) were 4, 24, and 43 ug/ml in LD, MD, and HD groups, respectively. At C-section, postimplantation loss was increased (2-fold) in HD dams compared to concurrent and historical controls. Mean fetal BW was decreased (30% below VC) in the HD group. Incidences of skeletal malformations, external/visceral variations, and skeletal variations were increased in HD litters (**Table VI.7**). Although classified as malformations, several of the skeletal anomalies (hemicentra) may have reflected retarded ossification. The increase in variations was due to a marked increase in growth retarded fetuses in HD litters; 60% of HD fetuses were stunted (BW <4 g). Among dams allowed to deliver, the duration of gestation was significantly increased at the HD. Postimplantation loss was slightly increased at the MD and HD (**Table VI.9**). Birth weights and postnatal weight gain were decreased in HD males and females (10-15%). Vaginal opening was delayed in MD and HD female pups. Two littermates in the HD group exhibited abnormal circling behavior, and 27 pups from 8 HD litters had chromodacryorrhea. Both have previously been associated with prenatal phenytoin

exposure. One of the HD circlers later died (PND 23). Locomotor activity was increased in HD males on PND 42; however, this was mostly due to increased activity in a single HD pup. No group differences were found in acoustic startle parameters on P 43 or in shuttle avoidance parameters during week 9.

Segment II (rabbit)

Pregnant rabbits (20/group) were treated with 0 (vehicle), 10, 25, or 50 mg/kg, iv, on gestation days 6 through 18. C-sections were performed on Day 30 of gestation. Maternal toxicity, characterized by clinical signs (chewing motions, ataxia, limb rigidity, and shallow, rapid breathing) and suppression of BW gain, occurred at the MD and HD. Mean maternal plasma phenytoin levels increased proportionally from about 7 (LD) to 36 ug/ml (HD). No T-R effects on maternal reproductive or fetal developmental parameters were apparent at C-section.

Segment III

Female rats (25/group) were treated with 0 (vehicle), 25, 50, or 100 mg/kg, iv, from Day 15 of pregnancy through Day 20 postpartum. Maternal toxicity, characterized by death, significant reductions in BW gain, and clinical signs (ataxia, hypoactivity, and imbalance), was observed primarily in HD group females. A D-R increase in gestation length was seen in treated dams, and postimplantation loss was dose-dependently increased at all doses (**Table VI.10**). Pup survival and BW at birth were significantly decreased at the HD, but were lower than controls at all doses. The effect on BW persisted into the maturation period in HD group offspring. Increased pup mortality and reduced postnatal growth have previously been reported after oral administration of 100 or 200 mg/kg of phenytoin on Days 7-18 of gestation. There was no increase in malformations among fosphenytoin exposed offspring, but treatment started after the major period of organogenesis. An increased incidence of structural variations in fetuses from dams that died around the time of parturition can be attributed to developmental delay. Hyperactivity was apparent in all treatment group male offspring, but values for activity parameters were outside the control range primarily in HD offspring. Enhanced avoidance responding and apparent memory enhancement were seen in treatment group offspring (MD & HD males, HD females), probably due to exposure-induced hyperactivity. Circling behavior, which has previously been reported following prenatal exposure to phenytoin and was seen in the segment II study, was not observed in this study. No apparent effects on the reproductive performance of F1 offspring were observed.

Table VIII.1 Summary of the Effects of Fosphenytoin and Phenytoin for Prevention of Tonic Extensor Seizures from Maximal Electroshock in Mice (All Fosphenytoin Doses are Expressed as Phenytoin Equivalents). Data Taken From Reference 16

	Dose Route (Time After Dose)	ED_{50} Value mg/kg (95% Confidence)	Rotorod Ataxia ED_{50}, mg/kg (95% Confidence)
Fosphenytoin	IV (10 min)	10.8 (8.4-17.5)	
	IV (30 min)	6.8 (6.1-7.5)	
Phenytoin	IV (10 min)	8.3 (6.1-11.2)	
	IV (30 min)	6.6 (5.1-8.0)	
Fosphenytoin	PO (6 hr)[a]	11.9 (9.7-14.9)	81.7[b] (75.4-88.6)
	IP (60 min)[a]	10.2 (8.57-11.4)	42.2[b] (38.9-45.7)
Phenytoin	PO (2 hr)[a]	9.04 (7.4-10.6)	86.7[b] (80.4-96.1)
	IP (2 hr)[a]	9.50 (8.1-10.4)	65.4[b] (52.5-72.1)

[a] ED_{50} values for each test were determined at the approximate time of peak effect after dosing.
[b] Data are taken from the US National Institutes of Health Antiepileptic Drug Discovery Project.

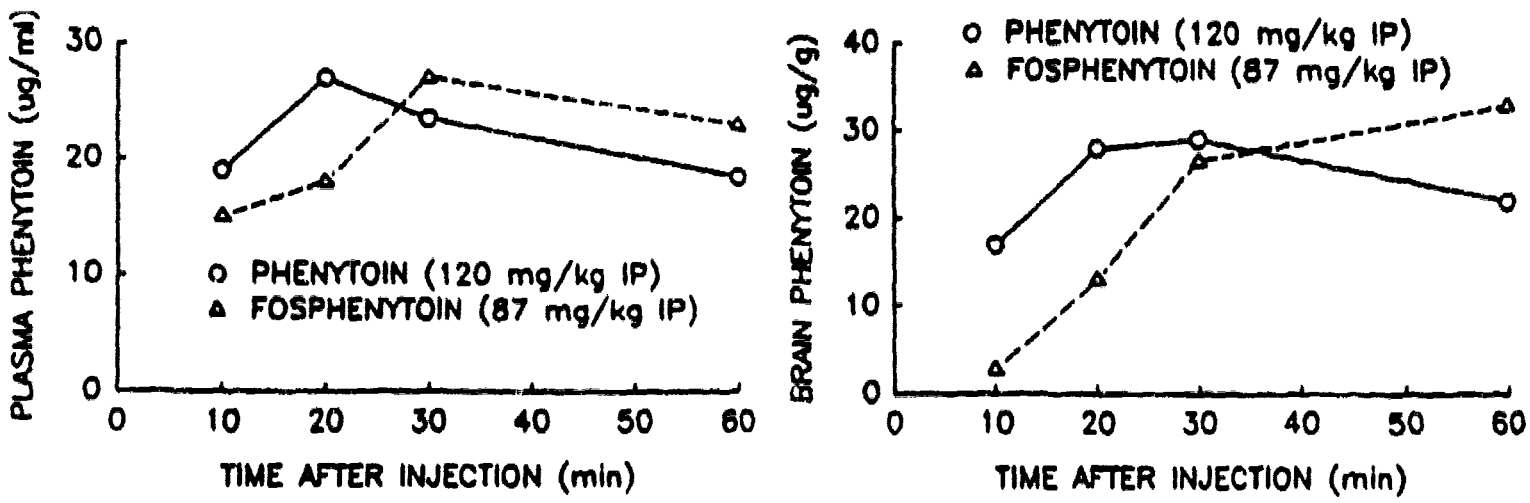


Figure VIII.1 Time Course of Changes in Phenytoin Concentrations in Plasma (above) and Brain (below) in Rats Given Doses of Fosphenytoin and Phenytoin IP in a Study of Action against Status Epilepticus

Rats were given a single intraperitoneal dose of either fosphenytoin (87 mg/kg phenytoin equivalents) or phenytoin (120 mg/kg) and samples of blood plasma or brain tissue were obtained at various times after dosing. Each data point is the mean from 3 individual samples. Data are from Reference 17.

VIII. EVALUATION

Fosphenytoin is a water soluble phosphate ester prodrug of phenytoin, intended as a replacement for parenteral phenytoin (poorly soluble, requires an alkaline organic solvent and precipitates in iv fluids). Fosphenytoin is quantitatively converted to phenytoin *in vivo* by ubiquitous phosphatases, with a conversion half-life of about 8, 3, and <1 min in man, dog, and rat, respectively. Because of the phosphate ester, 150 mg fosphenytoin yields 100 mg phenytoin. The properties of phenytoin are well established; therefore, the primary safety issues with fosphenytoin relate to possible differences in the pharmacological/toxicological profile of phenytoin resulting from administration of the prodrug. These differences could involve intrinsic effects of fosphenytoin, changes in phenytoin disposition, or effects of breakdown products, as discussed below.

Fosphenytoin and phenytoin were equipotent against MES-induced seizures in mice after oral, ip, or iv administration (**Table VIII.1**). Although time courses of anticonvulsant action were comparable when the two drugs were given iv, there was some indication of a delayed onset after fosphenytoin administration. This delay could be important in the treatment of status epilepticus. A published study by Walton and Treiman (Epilepsy Res 5:165-8,'90) indicated that fosphenytoin was less effective than phenytoin in a rat model of status epilepticus. Although similar final plasma and brain phenytoin concentrations were reached after ip administration of the two drugs, a slower rise in brain phenytoin levels following fosphenytoin administration was thought to reduce its anticonvulsant efficacy in this animal model (**Figure VIII.1**). Thus, the time required for conversion of fosphenytoin to phenytoin could have a negative impact on the effectiveness of treatment.

However, clinical iv PK studies have shown that free phenytoin concentration-time profiles similar to those seen with parenteral phenytoin can be obtained by increasing the fosphenytoin infusion rate. This is partly due to altered protein binding of phenytoin in the presence of fosphenytoin. *In vitro* studies and clinical PK data indicate that fosphenytoin displaces phenytoin from plasma binding sites, ie, the phenytoin free fraction increased with increasing fosphenytoin concentrations. In human volunteers, the extent of phenytoin displacement for a given dose, and therefore the Cmax and AUC values for free phenytoin, increased with the infusion rate. Following infusion of fosphenytoin (1200 mg PE - phenytoin equivalents) at 100 and 150 mg PE/min, increases in free fraction resulted in free phenytoin concentrations and tmax values similar to those seen after administration of an equimolar dose of phenytoin at the maximum recommended rate of 50 mg/min. Such infusion rates of fosphenytoin are reportedly well tolerated. At steady-state, administration of fosphenytoin could enhance the pharmacological or toxicological effects of phenytoin by displacing it from its binding sites, although the increase in free fraction would be transient. The potential for such displacement effects was not addressed in the preclinical studies; free phenytoin levels were not determined in any of the *in vivo* animal studies.

Phenytoin has been shown to produce significant reductions in blood pressure when infused iv in both animals and man. Phenytoin-induced hypotension appears to be dependent on both total dose and rate of infusion. The maximum recommended adult human infusion rate is 40-50 mg/min and the total dose is usually limited to 1250-1500 mg. In a study comparing the hemodynamic effects of phenytoin and fosphenytoin in dogs, qualitatively and quantitatively similar changes in CV parameters were seen: both drugs produced comparable decreases in blood pressure, heart rate, and contractility. When the CV effects of fosphenytoin (21 mg/kg PE) infusion over 15-30 min were compared with those seen after infusion of an equimolar dose of phenytoin over 30 min, the maximum effects were nearly identical and were observed at comparable plasma levels of phenytoin (**Figures I.4-6**). The rapidity of fosphenytoin infusion (within the range tested) appeared to affect the onset but not the maximum response. At times when plasma levels of both fosphenytoin and phenytoin (formed from fosphenytoin) were high, effects were not greater than those seen at comparable levels of phenytoin alone; therefore, it did not appear that fosphenytoin had any significant hemodynamic effects of its own. When higher equimolar doses (40 mg/kg PE) were rapidly infused (over 2 min), the magnitude of the changes in CV parameters produced by fosphenytoin appeared to be somewhat greater than those seen with phenytoin (**Figures I.1-3**). However, 3 of the phenytoin-treated animals (ie, the most sensitive to CV effects) died within 4 min of infusion onset following marked reductions in MAP and HR, while all 6 fosphenytoin dogs recovered; so the means depicted in the figures may be misleading. Although the CV changes produced by fosphenytoin seemed to correlate with plasma levels of phenytoin, and similar peak total phenytoin concentrations were achieved after phenytoin or fosphenytoin administration, it is possible that the

displacement effect described in the preceding paragraph resulted in higher maximal free phenytoin levels following rapid fosphenytoin infusion, which might have contributed to any increased response observed. In addition, formaldehyde formation could have added to the CV effects seen after rapid infusion of fosphenytoin. Formaldehyde has been shown to decrease the rate and contractility of isolated rat atria *in vitro*, and cardiodepression has been reported in rats infused with 0.12 mmol/kg/min formaldehyde (Strubelt et al, J Toxicol Clin Toxicol 28:221-33,'90). The rate of fosphenytoin infusion in the dog study was 0.08 mmol/kg/min. However, the theoretical maximal rate of exposure to formaldehyde clinically, based on the proposed maximal rate of fosphenytoin administration (225 mg/min), would be 0.01 mmol/kg/min (50 kg BW). Fosphenytoin exhibited intrinsic activity only in one *in vitro* assay: the prodrug inhibited developed tension in a guinea pig left atrial preparation with a potency equivalent to that of phenytoin. Fosphenytoin was inactive in isolated right guinea pig atria, however. This *in vitro* effect is unexplained but unlikely to be of any clinical importance.

The toxicological profile of fosphenytoin was essentially the same as that of phenytoin. The acute toxicity of fosphenytoin was equivalent to that of phenytoin when the two drugs were administered by iv infusion (30 min) to mice, rats, rabbits, and dogs (**Table III.1**). However, phenytoin was more toxic than fosphenytoin after single iv bolus administration to rats, probably due to a more gradual rise in phenytoin levels when fosphenytoin was given. When compared on an equimolar basis, im fosphenytoin produced more acute systemic toxicity than phenytoin in rats and dogs, presumably due to better absorption by this route (**Table III.2**). Fosphenytoin produced less injection site irritation than phenytoin by both the iv and im routes. Unfortunately, the only multiple dose toxicity studies that included a phenytoin positive control were the 3 month im rat and dog toxicity studies. Because of its lower bioavailability by the im route, phenytoin was less toxic than an equimolar dose of fosphenytoin, except with regard to injection site irritation. Toxicokinetic studies indicated that equivalent phenytoin exposures (AUCs) were achieved after iv or im administration of fosphenytoin to rats and dogs (**Tables II.5 and II.6**). Peak phenytoin levels following im administration were about the same as those seen with iv administration in dogs and were about 1/2 iv peak levels in rats. Fosphenytoin was not measured in these high dose toxicokinetic studies. At a lower dose (10 mg/kg PE), fosphenytoin exposures were equivalent following iv and im administration to dogs, but peak fosphenytoin levels were about 10-fold higher after iv administration (**Table II.3**). Therefore, possible intrinsic effects of fosphenytoin or effects related to systemic formaldehyde may not have been adequately assessed in im toxicity studies. Effects on serum hepatic enzymes and liver weights observed in multidose studies in rats and dogs are known effects of phenytoin in animals and are consistent with microsomal enzyme induction. Microscopic changes in the liver were attributed to increased cellular glycogen content secondary to phenytoin-induced hyperglycemia. Phenytoin causes hyperglycemia in animals and humans by inhibiting the insulin response to glucose stimulation.

The *in vivo* hydrolysis of fosphenytoin produces 1 mole each of formaldehyde and phosphate for each mole of prodrug. No attempt to measure blood formaldehyde levels was made in any of the preclinical studies, but the pharmacokinetics of formaldehyde and its major metabolite formate were modeled using data from a published report in which formaldehyde was administered iv to monkeys, and formaldehyde and formate concentrations resulting from first order input of 0.1 mmol/kg of formaldehyde were simulated (**Figures IV. 3 & IV.4**). This was considered to be the theoretical maximum human dose of formaldehyde, based on the complete conversion of an iv (bolus) fosphenytoin dose of 2100 mg (5.17 mmol or 0.1 mmol/kg using 50 kg BW). (The proposed MHD of fosphenytoin is 30 mg/kg at 225 mg/min.) Peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 min (formaldehyde is rapidly eliminated, with a t1/2 of 1.5 min in monkeys). Qualitative and quantitative similarities in formaldehyde metabolism between monkeys and humans suggest that these findings could be extrapolated to humans, but the actual data on which the PK model was based are very limited, ie, blood levels measured in 1 monkey. The toxicity of formaldehyde has been extensively examined, but inhalation has been the route of exposure in most studies. Effects were generally confined to the nasal and gastric epithelia after inhalation and oral administration of formaldehyde. Following a single iv injection, the median lethal dose of formaldehyde in rats was reported to be 87 mg/kg. The chronic toxicity of iv formaldehyde has apparently not been investigated. Formaldehyde is genotoxic in a variety of systems, and both chronic and subchronic inhalation exposures to high formaldehyde concentrations (15 ppm 6 h/d) have resulted in the induction of squamous cell carcinomas in the nasal cavity of rats. However, despite the widespread exposure of humans to formaldehyde, epidemiological studies have not demonstrated that it

represents a significant cancer risk to man (Heck et al, Critical Reviews in Toxicology 20:397-426,'90). OSHA (Third Annual Report on Carcinogens, USDHHS Public Health Service,'83) has set permissible formaldehyde exposure levels at 3 ppm as an 8 hr time weighted average and 10 ppm as a maximum peak concentration for 30 min in an 8 hr period, but there are no good estimates of acceptable plasma formaldehyde levels. It has been reported (J Piotrowski, Exposure Tests for Organic Compounds in Industrial Toxicology,'77) that workers exposed to formaldehyde at a concentration of 5.4 ppm (presumably 8-h TWA, but not stated) developed maximal blood levels of 0.13 mmol/L (ie, similar to predicted peak levels after fosphenytoin). However, occupational exposure patterns may be very different from the pattern of formaldehyde exposure in fosphenytoin-treated patients. Formaldehyde is generated during normal intermediary metabolism - the body turns over up to 50 g/day - and there are many sources of environmental exposure. Assuming that the simulations used by the sponsor are reasonably accurate, the formaldehyde formed from fosphenytoin would not be expected to overwhelm the body's detoxification capacity, and any elevation in blood levels would likely be transient; however, clinical data are needed to verify the model (see original IND review of this issue). Intravenous administration of high concentrations of phosphate can result in toxicity due to reduction of Ca^{2+} in the circulation and precipitation of calcium phosphate in tissues. This potential risk was not addressed by the sponsor. Although it is unlikely that the amount of phosphate which would be contributed by fosphenytoin administration (max ~5 mmol) would raise serum concentrations to the levels which are associated with such effects (3.2 mmol/L), transient or local effects are possible. No findings obviously attributable to increased formaldehyde or phosphate exposure were observed in the fosphenytoin acute studies or in the 4-week toxicity studies at iv bolus doses up to 5 (rats) and 1.5 (dogs) times the maximum human dose (mg/kg basis).

The major pathway for metabolism of formaldehyde involves oxidation to formate and incorporation into biological macromolecules via tetrahydrofolate-dependent one-carbon synthetic pathways. Since formate accumulation is thought to be responsible for the known toxic effects of high dose methanol exposure (ie, severe metabolic acidosis and ocular toxicity), formate toxicity also represents a potential concern with fosphenytoin administration and may be more relevant to short-term use. Hepatic alcohol dehydrogenase and catalase metabolize methanol to formaldehyde, then a glutathione-mediated pathway involving formaldehyde dehydrogenase rapidly metabolizes formaldehyde to formic acid. The accumulation of methanol-derived formate to toxic levels is primarily influenced by the rate of formate metabolism, which depends on the activity of formyltetrahydrofolate synthetase, methenyltetrahydrofolate dehydrogenase, and the cosubstrate tetrahydrofolate. Following MeOH administration, formate has been shown to accumulate in the blood of primates but not of rodents or other nonprimates, and this is thought to account for a species difference in susceptibility to MeOH poisoning. Tissue folate levels are thought to be key determinants of susceptibility to neuro-ocular toxicity following exposure to methanol. Primates have lower total liver folate concentrations, slower formate metabolism, and are thus more sensitive to methanol-induced toxicity compared to resistant species such as rodents. This interaction of formate and folate may be especially important in view of the fact that phenytoin and other AEDs have been shown to interfere with folate-dependent one-carbon metabolism. Folate depletion due to chronic AED therapy or other causes could increase formate levels during fosphenytoin administration. Furthermore, because of species differences in formate metabolism, the preclinical toxicity studies of fosphenytoin in rats and dogs are probably not appropriate for evaluating possible toxic effects related to the metabolism of the prodrug to formate. However, neuro-ocular toxicity in methanol- and formate-poisoned monkeys (Martin-Amat et al, Arch Ophthalmol 95:1847-1850,'77; Martin-Amat et al, TAP 45:201-208,'78) and in methanol-poisoned humans (Mahieu et al, Human Toxicol 8:135-137,'89; McMartin et al, Am J Med 68:414-418,'80) is reportedly associated with marked elevations in blood formate concentrations (>7-10 mM) for prolonged periods of time (often > 24 hr). In a folate-reduced rat model of methanol toxicity (Murray et al, Arch Ophthalmol 109:1012-1016,'91), exposure to blood formate concentrations of 8-12 mmol/L for more than 12 hr was required to produce changes in ERG and ultrastructural damage to the retina and optic nerve following administration of methanol (4 g/kg ip followed by 2 g/kg every 12 hr for 60 hr); formate levels up to 3 mmol/L were not toxic in this model (Louis-Ferdinand, personal communication). Formate has also been shown to be embryotoxic and dysmorphogenic to developing mouse and rat embryos *in vitro* at concentrations >10 mM (Dorman et al, Teratology 52:30-40,'95). In the PK simulations described above, maximal formate levels after administration of a 2100 mg dose of fosphenytoin were not predicted to exceed the range of background concentrations (0.1-0.56 mM). Based on these projected levels, formate formed from fosphenytoin should not constitute a significant hazard. However, while plasma formate levels were measured in 4 volunteers following administration of fosphenytoin and did

not increase significantly above those observed in a placebo group or baseline levels (all ~0.5 mmol/L), the dose and infusion rate used in this study (1200 mg over 30 min) were well below the maximum values in the proposed dosing recommendations (30 mg/kg at 225 mg/min); therefore, additional human data are needed. *Note to clinical reviewer*: Because the safety data related to formaldehyde and phosphate are so limited, a request that the sponsor measure blood levels of formaldehyde and/or formate and assess any changes in calcium concentration or acid-base equilibrium following administration of fosphenytoin to humans at the maximum recommended dose should be considered.

Developmental toxicity seen in rats given fosphenytoin is consistent with that previously reported with phenytoin; however, no direct comparisons were made in the current reproductive toxicology studies. Segment I studies were conducted using im administration. As noted above, toxicokinetic studies indicated that similar phenytoin exposures (AUCs) were achieved after iv or im administration of fosphenytoin, but the question of im fosphenytoin bioavailability has not been adequately addressed. In the female Segment I study, maternal and reproductive toxicity were evidenced at 75 and 150 mg/kg by decreased maternal body weight gain, altered estrous cycles, and delayed parturition. Developmental toxicity, including teratogenic and functional effects (decreased growth, increased intrauterine and postnatal death, cardiac and digit anomalies, chromodacryorrhea, and circling), occurred primarily at 150 mg/kg, although 1 brain malformation seen at the LD (16.6 mg/kg) may have been treatment-induced and there were effects on growth at the MD. In a rat iv teratology study, developmental toxicity (growth retardation, chromodacryorrhea, increased locomotor activity, circling) was seen at 100 mg/kg along with overt maternal toxicity (neurotoxicity, decreased weight gain, dystocia). In an iv Segment III study, decreased pup survival and growth and offspring behavioral changes (hyperactivity) were observed at doses as low as 50 mg/kg, with maternal toxicity over the same dose range. The developmental effects of fosphenytoin were very similar to those reported in the literature following administration of phenytoin to rats, and they occurred at maternal plasma phenytoin levels comparable to those associated with developmentally toxic doses of phenytoin (ie, therapeutic levels or greater). The appearance of neurotoxicity (lethargy, ataxia, and imbalance) has previously been reported at plasma phenytoin concentrations ≥30 ug/ml, which is consistent with the levels observed in the present study following neurotoxic doses of fosphenytoin. Embryolethality, IUGR, and defects encompassing the cardiovascular, urogenital, craniofacial, and skeletal systems have been variably demonstrated in mice, rats, and rabbits exposed to phenytoin *in utero*. Cardiac malformations similar to those seen in HD fetuses in the rat Segment I study with fosphenytoin are typical of the fetal hydantoin syndrome in humans as well as those previously reported in phenytoin-exposed rat fetuses. The incidence of ectrodactyly was also increased in HD fosphenytoin treated fetuses in this study, and digit malformations such as adactyly and digital phalangeal hypoplasia have been reported in rodents and humans following prenatal exposure to phenytoin. Decreased postnatal viability and growth, chromodacryorrhea, increased locomotor activity, and circling behavior have also been reported in rats after prenatal phenytoin exposure (Vorhees Teratology 35:287-303,'87). Thus, studies examining the reproductive and developmental effects of fosphenytoin confirm previous findings with phenytoin, but do not indicate any additional toxicity resulting from administration of the prodrug.

Fosphenytoin was clastogenic in V79 Chinese hamster lung cells *in vitro* but negative in *in vitro* mutagenicity assays and in the mouse micronucleus test *in vivo*. The sponsor postulated that the clastogenic effect was due to the generation of formaldehyde *in vitro*, since the effect was seen in the metabolic activation assay only. Phenytoin was reportedly not clastogenic in previous studies with CHO cells, while formaldehyde has been reported to induce chromosomal aberrations *in vitro* in CHO cells at concentrations as low as 5 ug/ml. As mentioned above, formaldehyde is genotoxic in a variety of *in vitro* assays, eg, increased mutation frequencies in Chinese hamster V79 cells were induced by formaldehyde at 0.3-1 mM concentrations; but no *in vivo* mutagenicity has been reported. Attempts to measure formaldehyde in cultures treated with fosphenytoin were unsuccessful. Addition of formaldehyde dehydrogenase to the S9 is a possible approach to addressing this question. Although one could assume that conversion to phenytoin would take place in the presence of S9, the extent of fosphenytoin hydrolysis *in vitro* was not measured in any of the genotoxicity assays. It seems likely that the clastogenicity of fosphenytoin is due to formaldehyde formation, but this has not been supported by data and could not be stated in the labeling without additional work.

Labeling

The Carcinogenicity and Pregnancy sections of the labeling are inaccurate and/or inadequate. Despite the findings in Chinese hamster lung cells, the statement is made that fosphenytoin was neither mutagenic nor clastogenic. The pregnancy category should be D, based on the known - or at least strongly suspected - human developmental toxicity of phenytoin; and since phenytoin has a pregnancy warning, fosphenytoin warrants the same. The warning needs to be updated or rewritten by the sponsor so that the information reflects the current scientific consensus regarding the effects of phenytoin on human development. Where adequate data are available, risk estimates and factors affecting risk should be included. The fosphenytoin animal findings, which are given 1 sentence in the proposed labeling, should be described in more detail. There are also some minor errors in the Mechanism of Action section. Suggested changes are as follows:

Mechanism of Action

In the second paragraph, replace the first three sentences with the following (in italics; sponsor's reference numbers retained):

After intravenous (IV) administration to mice, fosphenytoin *blocked the tonic phase of maximal electroshock seizures* at doses that are equivalent (on a molar basis) to those effective for phenytoin. *In addition to its ability to suppress maximal electroshock seizures in mice and rats[4], phenytoin exhibits anticonvulsant activity against kindled focal and secondarily generalized seizures in rats[3], audiogenic tonic-clonic seizures in mice[5], and generalized seizures produced by electrical stimulation of the brainstem in rats[6].* The cellular mechanisms of phenytoin ...

Carcinogenesis, Mutagenesis, Impairment of Fertility

Replace the second sentence in proposed text with the following:

The carcinogenic potential of fosphenytoin is not known. *Structural chromosome aberration frequency in cultured V79 Chinese hamster lung cells was increased by exposure to fosphenytoin concentrations ≥ 1000 ug/ml in the presence of metabolic activation. No evidence of mutagenicity was observed in bacteria or Chinese hamster lung cells in vitro, and no increase in micronucleus formation occurred after administration to mice in vivo.*

Add the following dosage information to the last sentence:

.... following administration of fosphenytoin during mating, gestation, and lactation *at doses of 75 and 150 mg/kg/day, or approximately 40% and 80%, respectively, of the maximum human daily dose (MHDD; 30 mg/kg) on a mg/m2 basis.*

Pregnancy - *Category D; see Warnings.*

Add the following sentence at the beginning of the first paragraph of the current, or updated, Dilantin Usage in Pregnancy warning:

Although there are no studies of fosphenytoin in pregnant women, epidemiological data indicate that prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly, and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and the neonate after birth.

Add the following paragraph after the human pregnancy information (sponsor's reference number)

Fosphenytoin demonstrated developmental toxicity, including structural and behavioral teratogenicity, in rats. When fosphenytoin was administered to female rats prior to and during mating, pregnancy, and lactation (25, 75, or 150 mg/kg/day), increased frequencies of malformation, death, and functional impairment were observed among the offspring of dams receiving 150 mg/kg/day, or approximately 80% of the maximum human daily dose (MHDD; 30 mg/kg) on a mg/m2 basis. This dose produced peak maternal plasma phenytoin concentrations approximately 2-4 times human therapeutic levels (10-20 ug/ml). Offspring growth was reduced by doses of 75 mg/kg/day (40% of MHDD on a mg/m2 basis) or greater, and maternal toxicity was evident over the same dose range. When pregnant rats were given fosphenytoin (10, 50, or 100 mg/kg/day) during the period of embryonic organogenesis, growth retardation and abnormal postnatal function were observed in offspring exposed to 100 mg/kg/day (50% of MHDD on a mg/m2 basis). Overt maternal toxicity was also associated with this dose. When female rats received fosphenytoin during the last third of pregnancy and throughout lactation (25, 50, or 100 mg/kg/day), decreased offspring viability and growth and alterations in offspring behavior were observed at doses of 50 mg/kg/day (30% of MHDD on a mg/m2 basis) or greater. Maternal toxicity was noted over the same dose range. The developmental effects of fosphenytoin in rats were similar to those which have been reported following administration of phenytoin to rats[3].

IX. RECOMMENDATIONS

The NDA is approvable with respect to the pharmacology/toxicology portion. Recommendations concerning the proposed labeling are made in the Evaluation section of the review.

cc:
NDA (20-450)
Div File
HFD-120/GFitzgerald/EFisher/RNighswander

GGF 1/30/96

E. Fisher, Ph.D.

NDA 20-950

Review and Evaluation of
Pharmacology and Toxicology
Continuation of Review # 1

Drug: 9653-010

Category:

Anticonvulsant; prodrug for phenytoin.

Summary:

It was pointed out in our team meeting for this new drug that the in vivo hydrolysis of 9653 occurs in 2 steps, producing one mole of formaldehyde for each mole of prodrug. In the initial clinical Phase I trial, the top dose of 2250 mg would produce 5.5 mmoles of HCHO. The possible hazard from this burden will be discussed from several different veiwpoints below. All calculations are gross approximations, based on available information.

1. OSHA has adopted a permissible exposure level for toxic effects of formaldehyde other than cancer of 3 ppm as an 8 hour time weighted average, and 10 ppm maximum peak concentration for 30 minutes in an 8 hour period (Third Annual Report on Carcinogens, USDHHS Public Health Service, September, 1983, page 73). It has been reported that workers exposed to formaldehyde at a concentration of 7 mg/m^3 developed blood levels of 0.6 - 4.0 mg/l. The duration of exposure was not given (J.Piotrowski, Exposure Tests for Organic Compaounds in Industrial Toxicology, Gant Printing Office, DC, 1977, p.122). [1m^3 = 1000 l; wt. of air = 1.293 gms/l at 0°C + 760 mm Hg; therefore 7 mg/m^3 = 7 mg/1.293 kg = 5.4 mg/kg = 5.4 ppm in air]

   Since 5.4 ppm of HCHO → a maximum of 4 mg/l in blood, the 10 ppm maximum allowed by OSHA would → approximately 7.4 mg HCHO/liter or 0.25 meq HCHO/l in blood. This figure should more or less represent the maximal allowable blood level of HCHO according to OSHA. If we then assume that the 5.5 mmoles of HCHO that are split from the prodrug all appear in the circulation (ave. volume 5 liters) the concentration would be 33 mg/l or 1.1 meq/l, or approximately 4 fold higher than the OSHA level allowed. However, this is a very crude estimate since the data are not readily available for taking the time factor allowed under the OSHA limit into consideration.

2. There is a great deal of information in the literature that suggests that it is formic acid that is repsonsible for the ocular toxicity and acidosis seen following acute methanol poisoning (methanol → formaldehyde → formate). This toxicity would be of greater concern when dealing with a drug to be used acutely than would potential carcinogenicity. Although a role for HCHO has not been clearly ruled out, experiments in monkeys suggest that the resultant formate levels are of more concern.

In a model in rhesus monkeys for methanol ocular toxicity and metabolic acidosis, formate blood and CSF levels of 7 to 34 meq/l were associated with optic disc edema, morphological alterations in optic nerve and swelling of oligodendroglial cytoplasm (Martin - Amat, Hayreh, Baumtach et al, Arch Ophthalmol., 95, 1847-50, 1851-58, 1859-61; Martin-Amat, et.al., TAP, 45, 201-208, 1978). Pretreatment with folate increased the metabolism of formate and decreased the toxicity (McMartin et al, JPET, 201, 564-572, 1977). In the proposed clinical trial, if we assume the 5.5 meq of HCHO goes to 5.5 meq of formate, with a blood concentration of 1.1 meq/l, there is a minimum of a 7-fold safety factor before ocular toxicity occurred in the monkey (which is thought to metabolize HCHO like the human).

3. It has been reported that the mechanism for ocular toxicity caused by methanol is the inhibition of cytochrome oxidase by formate (Nicholls, BBRC, 67, 610-616, 1975). Since cytochrome oxidase activity is low in white matter, it has been suggested that its activity may be critical in that tissue. The Ki values determined for formate inhibition of cytachrome oxidase are between 5 and 30 m M (above reference plus Martin-Amat, Arch Ophthol., 95, 1847-50, 1977). Based on this data, blood levels of formate of 1.1 m M would be somewhat lower then those expected to produce toxicity.

4. In dogs and cats administered 35 mg/kg (1.2 meq/kg) of formaldehyde by i.v. infusion, a blood HCHO concentration of 25 mg/l (0.83 meq/l) was produced which declined to about 1 mg/l by 1 hour after the infusion. (4 x as much HCHO was in erythrocytes as in plasma). The peak plasma concentration of formate, however, was 144 mg/l (3.1 meq/l) at the end of the infusion, which declined with a $T_{1/2}$ of 1.5 hours. Toxicity was not addressed (G. Malorney et al, Naunyn - Schmiedebergs A.E.P.P., 250, 419-436, 1965). These data would suggest that peak levels of the possibly more toxic metabolite, formate, might be approximated as follows for top dose in the clinical trial:

   5.5 meq of HCHO (155 mg) = 3 mg/kg in a 50 kg person. If 35 mg/kg of i.v. HCHO → 144 mg/l of formate, 3 mg/kg or HCHO may result in peak blood levels of formate of 12 mg or 0.26 meq/l. (This is assuming comparable relative blood levles to body weight in humans and animals. Actually, dogs may have slightly larger blood volume/kg of body weight than humans, so the estimate for humans is possibly on the low side. The assumption for comparable metabolism is also made).

This figure is considerably lower than the Ki for formate inhibition of cytochrome oxidase and it is about 25-30 fold lower than the lowest levels of formate associated with ocular toxicity in monkeys (see numbers 2 and 3 above). If instead, we examine the blood HCHO concentration using these data, an i.v. dose of prodrug that yields 5.5 mmoles of HCHO (0.11 mmoles/kg) would be expected to result in a peak blood concentration of HCHO of 0.08 mmoles/liter, or 1/3 of the maximal allowable HCHO exposure according to OSHA.

Evaluation and Recommendations:

The above approximations are extremely crude, but they do provide some data for evaluating the risk involved from a drug which will be used acutely that is metabolized to produce a mole of formaldehyde for every mole of drug.

Based on OSHA limits for exposure to formaldehyde, the guestimate is that the top dose of prodrug planned in the rising dose trial (2250 mg) would result in anywhere from 1/3 of 10 times the maximal allowable blood level of formaldehyde. If we assume that formate is responsible for the expected acute toxicty (occular and acidosis), there may be anywhere between a 7 fold and a 30 fold safety factor, based on toxicity observed in monkeys and blood levels of formate measured after i.v. administration of HCHO to dogs. If we believe that formate toxicity occurs through cytochrome oxidase inhibition, there is at least a small margin of safety based on the Ki.

In any case, it is a close call, and there are a couple of precautions that might be considered. Monitoring of blood formic acid, blood pH, bicarbonate and pCO_2 is recommended. Since folinic acid pretreatment hastens the elimination rate, a supplement of 2 mg, p.o., might be given the day before the trial. However, if it is considered that this is an appropriate time to determine whether or not formate levels in blood are detectable (since in practice there would not be time to give folinic acid) I would recommend careful monitoring for formate levels at all doses before proceeding to the next higher dose. SRD is May 4, so sponsor should be phoned.

Glenna G. Fitzgerald MD

cc: Orig.IND
HFN-120
HFN-120/JContrera/5/2/86
/GFitzgerald
rd/pjd/5/15/86:ft/5/16/86
doc 0471f

Review and Evaluation of Pharmacology and Toxicology

Memo to File

NDA: 20-450

Sponsor: Parke-Davis Pharmaceutical Research
Ann Arbor, MI 48105

Drug: Cerebyx (fosphenytoin sodium)

Category: Parenteral antiepileptic; prodrug of phenytoin for use in status epilepticus and neurosurgery

Related IND(s):

Submission: Response to NDA approvable letter (received 7/15/96)

Contents for Pharm/Tox review: Sponsor's final labeling (Tab 3)

Evaluation and Recommendations:

The sponsor's changes are acceptable, but the following corrections/additions need to be made:

Usage in Pregnancy,
B. *Risks to Fetus* - p 12, last sentence of first paragraph

Change contribution to contributions.

Preclinical - pp 12 and 13

Make wording of dose comparisons and plasma level data consistent (changes in italics):

paragraph 1, sentence 2: ... (*approximately* 30% of the maximum human loading dose or higher on a mg/m2 basis), which produced peak maternal plasma phenytoin concentrations *of approximately 20 ug/ml or greater.*

paragraph 1, sentence 4: ... (approximately *10%* of the maximum human loading dose on a mg/m2 basis) ...

paragraph 2, sentence 1: .. (*approximately* 50%...

paragraph 2, sentence 2: ...(*approximately* 120%..

Carcinogenesis, Mutagenesis, Impairment of Fertility - p 18, last sentence of second paragraph

Add the following (in italics): Maternal toxicity and altered estrous cycles, delayed mating, prolonged gestation length, and developmental toxicity were observed following administration of fosphenytoin during mating, gestation, and lactation at doses *of 50 mg PE/kg or higher (*approximately 40% of the maximum human loading dose or higher on a mg/m2 basis*)*.

cc:
NDA (20-450)
Div File
HFD-120/GFitzgerald/EFisher/RNighswander

JEF 7/25/96

JE. Fisher, Ph.D.
July 24, 1996

BIO
Review

Clinical Pharmacology and Biopharmaceutics Review
NDA 20-450 -- Fosphenytoin Sodium Injection

Sponsor:	Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road, P.O. Box 1047 Ann Arbor, MI 48106-1047
Submission dates:	February 22, 1995 October 19, 1995 November 3, 1995 November 20, 1995
Reviewers:	Robert Harris, Ph.D. Raymond Miller, Ph.D. Gene Williams, Ph.D. Raman Baweja, Ph.D. (team leader)

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IMPORTANT NOTE

A previous Division of Biopharmaceutics reviewer requested that the Human Pharmacokinetics and Bioavailability portion of the NDA be written with fosphenytoin doses and administration rates expressed in phenytoin equivalents. Since the molecular weight of fosphenytoin is 1.5X the molecular weight of phenytoin, phenytoin equivalents were calculated by multiplying the dose or adminstration rate of fosphenytoin by 0.67.

Not all of the NDA has fosphenytoin doses and rates expressed in terms of phenytoin equivalents. Fosphenytoin was initially developed by and Parke-Davis did not convert studies to express fosphenytoin doses and rates in phenytoin equivalents.

The studies conducted after Parke-Davis' acquisition of fosphenytoin are the most critical in evaluating the application. Thus, they constitute the majority of the Synopsis and Summary. In order to provide consistency between photocopied portions of the NDA and portions of the review constructed *de novo* by the reviewer, doses and rates of fosphenytoin will be expressed in phenytoin equivalents in all portions of this review prior to the individual study reports. The convention used in the individual study reports (Appendix 2) varies according to that used in the NDA and is detailed below.

The following studies were conducted by doses and rates are expressed WITHOUT conversion to phenytoin equivalents: 98201, 98202, 98205, 98206, 98207, 98210, and 98211. Studies 98213, 98214, 98215, 98216, 98218, 98220, and 98224 have doses and rates of fosphenytoin expressed as phenytoin equivalents.

During site visits by the Division of Scientific Investigations, it was determined that plasma concentration measurements of fosphenytoin from studies conducted by Parke-Davis were inaccurate due to an error in the weighing of standards. This error did not affect dosing of fosphenytoin. Parke-Davis has since determined that the accuracy of plasma concentration measurements of fosphenytoin from studies is uncertain. A description of these inaccuracies is given in the "Response to EIRs identified in 483 Forms" section of this review (p.20). The errors in fosphenytoin concentrations have NOT been documented in the individual study reports (Appendix 2). The values have little bearing on the interpretation of studies -- the specie of clinical interest is generally plasma phenytoin, not plasma fosphenytoin. The errors are accounted for in all portions of this review prior to the individual study reports (Appendix 2).

Synopsis

Fosphenytoin is a phosphate ester prodrug of phenytoin developed as an alternative for parenteral phenytoin. Only one fosphenytoin formulation (the to-be-marketed formulation) was studied clinically. Since fosphenytoin is a phenytoin prodrug and no new therapeutic claims beyond those approved for parenteral phenytoin are being made, proof-of efficacy studies were not conducted. Rather, the development program hopes to establish that fosphenytoin and phenytoin are bioequivalent sources of phenytoin.

Study 98224 demonstrates that using the 90% confidence interval approach and the log 80 - 125% C. I. criteria, 1200 mg of IV fosphenytoin at 150 mg/min is bioequivalent to 1200 mg IV phenytoin at 50 mg/min in terms of maximal free phenytoin concentration observed (Cmax) and area under the free concentration/time curve from t = 0 to the least quantifiable concentration (AUC_{0-TLDC}). A desired indication for fosphenytoin is treatment of acute status epilepticus. Because rapid attainment of sufficient phenytoin plasma concentration is critical in treatment of status epilepticus, analyses were performed to compare cumulative AUC over time. Using the forementioned confidence interval approach, cumulative $AUC_{free\ pht}$ following administration of 1200 mg of fosphenytoin at 150 mg/min is bioequivalent to the cumulative $AUC_{free\ pht}$ following 1200 mg of phenytoin at 50 mg/min from 30 minutes onward. At doses of 1200 mg and rates of 50 and 100 mg/min, fosphenytoin is equivalent to 1200 mg phenytoin dosed at 50 mg/min in terms of total $AUC_{free\ pht}$ but not $Cmax_{free\ pht}$.

Fosphenytoin exhibits non-linear pharmacokinetics: as dose and rate of administration are increased, clearance increases. Fosphenytoin is highly protein bound, and its non-linear clearance is hypothesized to result from protein binding considerations: as dose and rate of administration increase, protein binding saturates and greater concentrations of free drug are available to be cleared. Independent of dose and rate of administration fosphenytoin is a short-lived specie; terminal elimination half-life of the drug is approximately 15 min and, regardless of dose or rate of administration, fosphenytoin is rarely quantifiable 5 hrs post-dosing. The conversion of fosphenytoin to phenytoin is consistent and essentially complete.

Unlike phenytoin, fosphenytoin is readily absorbed when administered IM. Average bioavailability of phenytoin from 250 mg of IM fosphenytoin is 101%.

Study 98207 examined the disposition of fosphenytoin in renal failure and hepatically compromised patients. Fosphenytoin clearance is more than 2-fold as great in cirrhosis patients and about 1.8-fold as great in renal failure patients as in healthy volunteers. This is consistent with decreases in plasma protein concentrations in these patients reducing fosphenytoin binding and increasing the concentration of fosphenytoin available to be cleared.

Because treatment of status epilepticus often includes concomitant administration of phenytoin and diazepam, a drug interaction study of fosphenytoin with diazepam was performed. Neither drug affected the pharmacokinetics of the other. However, submaximal doses of fosphenytoin and diazepam were used in the study.

The analytical methodology presented throughout the NDA was a validated assay. However, commercially available fluoresence immunoassays for phenytoin are routinely used to monitor phenytoin plasma concentrations. Cross-reactivity of these assays to fosphenytoin occurs.

Differences in fosphenytoin disposition between age, gender, race or any other sub-group were not observed and there is no evidence of atypical phenytoin pharmacokinetics due to differences in fosphenytoin disposition between individuals.

Recommendation:

The Human Pharmacokinetics and Bioavailability portion of New Drug Application 20-450 meets the requirements of the Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology and Biopharmaceutics. Our labeling revisions have been included in the comprehensive copy of labeling provided as Appendix 1 of this review. Please note the **"Comments to the Medical Officer"** below.

Comments to the Medical Officer:

1. Study 98207, Conversion Of CI-982 To Phenytoin In Patients With Renal Or Hepatic Disease - A Pilot Study, was performed at low dose and low rate of fosphenytoin (250 mg at 8.3 mg / min), and did not measure free phenytoin. The use of low dose and low rate fosphenytoin is not optimal because the conditions with greatest potential for maximal deviation from the norm are high dose and high rate. Failure to measure free phenytoin is problematic because it is free phenytoin which would be best correlated with efficacy and toxicity. Although the results obtained do allow the sponsor to label that fosphenytoin clearance is enhanced in patients with renal or hepatic disease, they are of little value in advising a clinician on how to administer high dose and high rate fosphenytoin (as would be recommended in status epilepticus) to individuals who are hepatically or renally compromised.
This study does demonstrate that neither renal nor hepatic disease have marked effects on the extent of conversion of fosphenytoin to phenytoin.

2. Study 98211, Evaluation Of The Pharmacokinetic Interaction Between Diazepam and CI-982 In Healthy Male Volunteers, was performed at submaximal dose and rate of fosphenytoin (750 mg at 50 mg / min) and submaximal dose of diazepam (10 mg at 5 mg / min). Diazepam, in status epilepticus, can be administered at doses up to 30 mg / 30 min. Although a drug interaction was not observed in this study, the conditions with greatest potential for maximal deviation from the norm (maximal dose and rate) were not studied.

List of Studies

Dose Ranging and Tolerance
- 98201 -- IV fosphenytoin

Bioavailability
- 98202 -- IV fosphenytoin and IV phenytoin
- 98210 -- IV fosphenytoin and IV phenytoin
- 98206 -- IM fosphenytoin and IV phenytoin

Bioequivalence
- 98220 -- IV fosphenytoin and IV phenytoin
- 98224 -- IV fosphenytoin and IV phenytoin

Dose Proportionality
- 98218 -- IV fosphenytoin

Clinical
- 98205 -- IM and IV fosphenytoin substituted for PO phenytoin in epileptic patients
- 98213 -- IM fosphenytoin substituted for PO phenytoin in epileptic patients
- 98214 -- IM fosphenytoin for seizure prophylaxis in neurosurgery patients
- 98215 -- IV fosphenytoin or IV phenytoin for seizure prophylaxis in neurosurgery patients
- 98216 -- IV fosphenytoin in status epilepticus patients

Special Populations
- 98207 -- IV fosphenytoin in hepatically compromised and renal failure patients

Drug Interaction
- 98211 -- IV fosphenytoin and IV diazepam

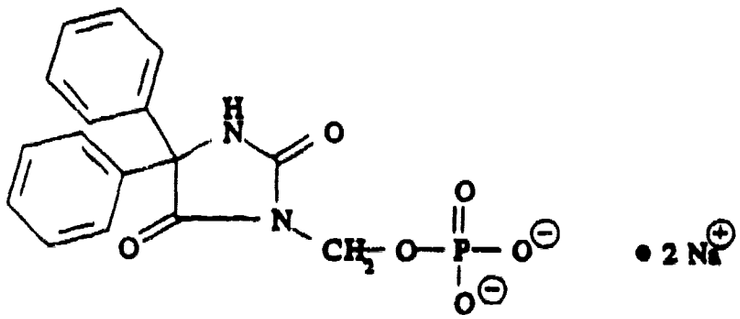
Research Reports
- RR 764-02124 -- protein binding of fosphenytoin and phenytoin
- RR-X 764-02114 -- pharmacokinetic meta-anlysis of fosphenytoin clinical trials
- RR 764-02074 -- cross-reactivity of fosphenytoin in phenytoin immunoassays
- RR 764-02073 -- stability of fosphenytoin in blood and plasma containing heparin or EDTA

Introduction

The following (pp. 7 - 9) are excerpted from the NDA and provide a suitable introduction to the pharmacology and chemistry of fosphenytoin. Statements regarding BA/PK/PD within this Introduction are the sponsor's contentions and not necessarily the reviewer's conclusions.

The nomenclature for fosphenytoin is as follows:

Structural Formula



Molecular Formula	$C_{16}H_{13}N_2O_6PNa_2$
Molecular Weight	406.24
Chemical Name	5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
Code Designations	CI-982 disodium salt PD 135711-15B 9653
USAN	Fosphenytoin sodium
CAS Registry Number	92134-98-0
Other Name	Cerebyx®

Fosphenytoin sodium (hereafter referred to as fosphenytoin) is a prodrug of the anticonvulsant phenytoin, intended for parenteral administration. Fosphenytoin is rapidly and completely converted to phenytoin in vivo. The pharmacological effects of phenytoin derived from fosphenytoin are essentially the same as those of parenteral phenytoin. The anticonvulsant effects of phenytoin have not been observed with fosphenytoin prior to conversion to phenytoin.

2.3.2. Scientific Rationale

Parenteral phenytoin is used for the acute treatment and control of seizures in patients with status epilepticus, for the treatment or prophylaxis of seizures in patients with epilepsy or in neurosurgical patients, and as a substitute for oral phenytoin when oral administration is not feasible. The current parenteral formulation is prepared in a vehicle of 40% propylene glycol and 10% ethanol adjusted to pH 12 with sodium hydroxide, and can be administered either intravenously or intramuscularly. Intravenous administration of phenytoin often produces local pain and burning and has also been associated with hypotension, cardiac rhythm disturbances, and severe tissue necrosis following extravasation. Intramuscular administration of phenytoin is not widely used because its absorption is erratic and unreliable, it crystallizes at the injection site, and it also produces local reactions.

Unlike phenytoin, fosphenytoin is freely soluble in aqueous solutions and is formulated in TRIS buffer at a pH of 8.6 to 9.0. Fosphenytoin is rapidly and completely converted to phenytoin in vivo. Parke-Davis developed fosphenytoin as an alternative to parenteral phenytoin based on the assumption that its formulation without organic solvents at a lower pH would result in better injection- or infusion-site tolerance and fewer of the complications associated with parenteral phenytoin administration. The development program focused on demonstrating bioequivalence between fosphenytoin and phenytoin and the safety of fosphenytoin. Since fosphenytoin is a phenytoin prodrug and no new therapeutic claims are being made beyond those already approved for parenteral phenytoin, proof-of-efficacy studies were not conducted.

2.3.3. Potential Clinical Benefits

Fosphenytoin is rapidly and completely converted to phenytoin. With IV administration of equimolar loading doses at the proper rate, fosphenytoin produces plasma concentrations of unbound phenytoin that are equivalent to those of IV Dilantin. Fosphenytoin administered IM is readily absorbed and is fully bioavailable. Fosphenytoin achieves therapeutic plasma phenytoin concentrations with the following clinical benefits:

- Fosphenytoin is significantly better tolerated at the injection or infusion site than parenteral Dilantin.

- Intravenous administration of fosphenytoin has fewer complications than parenteral Dilantin, including decreases in infusion rate because of local irritation or hypotension, changes in the IV site, and complications from infiltration.

- Fosphenytoin can be mixed with normal saline or 5% dextrose in water and administered without an in-line filter.

- Fosphenytoin offers IM administration as a viable alternative route.

2.3.4. Intended Use

This New Drug Application (NDA) supports the short-term (up to 14 days) use of fosphenytoin for the acute treatment and control of seizures in patients with status epilepticus, for the treatment or prophylaxis of seizures in patients with epilepsy or in neurosurgical patients, and as a substitute for oral phenytoin when oral administration is not feasible.

Bioequivalence

It is imperative to read IMPORTANT NOTE on p. 3 before reading the following.

As stated in the Introduction, the sponsor did not perform proof-of-efficacy studies with fosphenytoin, and desires that the drug be approved on the basis of bioequivalence with phenytoin.

Because phenytoin is highly (≈ 90%) protein bound in vivo, free phenytoin is the specie of clinical importance. Studies 98220 and 98224 are crossover studies comparing plasma free phenytoin concentrations following IV administration of fosphenytoin and Dilantin.

Study No. and Description	No. Entered	Demography	Drug Administration						
			Drug, Route	Dose (mg)	Dose (mgPE)	Regimen	Rate (mg PE/min)	No. of Participants	Duration of Dosing
98220	Total	Age Range	FOS, IV	1800	1200	Single dose	50	12	Single dose
	12	18-49	DIL, IV	1200	1200	Single dose	50	12	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects			PBO, IV[b]	NA	NA	Single dose	NA	12	Single dose
	Treatment	Gender							
	12 PBO	12 Males							
	12 FOS	0 Females							
	12 DIL								
	Analyzed[a]	Race							
	12 FOS	10 White							
	12 DIL	1 Black							
		1 Other							
98224	Total	Age Range							
	12	20-42	FOS, IV	1800	1200	Single dose	100	12	Single dose
			FOS, IV	1800	1200	Single dose	150	12	Single dose
Nonblind, randomized, 3-way crossover, single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects	Treatment	Gender	DIL, IV	1200	1200	Single dose	50	12	Single dose
	12 FOS	12 Males							
	12 DIL	0 Females							
	Analyzed[a]	Race							
	12 FOS	10 White							
	12 DIL	2 Other							

The results from these studies are excerpted on the following page.

TABLE 3. Comparison of Mean Free Phenytoin Pharmacokinetic Parameter Values Following IV Administration of 1200 mg Fosphenytoin and Dilantin (N = 12): Studies 982-20 and -24

Parameter	Fosphenytoin		Dilantin		Ratio	90% Confidence[a] Interval
	Mean	%RSD	Mean	%RSD		
	50 mg/min		50 mg/min			
Cmax, µg/mL	2.58	20.4	4.04	33.2	64.6[b]	53.8 - 77.8[b]
tmax, hr	0.49	35.2	0.46	22.2	108.2	94.7 - 121.7
AUC(0-tldc), µg·hr/mL	66.1	30.9	74.1	24.8	87.2[b]	83.0 - 91.7[b]
	100 mg/min		50 mg/min			
Cmax, µg/mL	2.78	21.8	3.30	25.6	84.7[b]	72.7 - 98.8[b]
tmax, hr	0.52	37.0	0.53	17.3	99.[illegible]	69.7 - 129.2
AUC(0-tldc), µg·hr/mL	79.5	14.1	87.1	22.0	92.2[b]	88.4 - 96.2[b]
	150 mg/min		50 mg/min			
Cmax, µg/mL	3.18	28.3	3.30	25.6	95.8[b]	82.1 - 111.7[b]
tmax, hr	0.57	58.5	0.53	17.3	109.[illegible]	79.8 - 139.3
AUC(0-tldc), µg·hr/mL	85.5	16.6	87.1	22.0	98.9[b]	94.8 - 103.2[b]

Mean = Arithmetic mean of untransformed data.
%RSD = Relative standard deviation (% of mean value).
Ratio = Ratio of treatment least-squares mean values (Fosphenytoin/Dilantin) expressed as a percentage.

[a] 90% Confidence Interval is the 90% confidence estimate for ratio of treatment least-squares mean values.

[b] These values are based on antilogs of treatment least-squares mean values.

Study 98224 demonstrates that, using standard bioequivalence criteria on free phenytoin data, 1200 mg IV fosphenytoin at 150 mg / min is bioequivalent to 1200 mg IV Dilantin at 50 mg / min based on AUC and Cmax. Dissimilarly, at the 100 mg/min rate and using free phenytoin data, fosphenytoin and Dilantin are equivalent for AUC but not equivalent for Cmax.

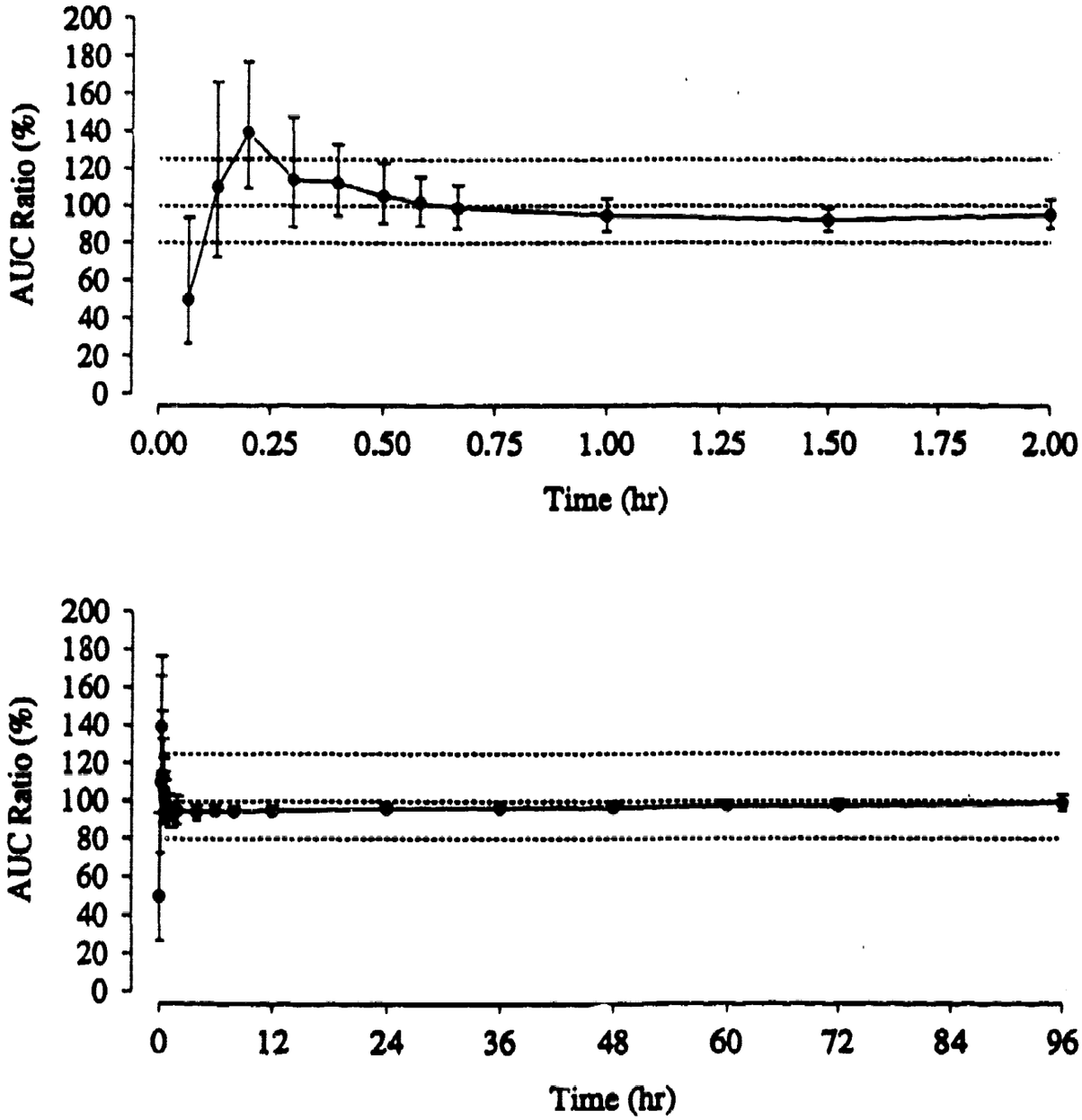


FIGURE 13. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 150 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

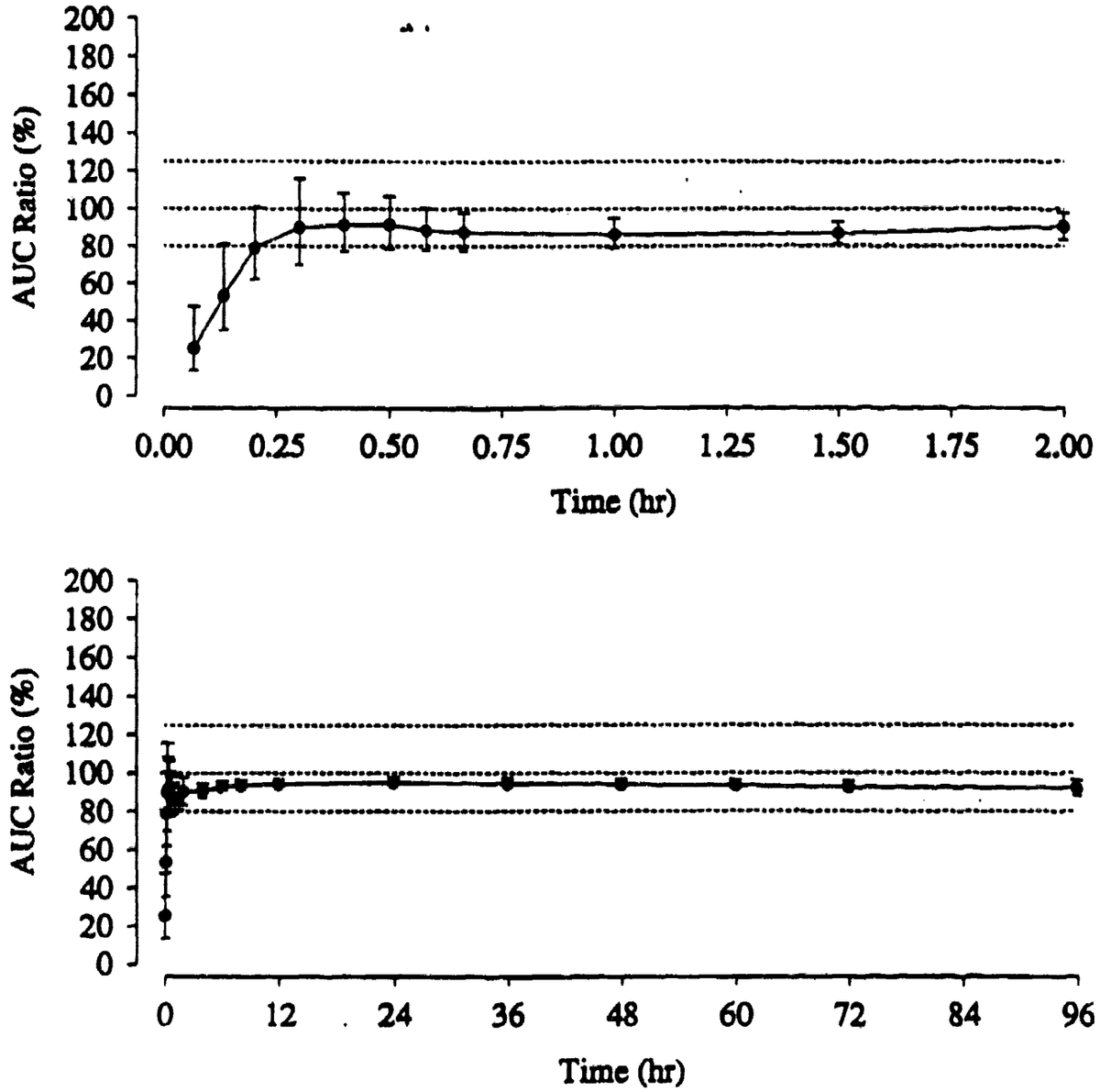


FIGURE 14. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 100 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

One of the desired indictions for fosphenytoin is acute status epilipticus. Efficacy in this disorder is presumably due to rapid attainment of high concentrations of plasma free phenytoin. Therefore, free phenytoin $AUC_{(0-TLDC)}$ may not be a measure of relevant exposure, and the sponsor was requested to calculate, across the first 2 hours post-initiation of dosing, the ratio of cumulative free phenytoin AUC from fosphenytoin administration to that from phenytoin administration. At both the 100 and 150 mg/min infusion rates, the 90% confidence interval for Cumulative AUC falls within the 80 - 125% range from about 30 minutes onward.

Studies 98220 and 98224 are the only investigations which attempt to show bioequivalence of free phenytoin from fosphenytoin and Dilantin. They provide a scientific basis for dosing recommendations when maximal dose / infusion rate is desired (eg. status epilepticus).

Fosphenytoin Pharmacokinetics

Plasma fosphenytoin concentrations increase with increasing dose and infusion rate and then decline with a terminal $t_{1/2}$ of approximately 0.25 hr independent of dose and infusion rate.

Fosphenytoin clearance is dependent upon both dose and infusion rate. Fosphenytoin is highly bound to plasma albumin (approximately 95 % bound at Cmax following high dose / high rate administration), and the changes in clearance are hypothesized to be a result of nonlinear protein binding: as dose and infusion rate increase, higher plasma fosphenytoin concentrations are attained, protein binding saturates, more free fosphenytoin is available to be metabolized, and fosphenytoin clearance is enhanced. The figure below illustrates the changes in clearance observed with changes in dosing regimen.

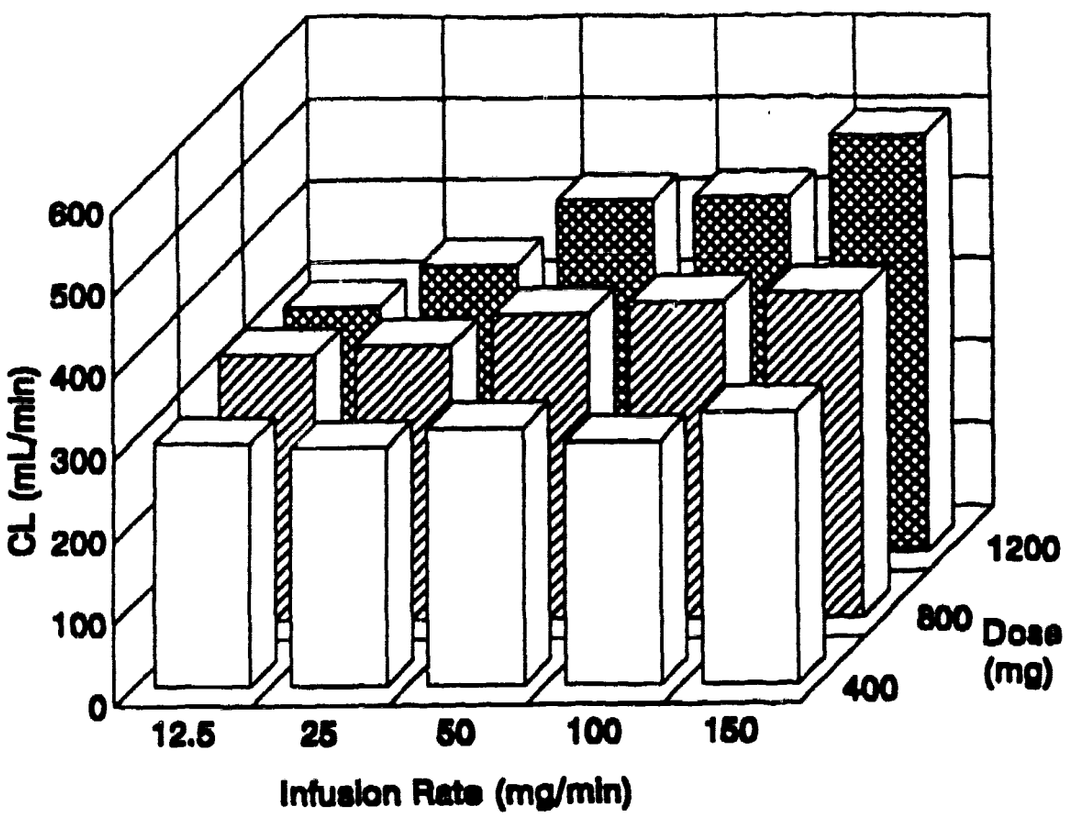


FIGURE 1. Relationship Between Mean Fosphenytoin Clearance Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects

The effect of the above mentioned changes in clearance on the concentration-time profile are not easily summarized. No structure exists which allows for the change in clearance to be used to describe changes occuring "early" in the concentration-time profile. What is meant by "early" is prior to the terminal linear phase of elimination. The sponsor has shown that concentration-dependent changes in clearance are accompanied by proportional changes in fosphenytoin volume of distribution during the terminal linear phase of metabolism (Vd_{area} varies from 4.3L when 100 mg is infused at 3.3 mg / min to 10.8 L when 1200 mg is infused at 150 mg / min). These Vd changes are consistent with a protein binding interaction model: as concentration increases free fraction increases and drug leaves plasma. The combination of increased clearance with increased Vd_{area} result in a constant elimination $t_{1/2}$.

Independent of dose, route or rate of administration, fosphenyotin is a short lived specie. The total number of individuals receiving serial sampling in studies 98213, 14, 15,

16, 18, 20 and 24 was 124. Of these 124 only 7 (< 6%) had detectable fosphenytoin plasma concentrations at 5 or more hours post-initiation of administration.

Based upon equal AUC of total phenytoin from IV phenytoin and from fosphenytoin, it appears that conversion of fosphenytoin is essentially complete.

Special Populations

A study with renal failure patients and hepatically compromised patients was performed. Before examining the first table below (Table 3.), please note that the values listed for Cmax, AUC, Cl and Vd require adjustment -- the values for Cmax and AUC can be determined by multiplying the table values by 0.753. The values for Cl and Vd can be determined by dividing the table values by 0.753. The values for Tmax, lambda$_z$ and $t_{1/2}$ do not require adjustment. The second table below (Table 7.) is for phenytoin and no correction factor is required.

TABLE 3. ACC-9653 PHARMACOKINETIC PARAMETERS
(MEAN ± SD)

note: portions of this table require correction -- see text above

Parameter (Units)	Volunteer Group Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (µg/mL)	35.6 ± 13.2(a)	25.9 ± 10.5	43.4 ± 8.9
T_{max} (min)	36.1 ± 6.1(a)	26.7 ± 5.9	31.6 ± 1.4
λ_z (hr^{-1})	5.59 ± 2.20	10.42 ± 3.65(a)	4.71 ± 1.61
$t_{1/2}$ (min)	8.56 ± 3.91(b)	4.38 ± 1.77(b)	9.51 ± 2.71(b)
AUC_{0-T} (µg*hr/mL)	17.8 ± 8.8	12.9 ± 5.7	25.5 ± 8.2
$AUC_{0-\infty}$ (µg*hr/mL)	17.9 ± 7.9	13.0 ± 5.7	25.5 ± 8.2
Cl (L/hr)	21.3 ± 8.4	29.3 ± 11.7	13.7 ± 3.7
Cl (L/hr/kg)	0.291 ± 0.142	0.337 ± 0.147	0.158 ± 0.047
V_d (L)	4.04 ± 1.58	2.80 ± 0.57	2.97 ± 0.43
V_d (L/kg)	0.0528 ± 0.0193	0.0327 ± 0.0106	0.0344 ± 0.0077

(a) - N=3

(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 7.44 ± 2.93, 3.99 ± 1.88, and 8.83 ± 3.36 minutes for the renal, hepatic, and healthy volunteer groups, respectively.

(c) - Significant difference from healthy subjects ($p < 0.05$). (Hepatic vs Healthy)

TABLE 7. PHENYTOIN PHARMACOKINETIC PARAMETERS
(MEAN ± SD)

Parameter (Units)	Volunteer Group		
	Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (µg/mL)	4.59 ± 1.29[a]	4.41 ± 1.33	4.28 ± 0.62
T_{max} (hr)	0.79 ± 0.39[a]	0.71 ± 0.22	1.38 ± 0.51
λ_z (hr^{-1})	0.0421 ± 0.0132	0.0293 ± 0.0188	0.0338 ± 0.0077
$t_{1/2}$ (hr)	17.0 ± 5.0[b]	26.5 ± 11.2[b]	21.3 ± 4.0[b]
AUC_{0-T} (µg•hr/mL)	50.9 ± 17.4	50.4 ± 11.1	62.2 ± 9.4
$AUC_{0-\infty}$ (µg•hr/mL)	97.4 ± 40.9	104.7 ± 27.2	112.1 ± 26.6

(a) - N=3.
(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 18.5 ± 5.6, 23.7 ± 7.9, and 20.5 ± 4.8 hours for the renal, hepatic, and healthy volunteer groups, respectively.
No statistically significant differences were observed between volunteer groups ($p > 0.05$).

Using the corrected values, fosphenytoin clearance is more than 2-fold as great in cirrhosis patients and about 1.8-fold as great in renal failure patients than in healthy volunteers; however, it should be noted than the number of patients in each group of this study is small. Based on these data plasma concentration monitoring for patients with renal and hepatic disease is recommended in labeling.

Visual inspection of fosphenytoin concentration-time profiles does not show differences across age, gender, race or any other sub-group. This is consistent with the fact that phosphatase activity is extensive and differences between individuals are likely to result in little or no difference in the conversion of fosphenytoin to phenytoin.

The conversion of fosphenytoin to phenytoin is consistent and essentially complete. There is no evidence of atypical phenytoin pharmacokinetics due to differences in fosphenytoin disposition between individuals.

Drug interactions

Standard treatment for status epilepticus at many institutions includes concomitant administration of IV diazepam and IV phenytoin. Therefore, the sponsor performed a drug interaction study examining the effect of concomitant administration of fosphenytoin and diazepam on the pharmacokinetic profiles of fosphenytoin, diazepam and phenytoin derived from fosphenytoin. No differences in the kinetics of fosphenytoin, phenytoin or diazepam occurred. However, the doses of fosphenytoin and diazepam used in the study were submaximal: 750 mg of fosphenytoin was administered, labeling is for up to 20 mg/kg (1400 mg in a 70 kg individual). Ten mg of diazepam was administered, labeling is for doses up to 30 mg. Thus, conditions likely to show an interaction (maximium dose of both agents) were not examined.

The metabolism of fosphenytoin to phenytoin is accomplished by phosphatases. Since phosphatases are generally not responsible for xenobiotic drug metabolism, pharmacokinetic drug interactions between fosphenytoin and agents which are not phosphate pro-drugs are unlikely. Given the abundance and wide distribution of phosphatases, it is unlikely that drug interactions between fosphenytoin and other phosphatase-converted pro-drugs would be significant.

IM administration

Because phenytoin is not usually administered IM, fosphenytoin IM was compared to phenytoin PO and phenytoin IV.

Average absolute bioavailability of phenytoin derived from a maintenance dose (250 mg) of IM fosphenytoin administered to healthy volunteers is 101% (Study 98206).

In epilepsy patients being maintained on PO Dilantin, substitution of equimolar IM fosphenytoin for PO Dilantin results in an increase in $Cmax_{free\ phenytoin}$ (38%), $AUC_{free\ phenytoin}$ (24%), and $trough_{free\ phenytoin}$ (16%) (study 98213). This observed increase in Cmax may be due to differences in dosing frequency: PO Dilantin was administered QID while IM fosphenytoin was given QD.

Formulation

Only one fosphenytoin formulation (the to-be-marketed formulation) was studied clinically.

Analytical methods

Page

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Response to EIRs identified in 483 Forms

Following site inspections for the 98214, 98218 and 98224 studies, the Division of Scientific Investigations issued multiple Form 483 to Parke-Davis. A review of the EIRs detailed in these 483 is provided as Appendix 5. We find that two of the EIRs need be addressed. The first is identified as 1. in Appendix 5 and is reproduced below.

1. Reported fosphenytoin concentrations were in error since the water content of the fosphenytoin reference standard was not taken into account in calculations.

The water content of the fosphenytoin sodium reference material was reported to be 22.5%. The salt form represented only 77.5% of the weight of the undried powder. The firm did not dry the powder on the grounds that the material was unstable with respect to heat. Therefore, the reported concentrations of fosphenytoin in plasma are in error, and need to be corrected. Similarly, some of the derived pharmacokinetic parameters for fosphenytoin (Cmax, AUC, CL, Vd) require correction.

In response to the identification of this deficiency, Parke-Davis audited the NDA to determine if errors in the calculation of fosphenytoin concentrations occured in studies other than 98214, 98218 and 98224. A portion of their conclusions is presented on the following page.

Parke Davis-generated studies

As noted in the October 19, 1995, submission, fosphenytoin concentrations and estimates of fosphenytoin Cmax, AUC, CL and Vd in clinical trials conducted by Parke-Davis may be corrected by applying a correction factor of 0.753. Fosphenytoin free fraction, tmax, elimination rate and half life estimates are unaffected as their estimation does not depend on the absolute value of concentrations used in their derivation. Therefore, parameters documenting the rate of fosphenytoin conversion to phenytoin are not affected. Further, phenytoin and free phenytoin concentrations, whether derived from Dilantin or fosphenytoin, are unaffected and thus the bioequivalency of fosphenytoin and phenytoin as presented in the pending NDA are not affected.

Generated studies

Our submission of October 19, 1995, indicated that we were attempting to determine if the fosphenytoin concentrations reported in the initial studies generated by were also in error. We have since determined that these concentrations in the clinical studies are most likely in error. We have determined the lot number and water content of fosphenytoin reference standard used in Protocols 982-007 (renal and hepatic disease) and 982-011 (diazepam interaction). Our findings indicate that it is likely that fosphenytoin concentrations and parameters in these reports can be corrected by applying the same correction factor used in Parke-Davis studies. Since these reports were prepared by we have not modified the original reports, but have added appropriate information to the cover page. Lot numbers, and thus the water content, of fosphenytoin reference standards used in other studies cannot be unequivocally determined at this time. We have also added information identifying this potential problem to the cover pages of these reports. These early studies document phenytoin pharmacokinetics following low fosphenytoin doses (Studies 982-1,3), the absolute bioavailability of phenytoin following intravenous and intramuscular fosphenytoin dosing (Studies 982-2,5,6,10), the effects of hepatic and renal insufficiency on fosphenytoin conversion to phenytoin (Study 982-7), and a diazepam-phenytoin drug-drug interaction study following fosphenytoin administration (Study 982-11). These studies are intended to address questions of rate and extent of fosphenytoin conversion to phenytoin. Parameters used to reflect these processes (fosphenytoin half-life and phenytoin AUC, Cmax, and tmax) are unaffected. Therefore, the conclusions from these studies are not affected by our inability to accurately modify the fosphenytoin concentrations in these early studies.

The errors in fosphenytoin concentrations have NOT been accounted for in the individual study reports (Appendix 2). The values have little bearing on the interpretation of studies -- the specie of clinical interest is generally plasma phenytoin, not plasma fosphenytoin.

The second EIR of significance is identified as 3. in Appendix 5 and is reproduced below.

3. Failure to use the appropriate matrix to prepare QC samples for validating stability in storage and reliability of the ultrafiltration step (assays of free phenytoin in plasma ultrafiltrate) and for validating stability in frozen urine.

The assay for phenytoin in sample plasma ultrafiltrate included the following stages: frozen storage, thawing, possible refreezing and rethawing, ultrafiltration, dilution, extraction, and chromatography. In the case of the QC samples, used both for validating stability in storage and monitoring daily performance of the assay, the stages of frozen storage, thawing, and freeze/thaw cycles were conducted after ultrafiltration, out of the sequence for study samples. Thus, the possibilities that phenytoin stability was different in PUF vs. plasma, that the binding proteins were unstable, and that the binding equilibria between free and protein-bound phenytoin disproportionated during frozen storage, thawing, or freeze/thaw cycles, were not investigated. The recovery of free phenytoin during the ultrafiltration stage was not established. The within-day and between-day variability of the ultrafiltration stage was not considered. The reproducibility of the ultrafiltration stage was not monitored during the assay of subject samples, because plasma-based QC samples were not ultrafiltered with each run.

QC samples for the assay of phenytoin in PUF should have been prepared in fresh whole plasma. The firm replied that phenytoin stability in whole plasma was demonstrated, and contended that this established stability of phenytoin measured in PUF. The considerations outlined in the previous paragraph (differences in

stability, stability of binding proteins, disproportionation, recovery, ultrafiltration variability) were not addressed.

There is literature evidence that plasma proteins do not degrade with multiple freeze/thaw cycles, and there is also literature evidence that plasma phenytoin can be stored frozen for lengthy periods of time without degradation of phenytoin. The NDA provides evidence that fosphenytoin is stable when stored frozen in plasma. However, because of the improper handling of the standards, we cannot categorically rule out the possibility that differences in stability of fosphenytoin, phenytoin and/or binding proteins, did occur between the samples assayed in studies 98214, 98218 and 98224. We believe that such differences likely did not occur, but this belief is not based upon empirical evidence from the studies themselves.

Sign-off

This review was presented to the Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology and Biopharmaceutics on December 18, 1995. Attendees:

Office of Clinical Pharmacology and Biopharmaceutics: Drs. Lesko, Malinowski, Chen, Gillespie, Baweja, Harris, Miller, Williams

Division of Neuropharmacologic Drug Products: Drs. Leber, Feeney, Fitzgerald, Fisher

FT Robert Z. Harris 12/21/95 Robert Harris, Ph.D.

FT R. Miller 12/21/95 Raymond Miller, Ph.D.

FT Gene W. Williams 12/21/95 Gene Williams, Ph.D.

FT R. Baweja 12/21/95 Raman Baweja, Ph.D.
Team Leader

cc: NDA 20-450 (orig), HFD 120, HFD 860 (Harris, Miller, Williams, Baweja, Malinowski), HFD 340 (Viswanathan), HFD 019; Drug, Chron, and Reviewer files

APPENDIX 1

28 Pages

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APPENDIX 2

STUDY: A dose ranging tolerance study of CI-982 in healthy volunteers: A single center study

PROTOCOL NUMBER: 982-01 (9653-86-01)

RESEARCH REPORT NUMBER: RR 744-00024

STUDY DESIGN: This was a single blind, dose-ranging study with randomized placebo control. The drug was administered by iv infusions over 30 minutes. The dose administered was: 150 mg (n=5), 300 mg (n=4), 600 mg (n = 4), and 1200 mg (n=3). The maximum infusion rate was 40 mg/min. Blood was sampled up to 72 hours after the initiation of the infusion.

DOSAGE FORM: See Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

SAFETY RESULTS: No adverse experiences were reported at the 300 and 600 mg dose. Minor CNS adverse reactions including lightheadedness, headache and nystagmus were reported at the 600 and 1200 mg doses. None of the subjects prematurely discontinued the study.

PHARMACOKINETIC RESULTS: The pharmacokinetic results are summarized in Table 1 below. Fosphenytoin was rapidly converted to phenytoin with a half-life of approximately 7.7 minutes. Fosphenytoin appeared to display linear kinetics in this concentration range. This result is consistent with later studies because the highest dosage in this study (1200 mg fosphenytoin at a rate of 40 mg/min = 800 mg phenytoin equivalents at a rate of 27 mg/mL) is lower than the dosages at which nonlinearities have been observed. Phenytoin kinetics were consistent with those previously reported. Thus, at the relatively low doses used in this study it does not appear that fosphenytoin has a large effect on phenytoin pharmacokinetics. Subtle changes in phenytoin pharmacokinetics would not have been detected in this type of study.

CONCLUSIONS: In healthy volunteers, fosphenytoin is safely administered at the highest level studied (1200 mg given over 30 minutes). It is rapidly converted to phenytoin.

Table 1. Fosphenytoin and phenytoin pharmacokinetic parameters. Values are mean ± standard deviation.

	FOSPHENYTOIN				PHENYTOIN			
DOSE (mg)	Cmax (μg/mL)	CL (L/hr)	Vc (L)	T1/2 (min)	Cmax (μg/mL)	CL (L/hr)	Vc (L)	T1/2 (hr)
150	19.9 ±2.6	13.3 ±2.0	2.5 ±0.3	7.75 ±0.5	2.2 ±0.4	3.1 ±1.3	48 ±11	10.7 ±2.2
300	36.0 ±4.6	14.2 ±3.2	3.0 ±0.3	8.93 ±1.2	4.1 ±0.4	2.8 ±1.0	48 ±4.9	14.7 ±10.2
600	70.3 ±5.0	14.0 ±2.2	2.4 ±0.3	7.23 ±0.2	6.9 ±0.7	3.2 ±0.4	59 ±6.4	12.5 ±0.4
1200	135 ±13.0	14.2 ±1.8	2.3 ±0.5	6.55 ±7.4	18.8 ±1.3	1.4 ±0.3	41 ±1.5	20.4 ±3.9

STUDY: Absolute bioavailability of phenytoin after intravenous CI-982 administration of healthy male volunteers

PROTOCOL NUMBER: 982-02 (9653-86-02)

RESEARCH REPORT NUMBER: RR 744-00025

STUDY DESIGN: This was a randomized, open-label, two treatment crossover. The 250 mg phenytoin and 375 mg fosphenytoin doses were administered by iv infusions over 30 minutes. Twenty six blood samples were obtained per treatment up to 120 hours after drug infusion. Total drug concentration in the plasma was measured at all time points, total concentration in the blood was measured at six of the collection times points, and unbound concentration in the plasma was measured at two time points (at the end of the infusion and 30 minutes after the end of the infusion). Treatments were separated by two weeks.

SUBJECTS: Healthy male volunteers (n=12).

DOSAGE FORM: See Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study, and the temperature at which ultrafiltration was performed is not clear from the study report.

SAFETY RESULTS: No major adverse reactions were observed in this study. Fosphenytoin injection caused less injection site irritation than did phenytoin injection.

PHARMACOKINETIC RESULTS: The bioavailability of phenytoin after iv fosphenytoin administration compared to after iv phenytoin administration was 99.2% ± 0.031 (because of the low variability the two dosages are actually bioequivalent in terms of AUC; Table 3). The concentration time profiles were similar but not superimposable at early time points (Figure 1). The unbound fraction of phenytoin was highest immediately after the fosphenytoin infusion (Table 1, this result is consistent with fosphenytoin displacing phenytoin from plasma proteins. The effect is quite small because of the relatively small fosphenytoin dose used in this study). The blood to plasma ratio for fosphenytoin was approximately 0.5 for 5 of the six time points measured (Table 2). At the latest time point (3 hr) the ratio increased to approximately 2. This unexpected result is likely due to analytical errors caused by the very low fosphenytoin concentrations at this time point. As described in the analytical section above, the results of this part of the study are in question due to the use of heparin as the anticoagulant.

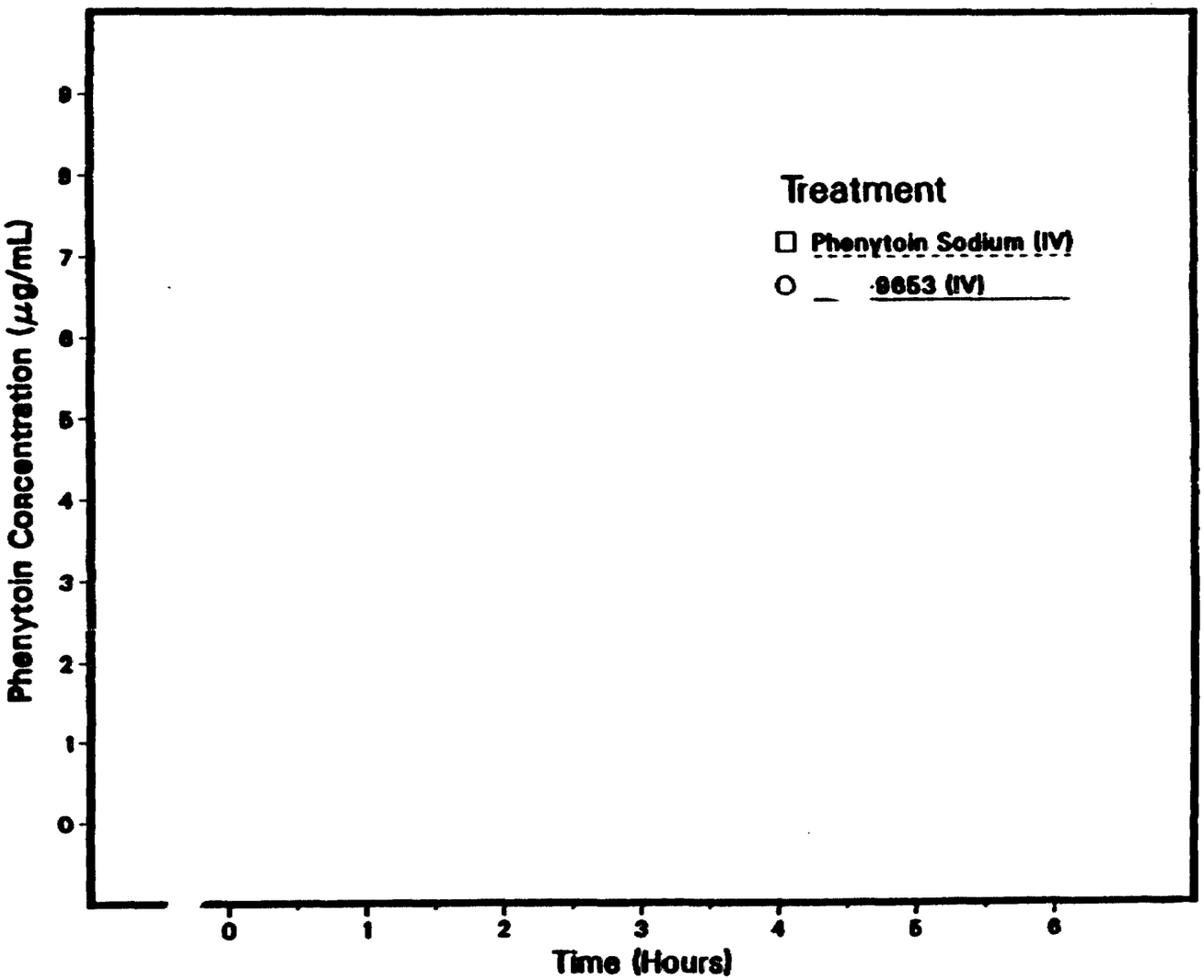
Bioavailability would have been better determined by a comparison of unbound AUCs instead of total AUCs. This is because bioavailability calculations are based on the assumption that clearance does not differ in the two treatments that are being compared. In this case, fosphenytoin can displace phenytoin from plasma proteins thereby increasing fu and total phenytoin clearance. Unbound clearance would not have been affected by this phenomenon and thus unbound AUC comparison would have been a better measure of bioavailability. However, because fosphenytoin is relatively short-lived in the plasma, and because the fu of phenytoin was only increased by approximately 1% due to fosphenytoin this effect should have had only a very

small influence on phenytoin AUC. The fact that the phenytoin concentration/time profiles were very similar for most of the time period also helps support the validity of the bioavailability conclusions made in this study.

CONCLUSIONS: Fosphenytoin is completely converted to phenytoin after intravenous administration. Fosphenytoin does not significantly distribute into red blood cells.

Figure 1
~~Figure 3~~

Mean Phenytoin Plasma Concentration Versus Time



* Significant difference between treatments.

Medical Summary
#9653-86-02

Table 1
~~Table 9~~

Mean Free Fraction of Phenytoin in Plasma -
Analysis of Difference Between Treatments At Each Time Point

Time Since Start	Free Fraction of Phenytoin (%)

* - Significant difference between treatments (P <0.05).

Table 2
~~Table 5~~

Mean Blood Concentration/Plasma Concentration Ratios
c ·9653 as a Function of Time

Time Since Start of Infusion (hr:min)	Ratio		
	N	Mean	(SEM)
0:10			
0:20			
0:30			
0:45			
1:00			
3:00			

Page

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STUDY: Because of similarities, Studies 98205 and 98213 are being reviewed together. Evaluation of Phenytoin Levels After IM and IV ACC-9653 Administration in Epileptic Patients on Chronic Oral Dilantin Monotherapy (Protocol 9653-86-05 or 982-05). A 5-Day, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Clinical Study of Tolerance and Safety of Multiple Doses of Intramuscularly Administered Fosphenytoin Sodium (CI-982) Substituted for Oral Dilantin in Epilepsy or Neurosurgery Patients (Protocol 982-013).

PROTOCOL NUMBER: 982-05 (9653-86-05), 982-013

RESEARCH REPORT NUMBER: RR 720-03273, RR 720-03148

STUDY DESIGN: 98205 -- a 2 arm crossover where a single dose of IM fosphenytoin (150 - 450 mg; n = 38) and a single dose of IV fosphenytoin (150 - 450 mg; n = 40) were substituted for oral Dilantin in 42 epilepsy patients being maintained on oral Dilantin BID. A single trough concentration was taken 12 hrs after PO Dilantin. Serial sampling was performed for 12 hours following IM and IV fosphenytoin

98213 -- 5 doses (200 - 500 mg/day) of IM fosphenytoin QD) were substituted for . Dilantin in epilepsy patients being maintained on oral Dilantin QID. Serial sampling was performed prior to receiving fosphenytoin (day -1) and on day 5 following the final dose of fosphenytoin in 11 patients.

SUBJECTS: 98205;

age: 39.1 $\pm$ 12.0 yrs
38 white, 5 black
32 male, 11 female

98213; analyses performed by reviewer on evaluable population (those having free concentrations following both PO Dilantin and IM fosphenytoin):

age: 38.3 $\pm$ 9.2 yrs
6 white males, 3 white females, 1 black male, 1 black female

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in Study 98205. EDTA was used as an anti-coagulant and ultrafiltration performed at 37° C in Study 98213.

SAFETY RESULTS: 98205 -- Parenteral fosphenytoin was well tolerated by the patients. No clinically significant changes in blood pressure, heart rate, respiration, neurological status (except nystagmus), and the electrocardiogram were observed following either IM or IV treatment.

98213 -- There were no clinically significant differences in the type and frequency of adverse events between fosphenytoin and Dilantin treatment groups, and the adverse event profile was similar to that expected with phenytoin therapy.

PHARMACOKINETIC RESULTS: 98205 (single dose fosphenytoin) -- The data are presented on the following 3 pages (Figures 1 and 2; Table 1), and show that, as expected, IV administration produces a steeper rise in the concentration time profile than IM administration.

98213 (multiple dose fosphenytoin) -- The data are presented on pp 68-69 (Figure 3, Table 2). For at least the first 4 hrs post-administration, free concentrations of phenytoin following IM fosphenytoin administration are considerably greater than those following PO Dilantin administration (Figure 3). This is consistent with a protein binding interaction: when fosphenytoin is present phenytoin is displaced and free phenytoin concentrations increase. It is also consistent with the total phenytoin data: total phenytoin is more bioavailable from IM fosphenytoin than from PO Dilantin (Figure 3, Table 2). This increase in total phenytoin concentrations results in the increased free phenytoin concentrations noted.

Quantitatively, $Cmax_{free\ phenytoin}$ is 38% greater, $trough_{free\ phenytoin}$ is 16% greater and $AUC_{free\ phenytoin}$ is 24% greater, following fosphenytoin IM than following Dilantin PO (Table 2).

Figure 8

MEAN PHENYTOIN PLASMA CONCENTRATIONS AS A FUNCTION OF TIME AFTER IV ADMINISTRATION OF -9653

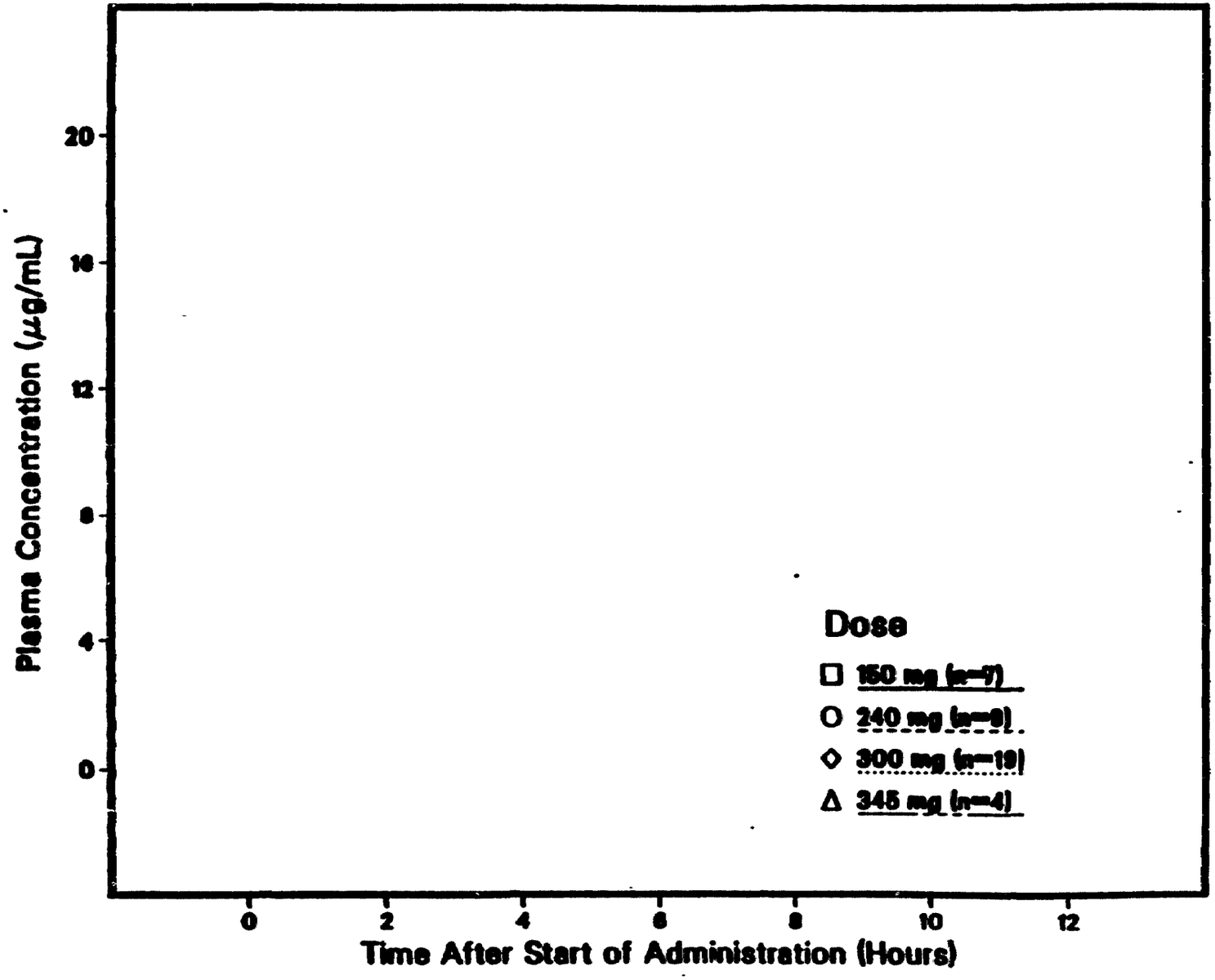


Figure 2

MEAN PHENYTOIN PLASMA CONCENTRATIONS AS A FUNCTION OF TIME AFTER IM ADMINISTRATION OF

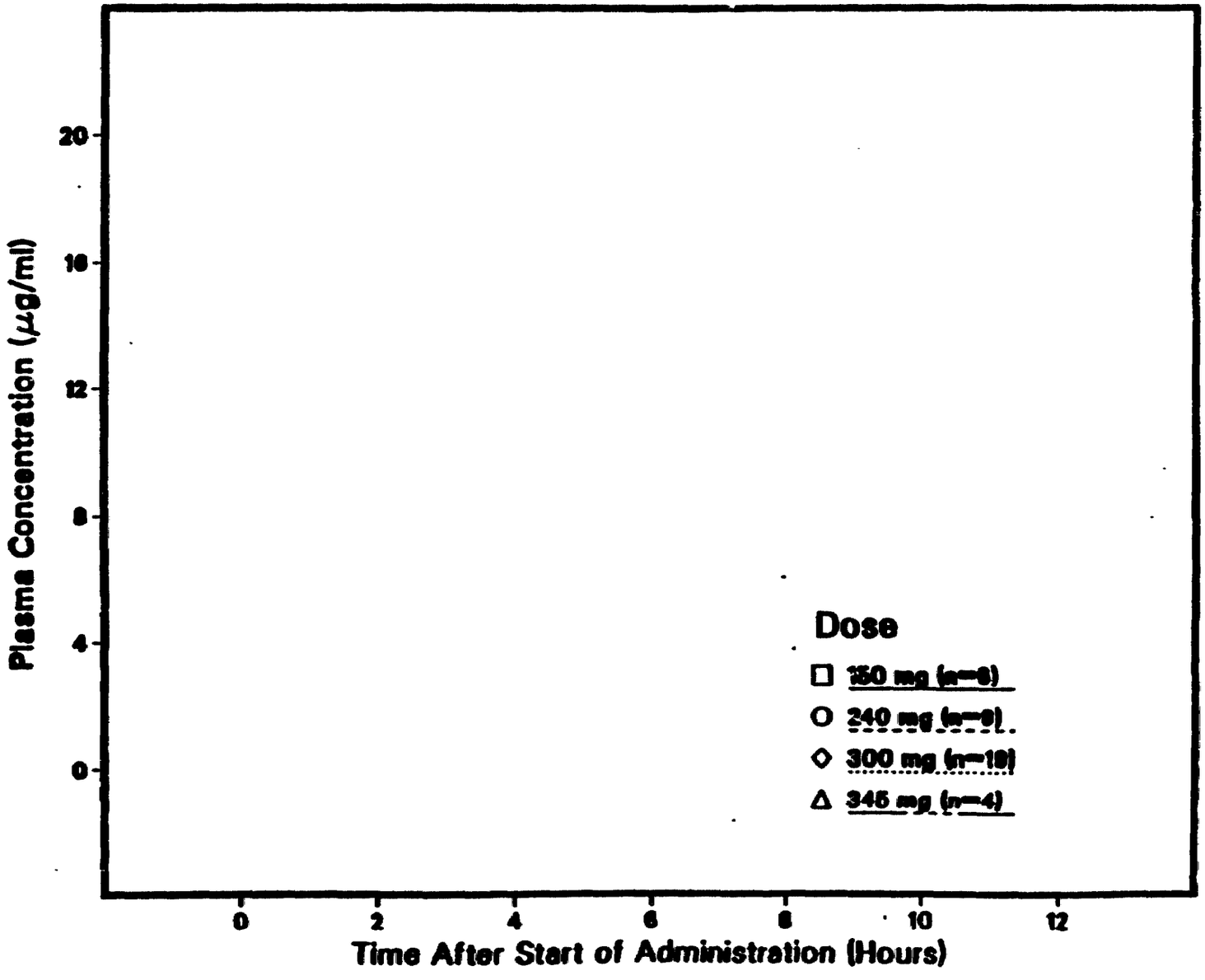


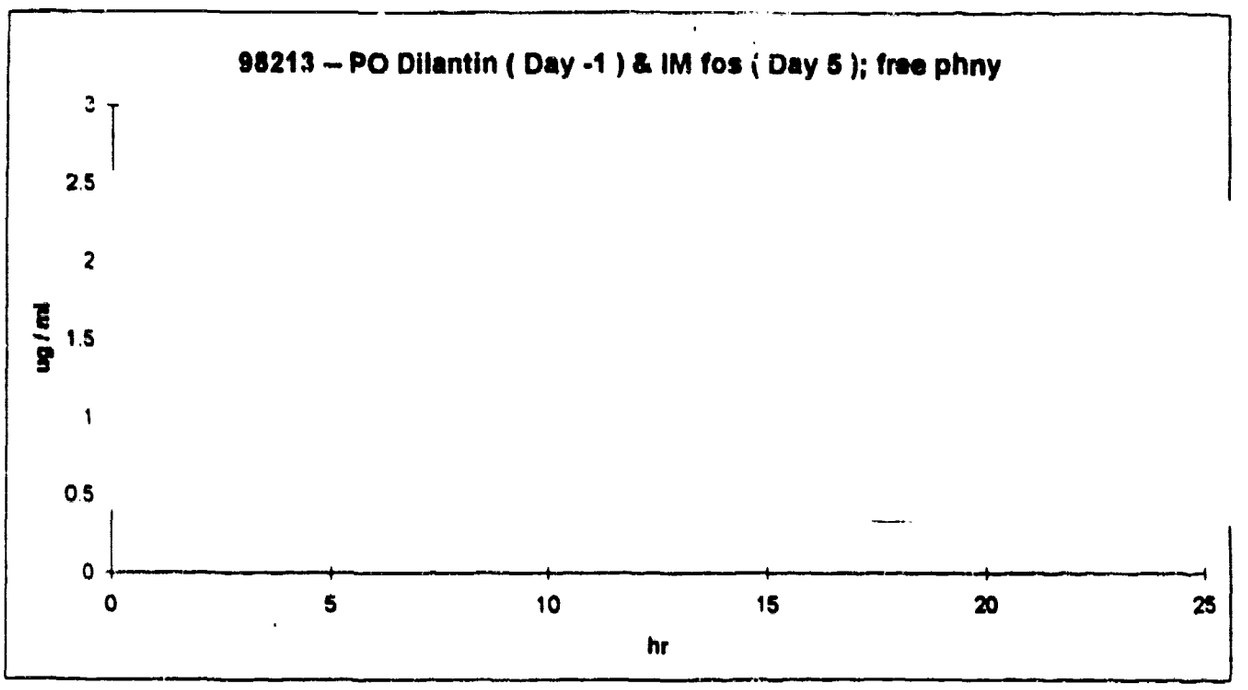
TABLE X

Trough Phenytoin Levels (µg/mL) After IV and IM Administrations of -9653*

Route	Dose (mg)	N	Baseline**	12 Hr Post -9653	Difference	P-Value
IV	150	7	12.0(1.6)	[illegible].0(1.5)	0.0(0.7)	0.946
	195	1	22.8(-)	21.3(-)	-1.5(-)	
	240	9	11.3(1.7)	10.4(1.6)	-1.0(0.6)	0.128
	300	16	13.9(1.9)	14.3(2.0)	0.4(0.5)	0.435
	345	4	12.9(1.8)	16.3(3.3)	3.4(2.6)	0.279
	450	1	7.2(-)	6.0(-)	-1.3(-)	--
IM	150	6	12.7(1.7)	12.1(2.3)	-0.7(0.8)	0.420
	195	1	22.4(-)	21.1(-)	-1.3(-)	--
	240	9	12.0(1.8)	11.3(1.7)	-0.7(0.3)	0.056
	300	16	14.7(2.0)	14.7(2.1)	0.0(0.6)	0.985
	345	4	14.8(1.6)	15.3(1.9)	0.5(1.1)	0.687
	450	2	13.4(9.7)	15.6(10.1)	2.2(0.5)	0.129

* - All data are expressed as mean (SEM).
** - Concentrations were determined 12 hours after the patient's last dose of oral Dilantin®.

Figure 3


98213 – PO Dilantin (Day -1) & IM fos (Day 5); free phny
ug / ml
3
2.5
2
1.5
1
0.5
0
0
5
10
15
20
25
hr

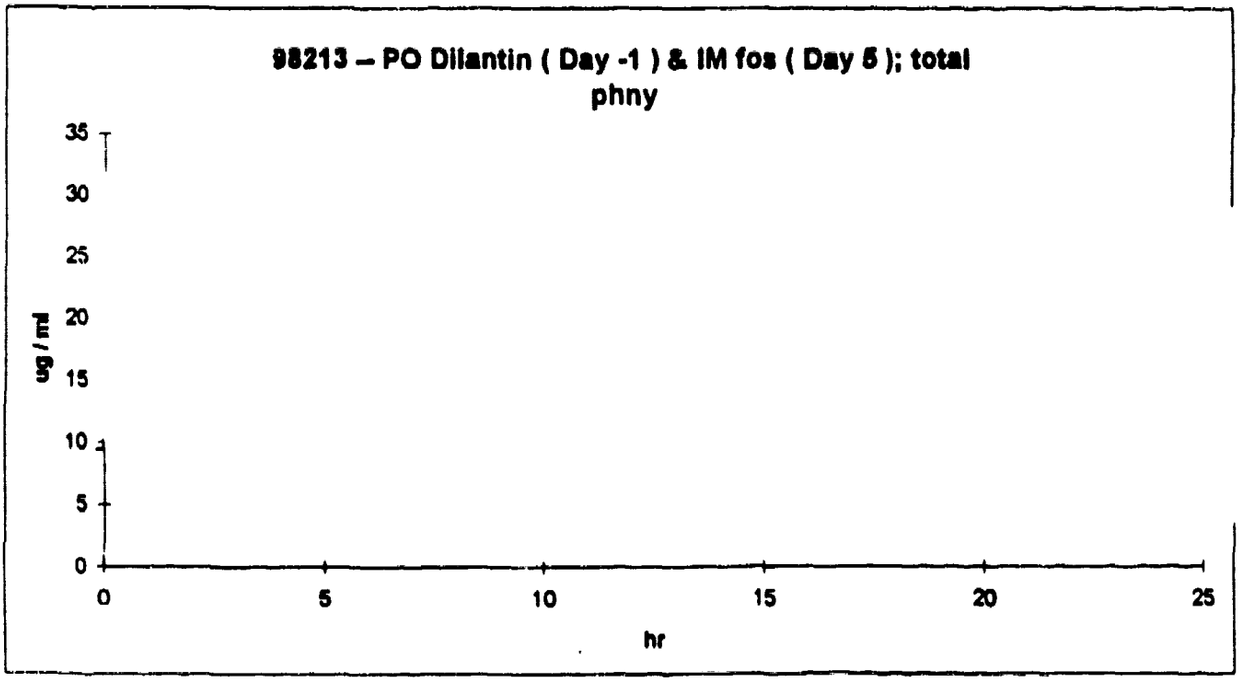

98213 – PO Dilantin (Day -1) & IM fos (Day 5); total phny
ug / ml
35
30
25
20
15
10
5
0
0
5
10
15
20
25
hr

Table 2

Study 98213 – densely sampled PK data from 1 center ***

free phenytoin

dose (mg / day)	n	Cmax (ug / ml) PO Dilantin	Cmax (ug / ml) IM fosphenytoin	AUC (ug hr / ml) PO Dilantin	AUC (ug hr / ml) IM fosphenytoin	trough (ug / ml) PO Dilantin	trough (ug / ml) IM fosphenytoin
200	1	2.59	2.17	38.05	39.68	1.40	1.73
300	2	1.19	1.74	24.94	33.57	0.99	1.21
400	5	1.54	1.97	31.61	36.71	1.14	1.19
500	3	1.29	2.45	26.66	39.97	0.95	1.27
200 - 500	11	1.51 ± 0.53	2.08 ± 0.67	29.63 ± 8.44	36.84 ± 12.42	1.09 ± 0.40	1.27 ± 0.61

total phenytoin

dose (mg / day)	n	Cmax (ug / ml) PO Dilantin	Cmax (ug / ml) IM fosphenytoin	AUC (ug hr / ml) PO Dilantin	AUC (ug hr / ml) IM fosphenytoin	trough (ug / ml) PO Dilantin	trough (ug / ml) IM fosphenytoin
200	1	24.4	36.6	505.9	548.6	17.5	19.1
300	2	13.6	15.7	276.3	283.4	10.3	9.9
400	5	17.9	19.7	366.5	378.1	12.9	13.?
500	3	21.9	8.9	459.1	556.8	17.2	
200 - 500	11	18 ± 5.?	23.0 7.9	388.1 ± 121.4	425.1 ± 149.0	14.0 ± 5.0	14.9 ± 6.1

*** dataset is the same as in the graphs on the previous page
values are means; values for 200 - 500 are mean ± S.D.
Cmax from inspection of C vs T data, AUC from trapezoids

CONCLUSIONS: Substitution of equimolar IM fosphenytoin for PO Dilantin results in an increase in $Cmax_{free\ phenytoin}$ (38%) and $AUC_{free\ phenytoin}$ (24%) (study 98213). The increase in Cmax may be due to differences in dosing frequency: PO Dilantin was administered QID while IM fosphenytoin was given QD.

The effect of substitution of IV fosphenytoin for PO Dilantin on Cmax of free phenytoin can be inferred. IM administration of fosphenytoin results in higher $Cmax_{phenytoin}$ than PO administration of phenytoin, and IV administration of fosphenytoin results in higher $Cmax_{phenytoin}$ than IM administration of fosphenytoin. Thus, IV administration of fosphenytoin is likely produces an even greater increase in $Cmax_{phenytoin}$ than does IM administration of fosphenytoin. This increase in $Cmax_{phenytoin}$ would be expected to result in an increase in $Cmax_{free\ phenytoin}$. Also, IV administration results in greater $Cmax_{fosphenytoin}$ than does IM administration. Based upon this increased piasma fosphenytoin causing displacement of phenytoin protein binding, $Cmax_{free\ phenytoin}$ should be higher following IV administration of fosphenytoin than following IM administration of fosphenytoin.

STUDY: Absolute bioavailability of phenytoin after intramuscular CI-982 administration to healthy male volunteers

STUDY NUMBER: 982-06 (9653-86-06)

RESEARCH REPORT NUMBER: RR 744-00028

STUDY DESIGN: This was a randomized, open-label, two treatment crossover. Fosphenytoin (250 mg) was injected into the gluteus maximus muscle over approximately 30 seconds. Six volunteers received 2 simultaneous 2.5 mL injections and 6 volunteers received a single 5 mL injection. Phenytoin (250 mg) was administered via an iv infusion over 10 minutes. Twenty six blood samples were obtained per treatment up to 120 hours after drug infusion. Only total fosphenytoin and phenytoin concentrations in the plasma was measured. Treatments were separated by two weeks.

SUBJECTS: Healthy male volunteers (n=12).

DOSAGE FORM: See Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

SAFETY RESULTS: No major adverse reactions were observed in this study. IM fosphenytoin injection caused less injection site irritation than did IV phenytoin injection.

PHARMACOKINETIC RESULTS: The pharmacokinetic results of this study are summarized in Tables 1 - 3. The plasma concentration time curves for phenytoin and fosphenytoin are given in Figures 1 - 3. The elimination half-life for fosphenytoin after IM injection averaged 44 minutes (Table 1), considerably longer that the 15 minute half-life typically observed after IV fosphenytoin injection. This result suggests that flip-flop kinetics are occurring (i.e. terminal rate reflects absorption from muscle tissue). The Cmax was higher and the Tmax was earlier when the dose was administered by 2 IM injections compared to a single IM injection (Table 3).

The bioavailability of phenytoin from IM fosphenytoin (compared to IV phenytoin) was 101.2 ± 1.6% (Table 2). Bioavailability was not affected by whether the drug was given as one or two injections, although the rate of absorption was faster after two injections (Table 3). Not surprisingly, phenytoin Cmax was lower and the Tmax was later after IM fosphenytoin injection compared to IV phenytoin infusion (Table 2, Figure 2).

CONCLUSION: Fosphenytoin is completely converted to phenytoin after intramuscular injection. Fosphenytoin absorption from muscle is fairly smooth and appears to follow simple first order kinetics with a half-life of approximately 0.75 hr. Thus, IM fosphenytoin appears to be a reasonable form of maintenance therapy.

2 Pages

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Table 3

ACC-9653 and Phenytoin Pharmacokinetic Parameters

Analysis of Difference Between Number of 9653 Injections

Compound	Variable	2 IM Injections N	2 IM Injections Mean[§]	2 IM Injections (SEM)	1 IM Injection N	1 IM Injection Mean[§]	1 IM Injection (SEM)	P-Value
9653	C_{max} (mcg/mL)	8	28.02	(2.98)	8	15.48	(1.13)	0.001*
	T_{max} (h)	8	0.36	(0.06)	8	0.83	(0.15)	0.014*
	Terminal Rate Const. (h^{-1})	8	1.23	(0.17)	8	0.85	(0.05)	0.085
	Half-Life (min)	8	37.89	(5.87)	8	50.04	(3.58)	0.061
	AUC (0-120) (mg-h/L)	8	31.92	(2.34)	8	30.16	(1.94)	0.572
	AUC (0-∞) (mg-h/L)	8	32.24	(2.32)	8	30.59	(1.98)	0.601
	% AUC accounted	8	98.99	(0.36)	8	98.57	(0.45)	0.482
	Clearance (L/hr)	8	10.58	(0.69)	8	11.10	(0.72)	0.598
Phenytoin	C_{max} (mcg/mL)	8	6.10	(0.20)	8	5.26	(0.24)	0.021*
	T_{max} (h)	8	2.67	(0.11)	8	3.58	(0.37)	0.040*
	Elim. Rate Const. (h^{-1})	8	0.041	(0.004)	8	0.042	(0.004)	0.915
	Half-Life (h)	8	17.87	(2.03)	8	17.39	(1.73)	0.860
	AUC (0-120) (mg-h/L)	8	173.2	(21.4)	8	141.2	(14.3)	0.243
	AUC (0-∞) (mg-h/L)	8	178.8	(22.7)	8	144.7	(15.1)	0.250
	% AUC accounted	8	97.48	(0.41)	8	97.75	(0.71)	0.751
	Bioavailability	8	1.008	(0.017)	8	1.018	(0.030)	0.846

§ - Means of C_{max}, AUC and clearance are weight adjusted.
* - Significant difference between number of IM injections given ($P < 0.05$).

Figure 1
Mean .9653 Plasma Concentration Versus Time

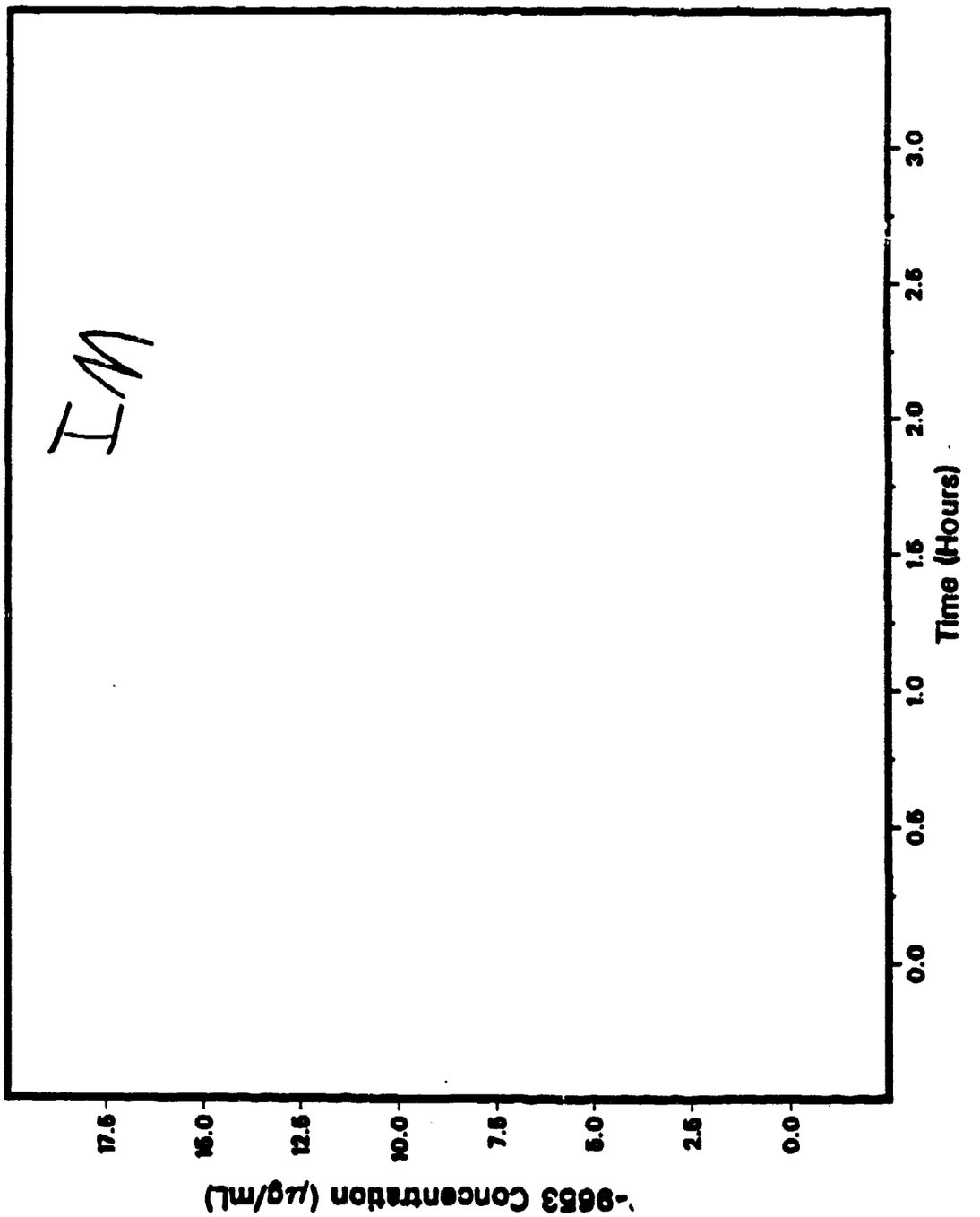
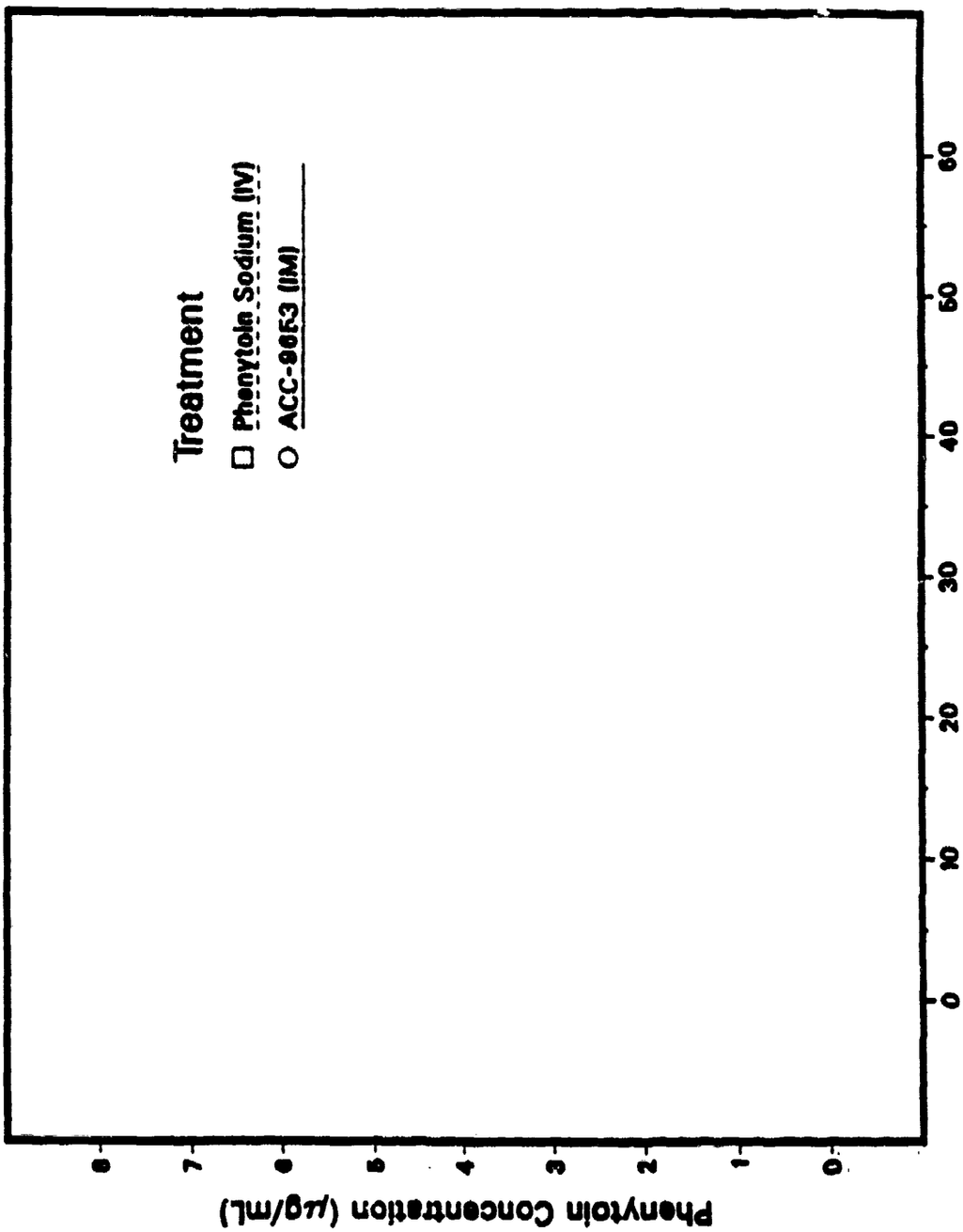


Figure 2
Mean Phenytoin Plasma Concentration Versus Time



* Significant difference between treatments.

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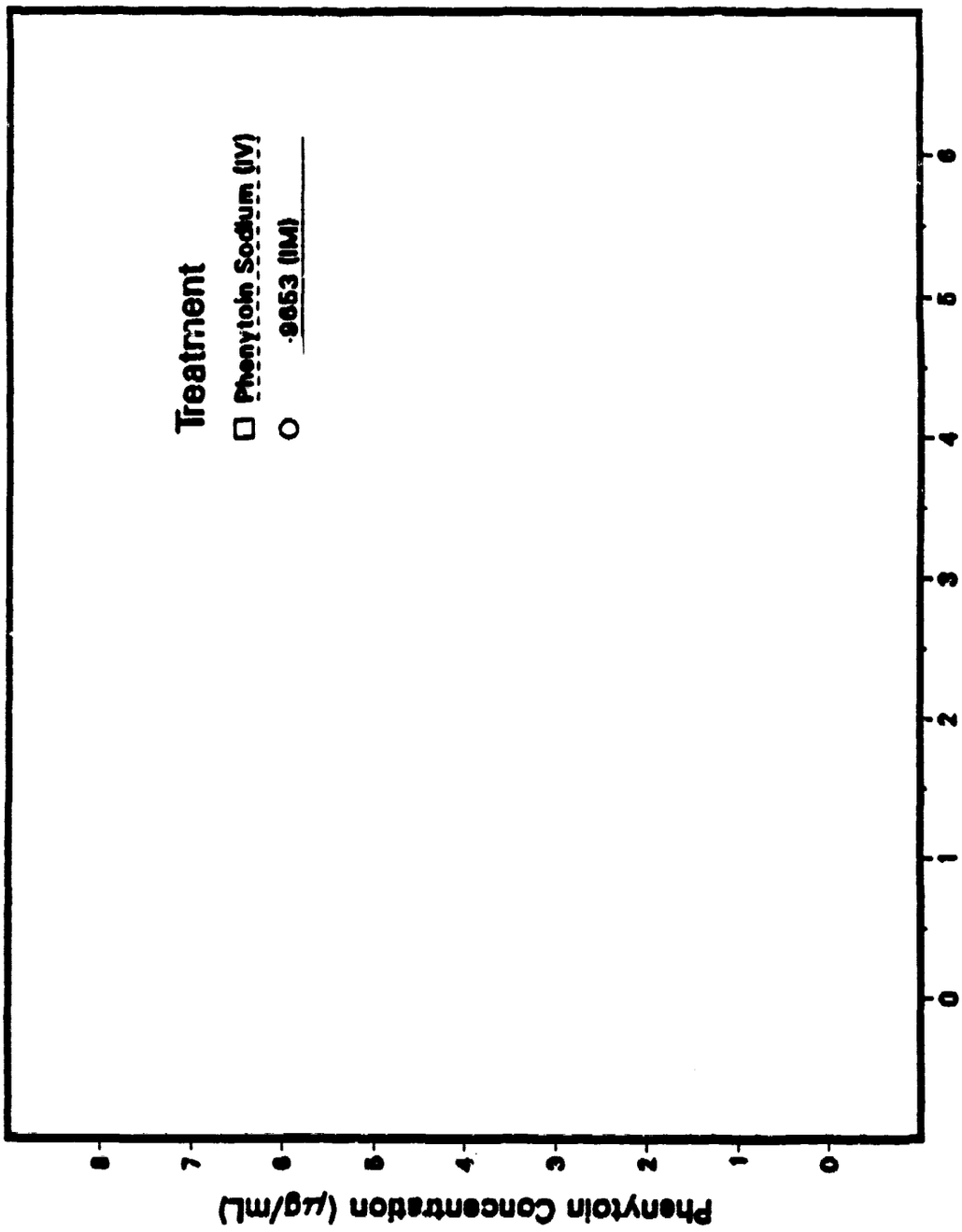
Figure 3
Mean Phenytoin Plasma Concentration Versus Time



* Significant difference between treatments.

STUDY: Conversion Of CI-982 To Phenytoin In Patients With Renal Or Hepatic Disease Compared To Healthy Subjects - A Pilot Study

PROTOCOL NUMBER: 982-07 (9653-87-07)

RESEARCH REPORT NUMBER: RR 744-00029

STUDY DESIGN: Single center, open label study with screening, baseline, treatment, and poststudy periods. Each individual received 250 mg phenytoin equivalents of fosphenytoin IV administered over 30 min. It should be noted that the protocol allowed patients to continue ongoing therapy during the trial. Documentation of ongoing therapy was not provided.

SUBJECTS: 15 males were enrolled in the study:

TABLE 1. DEMOGRAPHIC SUMMARY
(MEAN ± SEM)

Parameter (Units)	Volunteer Group		
	Renal (n=5)	Hepatic (n=4)	Healthy (n=6)
Age (years)	54.5 ± 2.5[a]	51.8 ± 5.6[b]	29.2 ± 1.1
Height (cm)	175.3 ± 2.4	179.7 ± 3.5	184.2 ± 2.1
Weight (kg)	77.1 ± 5.3	89.3 ± 9.2	86.8 ± 3.3

Values in the above table are mean ± SEM. Renal failure patients required maintenance hemodialysis, hepatic patients had: 1. liver biopsy evidence of cirrhosis, 2. a total serum bilirubin level less than 4 mg%, 3. a creatinine clearance rate of at least 60 ml / min.

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

PROTOCOL VARIATIONS: Volunteers' #1 (healthy) and #2 (healthy) plasma sample extracts were incorrectly processed and therefore omitted. Volunteer #7 (renal failure) was also omitted due to "Chromatographic interferences". Volunteer #13 received only a 24 minute infusion, and was therefore not included in Cmax or Tmax analyses. Volunteers #4 (hepatic), #12 (renal), #13 (renal), and #14 (renal), received modified, or no, treatment with their ongoing concomitant therapies.

SAFETY RESULTS: No adverse clinical events were reported and no clinically significant changes were observed in the physical examinations, clinical laboratory parameters, clinical observations, or electrocardiograms.

PHARMACOKINETIC AND STATISTICAL METHODS:

Demographic information was summarized for each group (renal, hepatic, and hepatic) separately. Differences among groups were assessed using a one-way ANOVA model for continuous data and Fisher's Exact Text for categorical data.

Maximum plasma concentration (C_{max}) and the time of the maximum plasma concentration (T_{max}) were determined by observation.

The terminal or "apparent" disposition rate constant (λ_n) was calculated as the slope of the terminal portion of the log-linear plasma concentration versus time curve.

The terminal or "apparent" disposition half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \frac{\ln 2}{\lambda_n}$$

Area under the plasma concentration versus time curve ($AUC_{0\to\infty}$) was calculated by the trapezoidal rule up to the last quantifiable concentration ($AUC_{0\to T}$) plus the residual area calculated as the ratio of the final plasma concentration divided by λ_n.

Clearance (CL) of ACC-9653 was calculated by:

$$CL = \frac{Dose}{AUC_{0\to\infty}}$$

Volume of distribution (V_d) of ACC-9653 was calculated by:

$$V_d = \frac{CL}{\lambda_n}$$

CL and V_d values were standardized to each volunteer's weight.

Differences in PK parameters among groups was assessed using a one-way ANOVA model. Statistical analysis and preparation of the summary tables were carried out using SAS. A result was deemed " statistically significant " when the accompanying statistical test yielded a two-tailed probability (p-value) of 0.05 or less.

PHARMACOKINETIC RESULTS:

TABLE 3. 9653 PHARMACOKINETIC PARAMETERS
(MEAN ± SD)

Parameter (Units)	Volunteer Group		
	Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (µg/mL)	35.6 ± 13.2(a)	25.9 ± 10.5	43.4 ± 8.9
T_{max} (min)	30.1 ± 8.1(a)	20.7 ± 5.9	31.8 ± 1.4
λ_z (hr^{-1})	5.50 ± 2.20	10.42 ± 3.85(a)	4.71 ± 1.61
$t_{1/2}$ (min)	8.58 ± 3.01(b)	4.26 ± 1.77(b)	9.51 ± 2.71(b)
$AUC_{0-\infty}$ (µg*hr/mL)	17.8 ± 8.0	12.9 ± 5.7	25.5 ± 8.2
$AUC_{0-\infty}$ (µg*hr/mL)	17.9 ± 7.9	13.0 ± 5.7	25.5 ± 8.2
CL (L/hr)	21.3 ± 8.4	29.3 ± 11.7	13.7 ± 3.7
CL (L/hr/kg)	0.291 ± 0.142	0.337 ± 0.147	0.158 ± 0.047
V_d (L)	4.04 ± 1.50	2.80 ± 0.57	2.97 ± 0.48
V_d (L/kg)	0.0528 ± 0.0193	0.0327 ± 0.0100	0.0344 ± 0.0077

(a) - N=3
(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 7.44 ± 2.93, 3.99 ± 1.80, and 8.83 ± 3.30 minutes for the renal, hepatic, and healthy volunteer groups, respectively.
(c) - Significant difference from healthy subjects ($p < 0.05$). (Hepatic ≠ Healthy)

TABLE 7. PHENYTOIN PHARMACOKINETIC PARAMETERS
(MEAN ± SD)

Parameter (Units)	Volunteer Group: Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (μg/mL)	4.59 ± 1.26[a]	4.41 ± 1.33	4.28 ± 0.82
T_{max} (hr)	0.79 ± 0.39[a]	0.71 ± 0.22	1.38 ± 0.51
λ_n (hr^{-1})	0.0421 ± 0.0132	0.0293 ± 0.0106	0.0338 ± 0.0077
$t_{1/2}$ (hr)	17.6 ± 5.6[b]	26.5 ± 11.2[b]	21.3 ± 4.8[b]
$AUC_{0-\tau}$ (μg*hr/mL)	80.9 ± 17.4	88.4 ± 11.1	82.2 ± 9.4
$AUC_{0-\infty}$ (μg*hr/mL)	97.4 ± 48.9	184.7 ± 27.2	112.1 ± 26.6

(a) - N=3.
(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 16.5 ± 5.6, 23.7 ± 7.9, and 20.5 ± 4.8 hours for the renal, hepatic, and healthy volunteer groups, respectively.
No statistically significant differences were observed between volunteer groups ($p > 0.05$).

TABLE 4. 9653 PROTEIN BINDING SUMMARY
(MEAN ± SD)

Parameter	Volunteer Group: Renal (n=3)	Hepatic (n=3)	Healthy (n=3)
Percent 9653 Unbound	12.66 ± 3.37[a]	8.84 ± 0.24	4.97 ± 0.47
Albumin (g/dL)	3.4 ± 0.7[a]	2.9 ± 0.7[b]	4.6 ± 0.3
Protein (g/dL)	6.4 ± 0.7	7.5 ± 0.6	7.8 ± 0.5

(a) - Significant difference from healthy subjects ($p < 0.05$). (Renal ≠ Healthy)
(b) - Significant difference from healthy subjects ($p < 0.05$). (Hepatic ≠ Healthy)

Based on the null hypothesis of no difference between groups, statistical significance ($p < 0.05$) is not reached in nearly all of the comparisons made above. However, the null hypothesis of no difference is inappropriate as differences would be expected based upon the protein binding nature of the drug and decreases in plasma protein which accompany renal and hepatic diseases. The study is insufficiently powered (3 - 4 in each group) to allow for the chosen statistical approach to be utilized, and trends are clearly observable.

CONCLUSIONS: The dose of fosphenytoin administered in this study was 250 mg phenytoin equivalents at 8.33 mg equivalents / min.. The sponsor has labeled the drug for administration at doses as large as 20 mg/kg at 150 mg/min. Clearly, the study fails to encompass the condition where changes in drug disposition are most easily observed and most clinically serious: following high dose and rate of administration. Further, free phenytoin concentrations were not measured in the study. Since free phenytoin is the specie of interest, and serum protein concentrations are altered by renal and hepatic disease (as would be expected these alterations were seen in the current study -- see Table on p.), this severely limits the ability to interpret the effect of renal and hepatic disease on the disposition of free phenytoin from fosphenytoin.

Fosphenytoin clearance is more than 2-fold greater in cirrhosis patients than in healthy volunteers, and over 1.5-fold greater in renal failure patients.

STUDY: Absolute bioavailability of phenytoin from CI-982 in patients with therapeutic serum phenytoin concentrations using stable isotope techniques

PROTOCOL NUMBER: 982-10 (9653-87-10)

RESEARCH REPORT NUMBER: RR 744-00030

STUDY DESIGN: This was a randomized, open-label study in epileptic patients on chronic oral phenytoin monotherapy. At separate injection sites in the same arm, each patient received 128 mg phenytoin equivalents of labelled fosphenytoin and 130 mg phenytoin equivalents of labelled phenytoin simultaneously. Blood was sampled at 25 time points up to 96 hours after drug administration. Urine was collected just prior to the infusions and from 0 - 1, 1 - 24, 24 - 48, 48 - 72 and 72 - 96 hours. Labelled and unlabeled phenytoin and fosphenytoin concentrations were measured in the plasma and urine via satisfactory HPLC and GC/MS methodologies. The phenytoin metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) was also measured in the urine.

SUBJECTS: Epileptic males on chronic oral phenytoin monotherapy (n=6).

DOSAGE FORM: ^{13}C-labelled fosphenytoin disodium (229.4 mg/3.2 mL, Lot #Z88-5-5) and ^{15}N-^{13}C labelled phenytoin sodium (189.9 mg/3.2 mL. Lot #Z88-5-5). see also Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

SAFETY RESULTS: No major adverse reactions were observed in this study.

PHARMACOKINETIC RESULTS: The pharmacokinetic results of this study are summarized in Tables 1 - 2. The pharmacokinetic parameters determined in these patients are very consistent with what was found in healthy volunteers. The AUC ratio of ^{13}C-phenytoin/^{15}N-^{13}C-phenytoin (i.e. AUC of phenytoin from fosphenytoin injection divided by AUC of phenytoin from phenytoin injection) was 0.96 with a 95% confidence interval for bioequivalence being 0.92 to 1.00. Thus, the bioavailability of fosphenytoin is virtually unity.

No fosphenytoin was detected in the urine. However, slightly more phenytoin was detected in the urine during the first 1 hour after fosphenytoin administration compared to after phenytoin administration (Table 3). This indicates that it is possible that a very small amount of fosphenytoin (approximately 1% of the dose) may be excreted in the urine, where it is subsequently hydrolyzed to phenytoin. The recovery of p-HPPH was higher after phenytoin administration than after fosphenytoin administration (Table 2), but this difference was small and not statistically significant.

CONCLUSION: This was an excellent method for determining bioavailability because intrasubject variability was completely eliminated. An intravenous dose of fosphenytoin was virtually completely converted to phenytoin in patients who were on chronic oral phenytoin therapy.

TABLE 5. PHENYTOIN PHARMACOKINETIC PARAMETERS IN PATIENTS (MEAN ± SD)

Parameter (units)	-9653 Infusion(b)	$^{15}N_2$-$^{13}C_3$-Phenytoin Infusion(b)
C_{max} (µg/mL)	3.25 ± 0.82	4.51 ± 1.07
T_{max} (min)	34.8 ± 36.8	12.7 ± 1.8
λ_n (hrs^{-1})	0.0274 ± 0.0059	0.0285 ± 0.006
$t_{1/2}$ (hrs)	26.4 ± 6.2(a)	25.4 ± 6.8(a)
AUC_{0-T} (µg•hr/mL)	69.2 ± 15.6(b)	73.8 ± 17.9
$AUC_{0-\infty}$ (µg•hr/mL)	75.7 ± 18.5	80.2 ± 20.8
AUC/Dose (µg•hr/mL•mg)	0.591 ± 0.144	0.618 ± 0.166
AUC Ratio (ACC-9653/Phenytoin)	0.963 ± 0.061	

C_{max} - Maximum plasma concentration.
T_{max} - Time of maximum plasma concentration.
λ_n - Terminal elimination rate constant.
$t_{1/2}$ - Terminal elimination half-life.
AUC_{0-T} - Area under the plasma concentration vs time curve from 0 to the time of the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from 0 to infinity.
(a) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 25.3 ± 5.4 and 24.3 ± 5.3 for the $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin infusions, respectively.
(b) - Statistically significant difference between infusions of $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin ($p < 0.05$).
Doses - 126.2 mg from the $^{13}C_3$-ACC-9653 infusion and 126.1 mg from the $^{15}N_2$-$^{13}C_3$-phenytoin infusion in terms of the equivalent amount of unlabelled phenytoin.

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TABLE 3. 9653 PHARMACOKINETIC PARAMETERS IN PATIENTS (MEAN ± SD)

Parameter (units)	-9653 Infusion		
Weight (kg)	85.2	±	13.5
C_{max} (µg/mL)	38.3	±	16.5
T_{max} (min)	13.6	±	1.1
λ_z (hrs^{-1})	0.42	±	2.67
$t_{1/2}$ (min)	8.88	±	7.24(*)
AUC_{0-last} (µg•hr/mL)	11.9	±	3.2
$AUC_{0-\infty}$ (µg•hr/mL)	12.2	±	3.4
Cl (L/hr)	16.4	±	6.3
Cl (L/hr/kg)	0.197	±	0.078
V_d (L)	3.13	±	1.92
V_d (L/kg)	0.0362	±	0.0157

C_{max} - Maximum plasma concentration.
T_{max} - Time of maximum plasma concentration.
λ_z - Terminal elimination rate constant.
$t_{1/2}$ - Terminal elimination half-life.
AUC_{0-last} - Area under the plasma concentration vs time curve from 0 to the time of the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from 0 to infinity.
Cl - Clearance
V_d - Volume of distribution.
(*) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation of half-life was 8.48 ± 2.57 minutes.
Dose - 250 mg $^{13}C_2$-ACC-9653 disodium salt, equivalent to 183.8 mg unlabelled ACC-9653 free acid.

TABLE 6. PHENYTOIN AND P-HPPH CUMULATIVE URINARY EXCRETION FROM PATIENTS (MEAN ± SD)

Elapsed Time (hrs)[c]	Phenytoin Excretion (% Dose) 9653	Phenytoin Excretion (% Dose) $^{15}N_2$-$^{13}C_3$-PHT	p-HPPH Excretion (% Dose) $^{13}C_3$-ACC-9653	p-HPPH Excretion (% Dose) $^{15}N_2$-$^{13}C_3$-PHT	Total Excretion (% Dose) 9653	Total Excretion (% Dose) $^{15}N_2$-$^{13}C_3$-PHT
1	0.90 ± 0.18[b]	0.10 ± 0.06	0.20 ± 0.11[b]	0.37 ± 0.18	1.27 ± 0.26[b]	0.55 ± 0.22
24	3.62 ± 0.81[b]	0.81 ± 0.18	10.81 ± 4.44[b]	21.14 ± 4.96	22.63 ± 4.87[b]	21.94 ± 5.08
48	4.15 ± 0.87[b]	1.16 ± 0.26	33.98 ± 8.60[b]	36.05 ± 9.7[illegible]	38.13 ± 9.09[b]	38.18 ± 9.94
72	4.24 ± 0.88[b]	1.19 ± 0.29	41.84 ± 10.70[b]	46.54 ± 12.18	46.09 ± 11.36	47.73 ± 12.46
96	4.27 ± 0.85[b]	1.22 ± 0.28	45.05 ± 10.81	50.81 ± 12.11	49.92 ± 11.13[b]	52.03 ± 12.23

Time Interval (hrs)[c]	Phenytoin Excretion Ratio 9653/$^{15}N_2$-$^{13}C_3$-PHT	p-HPPH Excretion Ratio 9653/$^{15}N_2$-$^{13}C_3$-PHT	Total Excretion Ratio 9653/$^{15}N_2$-$^{13}C_3$-PHT
0 - 1	0.81 ± 1.06	0.70 ± 0.11	2.47 ± 0.58
0 - 24	4.07 ± 1.00	0.00 ± 0.02	1.04 ± 0.02
0 - 96	3.62 ± 0.72	0.00 ± 0.02	0.96 ± 0.02

p-HPPH - [5-(4-hydroxyphenyl)-5-phenylhydantoin]
PHT - Phenytoin
Doses - 120.2 mg from the $^{13}C_3$-ACC-9653 infusion and 130.1 mg from the $^{15}N_2$-$^{13}C_3$-phenytoin infusion in terms of the equivalent amount of unlabelled phenytoin.
(a) - Relative to the start of the $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin infusions.
(b) - Statistically significant difference between infusions of $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin ($p < 0.05$).

STUDY: Evaluation of the Pharmacokinetic Interaction Between Diazepam and CI-982 in Healthy Male Volunteers

PROTOCOL NUMBER: 982-011 (9653-87-11)

RESEARCH REPORT NUMBER: RR 744-00031.

STUDY DESIGN: single center, randomized, nonblind, 3-way crossover study in healthy males. Solutions were infused undiluted by Harvard Syringe Pumps into indwelling catheters in the same arm. Treatments were separated by at least 13 days. The treatments were:

A) fosphenytoin (750 mg at 50 mg / min)
B) diazepam (10 mg/2 ml/5 min) followed 10 minutes later by fosphenytoin (750 mg at 50 mg / min)
C) diazepam (10 mg/2 ml/5 min)

SUBJECTS: The values below are approximate -- 11 individuals entered the study, but only 9 completed the PK portion; the table below is for the 11 who entered.

Variable (units)	Mean ± SEM	Range
Age (years)	25.1 ± 1.1	20 - 31
Height (cm)	180.1 ± 2.2	168.2 - 191.1
Weight (kg)	78.7 ± 2.8	69.0 - 99.4

All subjects were male Caucasians and non-smokers.

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study. Free fractions were determined by spiking with radiolabel and ultracentrifugation was performed at room temperature.

PROTOCOL VARIATIONS: There were no protocol variations. There were 2 dropouts. Subject #6 withdrew from the study after completing his first treatment (treatment B -- diazepam and fosphenytoin) following diagnosis of underlying borderline hypertension by hispersonal physician. Subject #10 was withdrawn from the study after participating in

treatments B and A (treatment B -- diazepam and fosphenytoin and treatment A -- fosphenytoin alone) because of a vasovagal episode during treatment A. Subjects 6 and 10 were included in the safety analysis but not in PK analysis.

SAFETY RESULTS: One subject (#10) experienced a vasovagal syncopal episode which included hypotension and bradycardia during Treatment A (fosphenytoin alone). These events required discontinuation of the study drug. This subject had previously completed treatment B (diazepam and fosphenytoin) without significant effects on heart rate, ECG intervals, or blood pressure. Follow-up evaluation of this episode, which included a 24 hour Holter monitor recording and a more extensive medical history, revealed no cardiologic abnormalities, but did detail a previously unreported episode of syncope during an intravenous drug study. In the investigator's clinical judgement, this episode was therefore related to the intravenous infusion but not to fosphenytoin. Ten of the 11 subjects who entered the study reported adverse clinical events in at least one treatment phase. These events are summarized below.

Symptom	9653 Site		Diazepam Site	
	Treatment Period			
	9653 Alone (N=9)	Diazepam and 9653 (N=11)	Diazepam Alone (N=9)	Diazepam and 9653 (N=11)
Subject's Evaluations				
Pain	1	0	1	2
Burning	0(*)	0(*)	4(*)	5(*)
Itching	1	1	1	0
Investigator's Evaluations				
Erythema	0	3	0	1
Swelling	0	1	0	2
Tenderness	2	3	1	3

TABLE 10. ADVERSE CLINICAL EVENTS SUMMARY
(NUMBER OF SUBJECTS REPORTING ADVERSE EVENT)

System and Adverse Event	Treatment: 9653 Alone (N=10)	Diazepam Alone (N=11)	Diazepam and 9653 (N=11)
Number of Subjects Reporting an Adverse Event	6	10	7
Body as a Whole	1	2	2
Headache	0	0	2
Infection Site Inflamed(a)	0	1	1
Injection Site Reaction(a)	1	0	0
Cardiovascular	2	0	0
Bradycardia	1	2	0
Hypotension	2	0	0
Gastrointestinal	1	0	1
Dry Mouth	0	0	1
Nausea	1	0	0
Central Nervous System	3	10(b)	2
Dizziness	1	3	0
Paresthesia	1	0	2
Somnolence	1	8(b)	0
Slurred Speech	0	1	0
Skin	2	0	2
Pruritus	2	0	2
Special Senses	1	0	0
Vision Abnormality	1	0	0

(a) - Injection site evaluations during the first 72 hours are provided in Table 11.
(b) - Statistically significant difference between treatments diazepam alone # 9653 alone and diazepam alone # diazepam and 9653
All adverse events were considered by the investigator to be possibly or probably related to the treatment(s).

PHARMACOKINETIC and STATISTICAL METHODS:

Pharmacokinetic parameters o -9653, phenytoin, and diazepam were calculated using non-compartmental methods. Calculations were based on the free acid form of ACC-9653 and the acid form of phenytoin.

Maximum plasma concentration (C_{max}) and the time of maximum plasma concentration (T_{max}) were determined by observation.

The terminal or "apparent" disposition rate constant (λ_n) was calculated as the slope of the terminal portion of the log-linear concentration versus time curve.

The terminal or "apparent" disposition half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \frac{\ln 2}{\lambda_n}$$

Area under the plasma concentration versus time curve ($AUC_{0\to\infty}$) was calculated by the trapezoidal rule up to the last quantifiable concentration ($AUC_{0\to T}$) plus the residual area calculated as the ratio of the final plasma concentration divided by λ_n.

Clearance (CL) was calculated by:

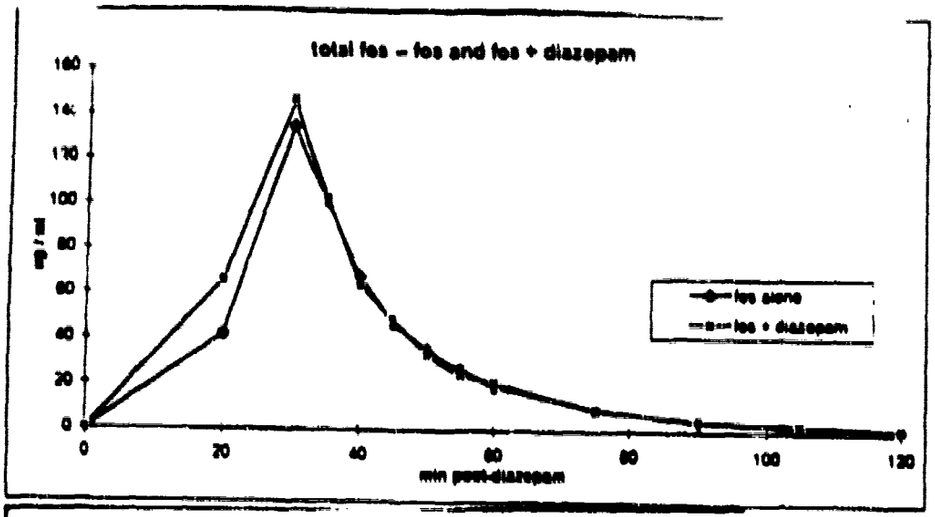
$$CL = \frac{Dose}{AUC_{0\to\infty}}$$

Volume of distribution (V_d) was calculated by:

$$V_d = \frac{CL}{\lambda_n}$$

CL and V_d values were standardized to each subject's weight.

PHARMACOKINETIC RESULTS:



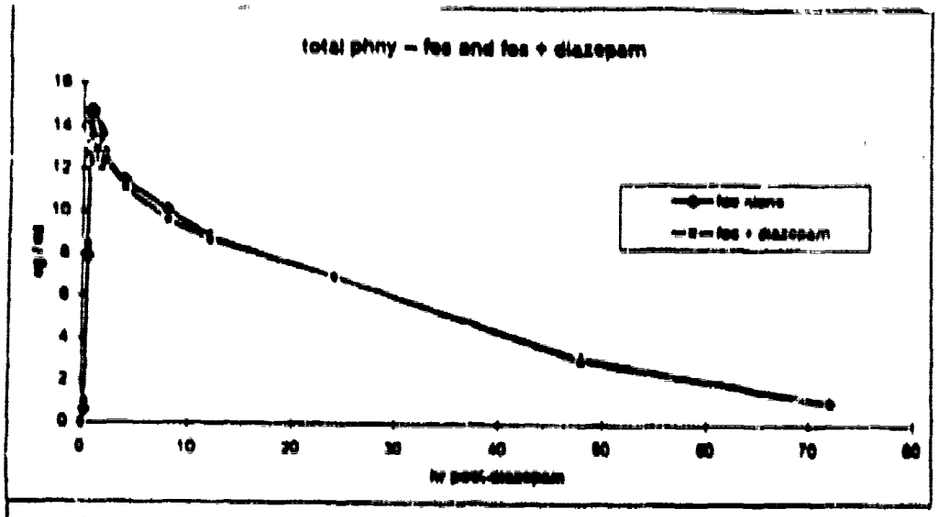
times are relative to the start of diazepam infusion; fosphenytoin was started at 15 minutes

n = 7 - 8

TABLE 3. ·9653 PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS (MEAN ± SD)

Parameter (units)	Treatment: ·9653 Alone (N=8)	Diazepam + ·9653 (N=8)
$C_{ss,max}$ (μg/mL)	135 ± 20	146 ± 13
$T_{ss,max}$ (min)	15.0 ± 0.2	15.1 ± 0.3
λ_z (hrs^{-1})	2.66 ± 0.61	2.92 ± 0.76
$t_{1/2}$ (min)	15.2 ± 3.1[a]	15.8 ± 3.4[a]
AUC_{0-t} (μg·hr/mL)	53.5 ± 11.8	57.6 ± 9.5
$AUC_{0-\infty}$ (μg·hr/mL)	54.2 ± 11.4	58.1 ± 9.7
CL (L/hr)	19.1 ± 4.6	17.7 ± 3.2
CL (L/hr/kg)	0.246 ± 0.039	0.229 ± 0.033
V_z (L)	8.82 ± 1.58	8.27 ± 1.58
V_z (L/kg)	0.0883 ± 0.0146	0.0818 ± 0.0166

$C_{ss,max}$ - Maximum plasma concentration.
$T_{ss,max}$ - Time of maximum plasma concentration relative to the start of the ·9653 infusion
λ_z - Terminal elimination rate constant.
$t_{1/2}$ - Terminal elimination half-life.
AUC_{0-t} - Area under the plasma concentration vs time curve from the start of t ·9653 to the time of the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from the start of t ·9653 infusion to infinity
CL - Clearance.
V_z - Volume of distribution.
(a) Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 14.6 ± 3.2 and 14.9 ± 3.6 minutes for the ·9653 treatment and the diazepam + ·9653 treatment, respectively.



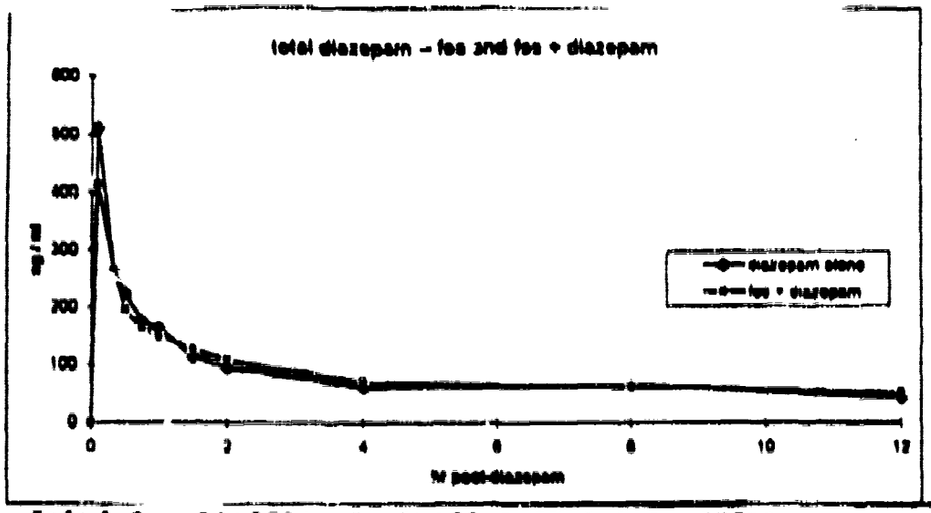
times are relative to the start of diazepam infusion; fosphenytoin was started at 0.25 hours

n = 7 - 8

TABLE 5. PHENYTOIN PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS (MEAN ± SD)

Parameter (units)	Treatment: 9553 Alone (Dose)	Diazepam and 9553 (Dose)
C_{max} (µg/mL)	18.4 ± 2.4	15.4 ± 2.8
T_{max} (min)	41.2 ± 16.0	66.6 ± 37.4
λ_n (hrs^{-1})	0.0360 ± 0.0078	0.0377 ± 0.0093
$t_{1/2}$ (hrs)	20.1 ± 4.8[a]	19.5 ± 5.1[a]
AUC_{0-inf}	393 ± 84	384 ± 65
AUC_{0-48}	427 ± 92	417 ± 95

C_{max} - Maximum plasma concentration.
T_{max} - Time of maximum plasma concentration relative to the start of the 9553 infusion
λ_n - Terminal elimination rate constant.
$t_{1/2}$ - Terminal elimination half-life.
AUC_{0-inf} - Area under the plasma concentration vs time curve from the start o 9553 infusion to the time of the last quantifiable concentration.
AUC_{0-48} - Area under the plasma concentration vs time curve from the start of f 9553 infusion to infinity.
CL - Clearance.
V_d - Volume of distribution.
(a) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 19.5 ± 4.2 and 18.4 ± 4.6 hours for \ 9553 treatment and the diazepam and 9553 treatment, respectively.



times are relative to the start of diazepam infusion; fosphenytoin was started at 15 minutes

n = 8 - 9

TABLE 7 DIAZEPAM PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS (MEAN ± SD)

Parameter (a)	Treatment: Diazepam Alone (N=8)	Diazepam and 0653 (N=8)
C_{max} (μg/mL)	511 ± 220	466 ± 252
T_{max} (min)	10.0 ± 7.5	14.0 ± 9.0
λ_z (hrs^{-1})	0.456 ± 0.099	0.511 ± 0.031
$t_{1/2}$ (hrs)	20.9 ± 20.1	19.1 ± 13.0
AUC_{0-last} (μghr/mL)	1660 ± 1470	1760 ± 1320
$AUC_{0-\infty}$ (μghr/mL)	2060 ± 2420	2060 ± 1860
CL (L/hr)	5.31 ± 3.44	5.25 ± 2.52
CL (L/hr/kg)	0.0660 ± 0.0430	0.0665 ± 0.0261
V_d (L)	140 ± 72	113 ± 37
V_c (L/kg)	1.76 ± 0.73	1.46 ± 0.46

C_{max} - Maximum plasma concentration.
T_{max} - Time of maximum plasma concentration relative to the start of the diazepam infusion.
λ_z - Terminal elimination rate constant
$t_{1/2}$ - Terminal elimination half-life
AUC_{0-last} - Area under the plasma concentration vs time curve from the start of the diazepam infusion to the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from the start of the diazepam infusion to infinity.
CL - Clearance.
V_d - Volume of distribution.
(a) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 18.8 ± 11.1 and 13.8 ± 8.8 hours for the diazepam treatment and the diazepam and 0653 treatment, respectively.

	9853 Percent Unbound		Phenytoin Percent Unbound	
	Treatment			
Protocol Time (hr.min)(a)	9853 Alone	Diazepam and ACC-9853	-9853 Alone	Diazepam and ACC-9853

(a) - Relative to the start of the diazepam infusion 9853 was started at 15 minutes
N=9 at all time points.
No statistically significant differences were observed between treatments ($p > 0.05$)

	Diazepam Percent Unbound
	Treatment

[redacted]

CONCLUSIONS: Co-administartion of fosphenytoin (750 mg/15 ml/15 min) and diazepam (10 mg/2 ml/5 min) resulted in plasma concentrations of fosphenytoin, phenytoin and diazepam similar to those observed when fosphenytoin or diazepam was administered alone. It should be noted that fosphenytoin was not administered at maximum dose and rate. The sponsor's labeling of fosphenytoin allows for doses up to 20 mg/kg (in a 70 kg individual this equals 1400 mg) and rates up to 225 mg/min. Thus the dose was approximately 50% of the labeled maximum, and the rate was approximately 25% of the labeled maximum. Similarly, Valium was not administered at maximum dose. The dose of Valium used was only 33% of the labeled maximum of 30 mg. Thus, conditions which have the greatest potential for pharmacokinetic and pharmacodynamic interaction (maximum dose and rate of both co-administered agents) were not addressed in the study.

SYNOPSIS

TITLE A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, RISING SINGLE-DOSE STUDY OF THE PHARMACOKINETIC AND TOLERANCE PROFILES OF INTRAVENOUS FOSPHENYTOIN SODIUM (CI-982) ADMINISTERED AT FIVE DIFFERENT INFUSION RATES TO HEALTHY SUBJECTS (PROTOCOL 982-18-0)

INVESTIGATOR

CI-982 ANALYST(S)

OBJECTIVES To evaluate, in healthy subjects, the safety and tolerance of escalating single doses and infusion rates of intravenously (IV) administered fosphenytoin compared with placebo and to define the pharmacokinetics of fosphenytoin and phenytoin following IV administration of fosphenytoin

STUDY DESIGN Randomized, double-blind, placebo-controlled, four-way crossover, tolerance, and pharmacokinetic study

DRUG TREATMENT Following a randomized, four-way crossover design, subjects received single IV infusion doses of fosphenytoin or placebo at weekly intervals. The first group received 600, 1200, or 1800 mg fosphenytoin at 18.75 mg/min (equivalent to 400, 800, or 1200 mg phenytoin at 12.5 mg phenytoin/min) or placebo (identical volume of fosphenytoin vehicle administered at the same rate as the fosphenytoin dose). Subsequent groups received these same doses of fosphenytoin and placebo at 37.5, 75, 150, and 225 mg/min (equivalent to 25, 50, 100, and 150 mg phenytoin/min). Escalation to the next dose and/or infusion rate was contingent on the absence of significant adverse events at the previous dose or rate.

SUBJECT CHARACTERISTICS AND DISPOSITION Twenty-one men ranging in age from 19 to 43 years (mean 26) participated in this study. Twenty subjects completed the study; one subject withdrew for personal reasons.

PHARMACOKINETICS In general, fosphenytoin plasma concentrations increased with dose and infusion rate, peaked near the end of infusion, and then declined with a $t_{\frac{1}{2}}$ of approximately 0.25 hour. Mean fosphenytoin AUC(0-∞) values decreased with increasing infusion rate; but increased with increasing dose, although less than expected for a drug with linear pharmacokinetics. When higher plasma fosphenytoin concentrations were achieved with increasing infusion rates, more free fosphenytoin was available for conversion to phenytoin resulting in increased fosphenytoin clearance.

Total phenytoin and free phenytoin pharmacokinetics were nonlinear. Mean total phenytoin Cmax values increased approximately proportionally with increases in dose. AUC(0-∞) values increased at a greater than dose-proportional rate; mean AUC(0-∞) values increased approximately

five-fold over the three-fold range of doses. While Cmax and AUC(0-∞) values increased with dose, they did not increase with increased rates, providing further evidence that extent of fosphenytoin conversion to phenytoin was independent of fosphenytoin infusion rate.

Fosphenytoin displaced phenytoin from plasma protein binding sites resulting in a phenytoin free fraction that increased with increasing plasma fosphenytoin concentration. Displacement was greatest after administration of 1200 mg phenytoin equivalents fosphenytoin, leading to increases in phenytoin free fraction during the first hour after the start of infusion. During the first hour, similar free phenytoin Cmax values were seen at 12.5 to 50 mg phenytoin equivalents/min, whereas higher free phenytoin Cmax values temporally related to increased free fraction were observed at 100 and 150 mg phenytoin equivalents/min. Following conversion of fosphenytoin to phenytoin, free fraction, and plasma free phenytoin concentrations were similar at all infusion rates. Free phenytoin concentration-time profiles after administration of 1200 mg phenytoin equivalents fosphenytoin at the two highest rates were similar to those historically observed following administration of 1200 mg Dilantin at 50 mg/min.

Renal phenytoin and free phenytoin clearances were independent of dose and infusion rate. Less than 2% of dose was excreted as phenytoin. Thus, transient alterations in phenytoin free fraction did not affect overall renal clearance of phenytoin.

SAFETY Overall, 88% of fosphenytoin-treated subjects experienced adverse events compared with 15% of placebo-treated subjects. A total of 220 adverse events occurred following fosphenytoin treatment; most were mild in intensity and attributed to drug treatment. In general, the overall frequency of adverse events increased with fosphenytoin dose. Dizziness was the most frequently reported adverse event following fosphenytoin treatment. Other than mild nystagmus observed at 800 and 1200 mg phenytoin equivalents of fosphenytoin, significant drug-related changes were not observed in clinical laboratory parameters, physical examinations, electrocardiograms, or vital signs. No deaths or serious adverse events occurred, and no subject withdrew from the study as the result of an adverse event.

CONCLUSIONS Fosphenytoin is rapidly converted to phenytoin; rate and extent of conversion are independent of dose and infusion rate. Fosphenytoin displaces phenytoin from plasma proteins, especially at infusion rates greater than 50 mg phenytoin equivalents/min, resulting in increased free phenytoin concentrations for approximately 30 minutes after the start of infusion. Free phenytoin concentration-time profiles similar to those of parenteral phenytoin can be obtained by selecting the proper fosphenytoin infusion rate. Fosphenytoin doses of 400 to 1200 mg phenytoin equivalents at rates of 25 to 150 mg phenytoin equivalents/min are acceptably tolerated. However, as with Dilantin and other antiepileptic drugs, dizziness, paresthesia, and other CNS symptoms are often reported.

TABLE A. Mean (%RSD) Fosphenytoin Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Cmax (µg/mL)		tmax (hr)		t½ (hr)		AUC(0-∞) (µg · hr/mL)		CL (mL/min)		Vd_{area} (L)	
400	12.5	51.2	(10.6)	0.53	(0.00)	0.17	(17.57)	30.7	(13.2)	295.1	(12.9)	4.32	(10.89)
400	25	73.5	(6.7)	0.27	(0.00)	0.24	(15.31)	31.1	(10.0)	289.6	(10.7)	5.90	(13.01)
400	50	87.0	(7.4)	0.14	(6.42)	0.20	(15.41)	29.1	(14.4)	312.6	(15.0)	5.29	(6.48)
400	100	96.5	(6.5)	0.10	(30.00)	0.25	(25.77)	30.3	(7.1)	306.5	(7.0)	6.22	(20.82)
400	150	85.4	(24.7)	0.11	(21.20)	0.26	(21.59)	28.5	(22.3)	308.4	(23.1)	7.12	(9.33)
800	12.5	99.1	(9.2)	1.03	(11.32)	0.23	(12.68)	95.9	(10.3)	323.3	(9.7)	6.39	(10.03)
800	25	97.3	(3.3)	0.53	(0.00)	0.25	(24.06)	93.6	(3.4)	332.9	(3.5)	7.05	(22.32)
800	50	119.2	(6.7)	0.27	(1.62)	0.23	(7.37)	98.7	(10.8)	378.5	(10.0)	7.37	(13.36)
800	100	145.9	(12.2)	0.13	(0.00)	0.26	(28.65)	98.9	(23.0)	364.6	(22.7)	8.14	(10.62)
800	150	136.4	(14.8)	0.12	(27.84)	0.27	(10.84)	95.9	(12.7)	384.6	(11.1)	9.02	(14.24)
1200	12.5	86.3	(14.6)	1.15	(22.59)	0.24	(11.79)	91.8	(15.6)	380.8	(13.9)	6.27	(21.12)
1200	25	84.7	(7.3)	0.77	(7.33)	0.29	(30.64)	76.7	(7.6)	350.3	(6.6)	8.57	(31.29)
1200	50	116.6	(8.5)	0.36	(11.55)	0.23	(20.94)	63.3	(12.8)	420.2	(12.5)	8.23	(16.75)
1200	100	168.7	(10.5)	0.20	(0.00)	0.57	(76.88)	63.2	(13.9)	432.5	(14.9)	21.12	(74.27)
1200	150	169.4	(10.1)	0.13	(0.00)	0.25	(5.98)	53.3	(11.6)	396.1	(10.9)	10.85	(8.91)

Rate = Rate of fosphenytoin infusion.
Cmax = Maximum observed plasma fosphenytoin concentration.
tmax = Time of Cmax, times differ from end of infusion.
t½ = Elimination half-life.
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinite time.
CL = Systemic plasma clearance.
%RSD = Relative standard deviation (% of mean value).

[redacted]

TABLE B. Mean (%RSD) Phenytoin Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Cmax (μg/mL)		tmax (hr)		t½ (hr)		AUC(0-∞) (μg·hr/mL)	
400	12.5	8.50	(10.65)	0.94	(9.79)	14.3	(49.9)	179.5	(41.1)
400	25	8.46	(6.96)	1.01	(59.85)	12.0	(11.8)	164.3	(20.7)
400	50	8.19	(9.47)	1.18	(52.59)	13.0	(26.5)	179.0	(29.9)
400	100	8.23	(10.63)	1.28	(41.27)	14.0	(18.7)	177.8	(20.2)
400	150	8.19	(8.50)	0.83	(55.94)	12.9	(11.7)	177.8	(14.7)
800	12.5	15.43	(12.19)	1.68	(20.41)	18.6	(56.5)	490.0	(37.8)
800	25	16.55	(11.82)	1.32	(41.48)	12.6	(8.8)	475.0	(19.2)
800	50	15.60	(13.72)	1.21	(37.33)	16.5	(37.1)	485.8	(28.9)
800	100	19.23	(23.58)	0.61	(84.45)	19.7	(16.0)	468.3	(24.7)
800	150	16.25	(6.66)	1.12	(34.55)	17.0	(21.1)	503.5	(18.4)
1200	12.5	23.48	(12.63)	2.50	(0.00)	25.1	(80.9)	1030.0	(42.8)
1200	25	24.00	(9.19)	1.62	(26.33)	17.6	(21.6)	920.0	(20.2)
1200	50	22.53	(4.85)	1.88	(11.55)	21.8	(40.5)	914.3	(29.2)
1200	100	22.88	(6.55)	1.22	(40.19)	28.9	(23.6)	940.8	(21.2)
1200	150	24.35	(7.67)	1.01	(50.65)	21.7	(35.3)	869.3	(25.8)

Rate = Rate of fosphenytoin infusion.
Cmax = Maximum observed plasma phenytoin concentration.
tmax = Time of Cmax, times differ from end of infusion.
t½ = Elimination half-life.
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinite time.
%RSD = Relative standard deviation (% of mean value).

TABLE C Mean (%RSD) Free Phenytoin Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Cmax (μg/mL)		tmax (hr)		AUC(0-ldc) (μg · hr/mL)	
400	12.5	0.000	—	—	—	0.00	—
400	25	0.334	(58.6)	0.47	(77.0)	0.28	(173.2)
400	50	0.422	(25.0)	0.69	(70.8)	1.75	(39.4)
400	100	0.460	(26.6)	0.43	(41.5)	1.51	(30.4)
400	150	0.389	(23.4)	1.18	(92.1)	1.10	(14.1)
800	12.5	0.645	(20.9)	1.48	(22.2)	3.23	(63.0)
800	25	0.880	(24.7)	0.88	(42.2)	8.45	(48.4)
800	50	0.837	(20.3)	0.43	(43.6)	10.88	(30.1)
800	100	1.537	(47.3)	0.34	(59.8)	11.54	(48.4)
800	150	0.774	(16.6)	0.61	(24.0)	13.50	(25.8)
1200	12.5	1.083	(13.5)	1.78	(2.4)	18.61	(52.8)
1200	25	1.200	(10.3)	1.84	(69.2)	26.25	(8.1)
1200	50	1.313	(15.6)	0.63	(34.0)	22.90	(26.7)
1200	100	2.083	(55.2)	0.40	(52.7)	24.55	(14.8)
1200	150	1.720	(7.59)	0.22	(27.7)	27.73	(39.4)

Rate = Rate of fosphenytoin infusion.
Cmax = Maximum observed plasma free phenytoin concentration.
tmax = Time of Cmax, times differ from end of infusion.
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to time of the last detectable concentration.
%RSD = Relative standard deviation (% of mean value).
— = Indeterminable.

TABLE D. Mean (%RSD) Urinary Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Phenytoin						p-HPPH			
		Ae (mg)		Ae% (%)		Clr (mL/min)		Ae (mg)		Ae% (%)	
400	12.5	3.14	(13.8)	0.85	(13.8)	0.346	(41.2)	81.6	(25.7)	19.3	(25.7)
400	25	2.84	(38.9)	0.77	(38.9)	0.288	(20.8)	49.5	(25.4)	11.7	(25.4)
400	50	3.22	(19.9)	0.88	(19.9)	0.328	(27.1)	58.4	(11.2)	13.8	(11.2)
400	100	3.77	(18.8)	1.03	(18.8)	0.377	(24.2)	61.2	(23.2)	14.5	(23.2)
400	150	3.24	(16.7)	0.88	(16.7)	0.329	(28.7)	64.2	(21.1)	15.2	(21.1)
800	12.5	8.83	(25.8)	1.20	(25.8)	0.365	(48.2)	141.6	(15.3)	16.8	(15.3)
800	25	8.12	(25.1)	1.10	(25.1)	0.290	(5.25)	128.6	(18.7)	15.2	(18.7)
800	50	9.40	(41.2)	1.28	(41.2)	0.340	(22.7)	107.0	(26.1)	12.7	(26.1)
800	100	9.52	(17.8)	1.29	(17.8)	0.385	(27.4)	115.8	(11.5)	13.7	(11.5)
800	150	8.89	(17.0)	1.21	(17.0)	0.320	(31.9)	133.0	(34.3)	15.8	(34.3)
1200	12.5	17.63	(36.0)	1.60	(36.0)	0.371	(62.4)	218.1	(19.5)	17.2	(19.5)
1200	25	16.13	(29.5)	1.46	(29.5)	0.301	(12.5)	172.9	(9.55)	13.7	(9.55)
1200	50	18.69	(30.9)	1.69	(30.9)	0.379	(8.60)	179.7	(22.4)	14.2	(22.4)
1200	100	16.77	(18.9)	1.52	(18.9)	0.350	(20.6)	174.2	(21.6)	13.8	(21.6)
1200	150	16.42	(33.4)	1.49	(33.4)	0.362	(44.8)	190.0	(39.5)	15.0	(35.9)

Ae = Amount excreted in urine.
Ae% = Amount excreted in urine expressed as percent of dose.
CLr = Renal clearance.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).

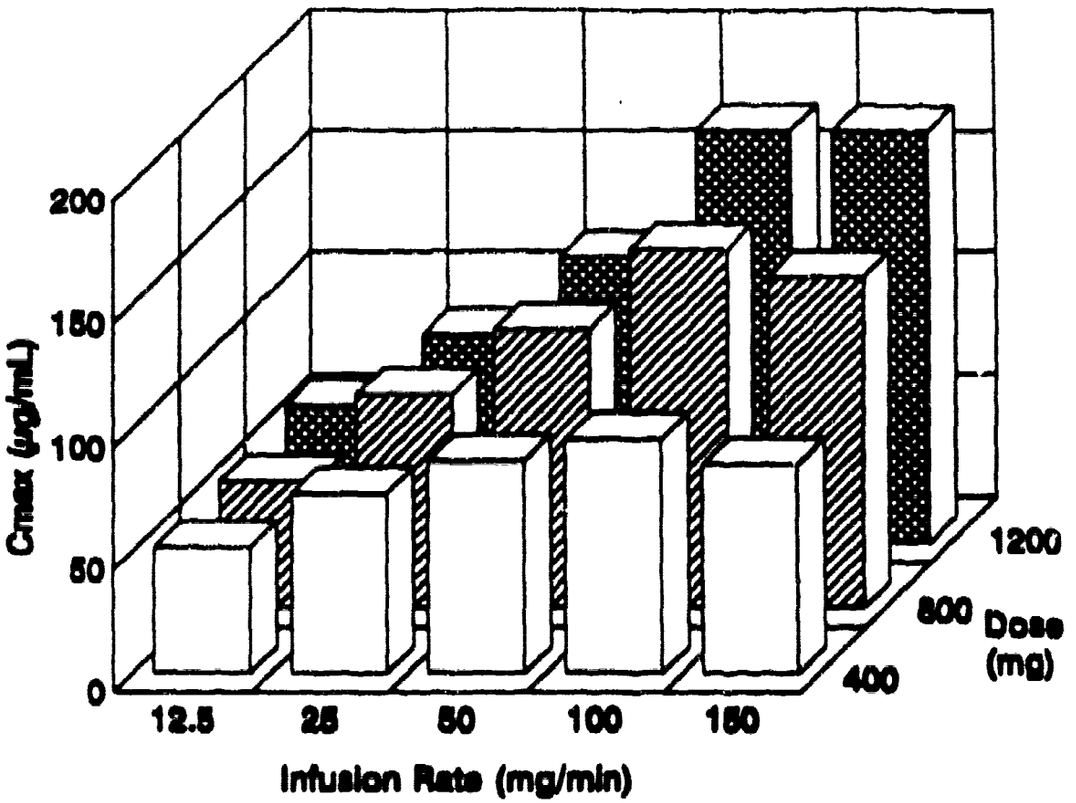


FIGURE A. **Relationship Between Mean Fosphenytoin Cmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)**

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

Note: The Y-axis has been [illegible] to reflect the adjusted fosphenytoin Cmax values.

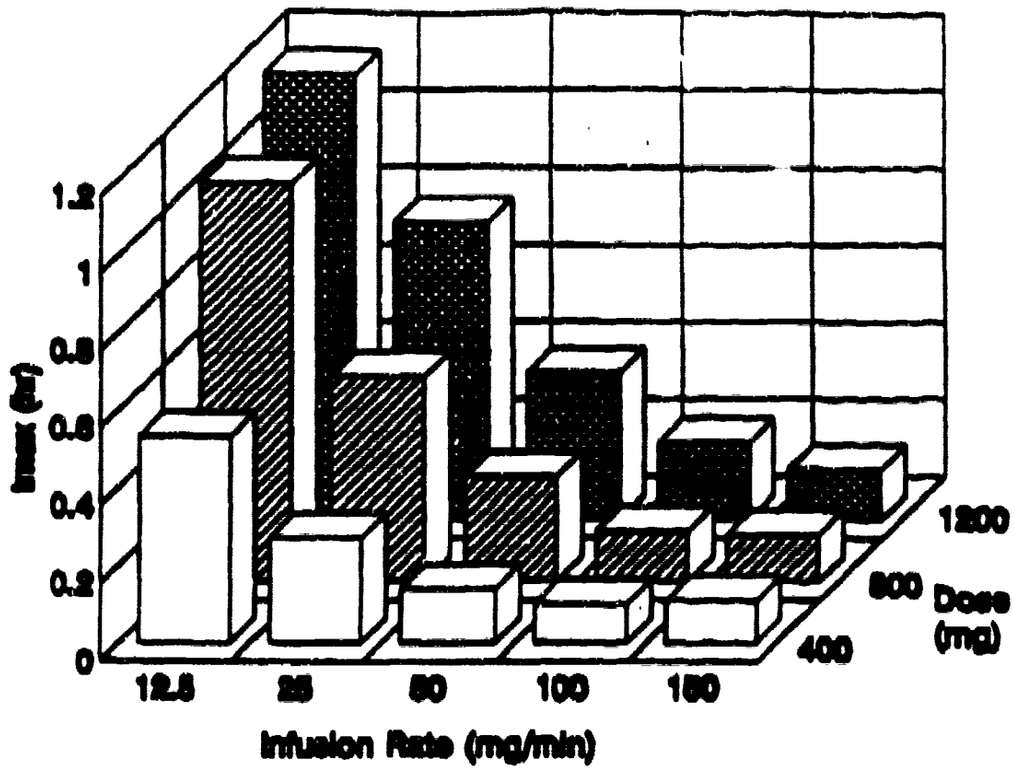


FIGURE B. **Relationship Between Mean Fosphenytoin tmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)**

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

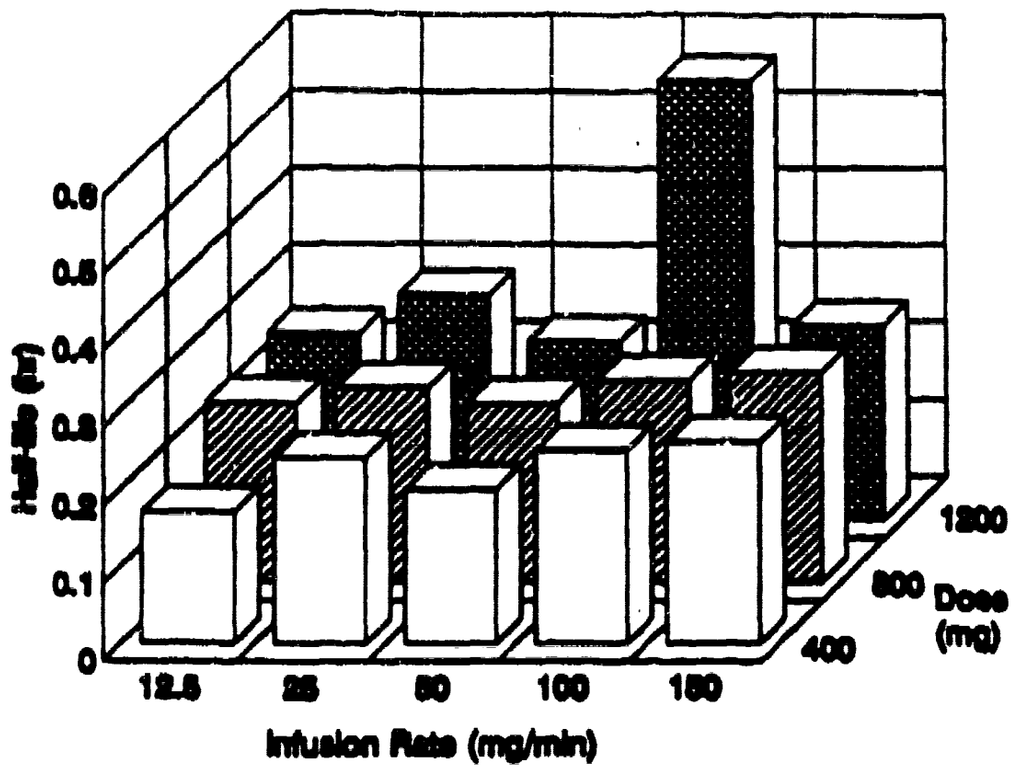


FIGURE C. **Relationship Between Fosphenytoin Mean Half-Life Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)**

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

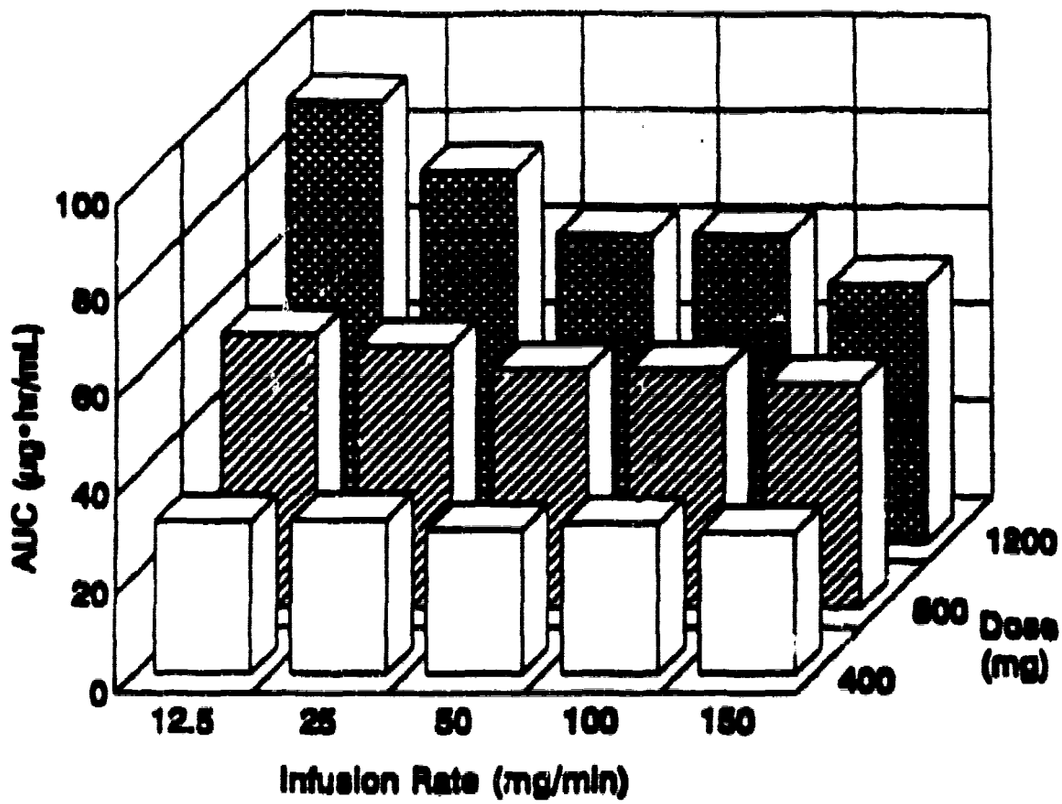


FIGURE D. Relationship Between Fosphenytoin Mean AUC(0-∞) Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

Note: The Y-axis has been rescaled to reflect the adjusted fosphenytoin AUC values.

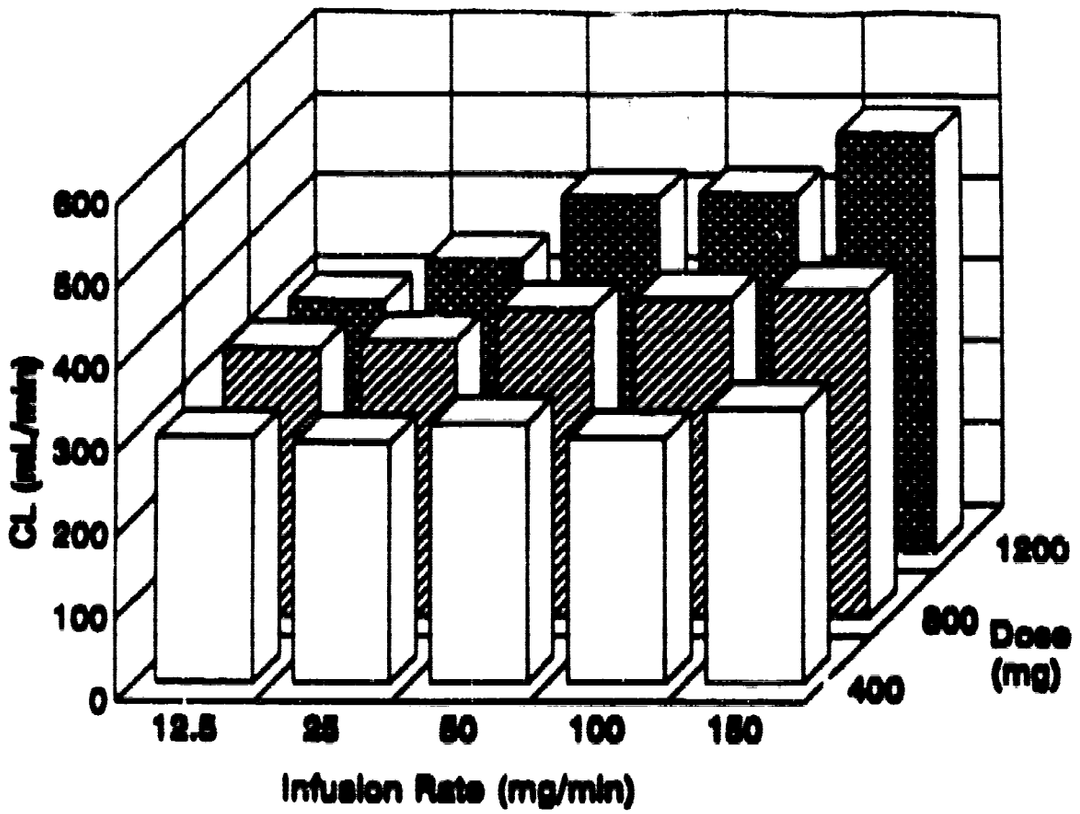


FIGURE E. Relationship Between Mean Fosphenytoin Clearance Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

Note: The Y-axis has been rescaled to reflect the adjusted fosphenytoin clearance values

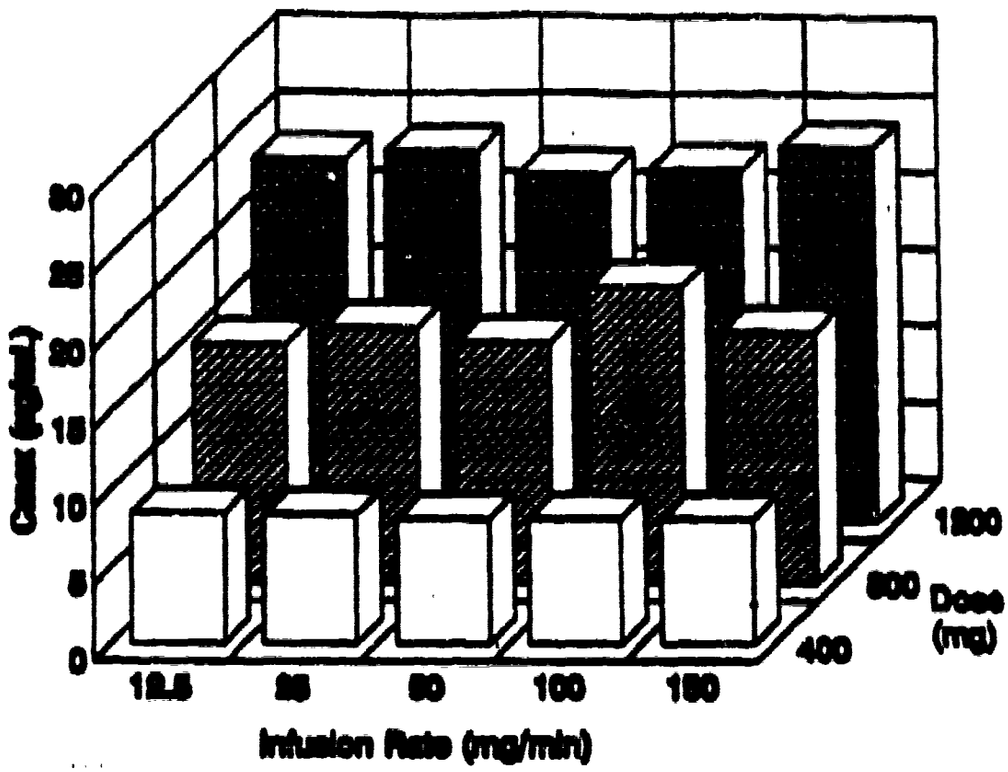


FIGURE F. Relationship Between Mean Total Phenytoin Cmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

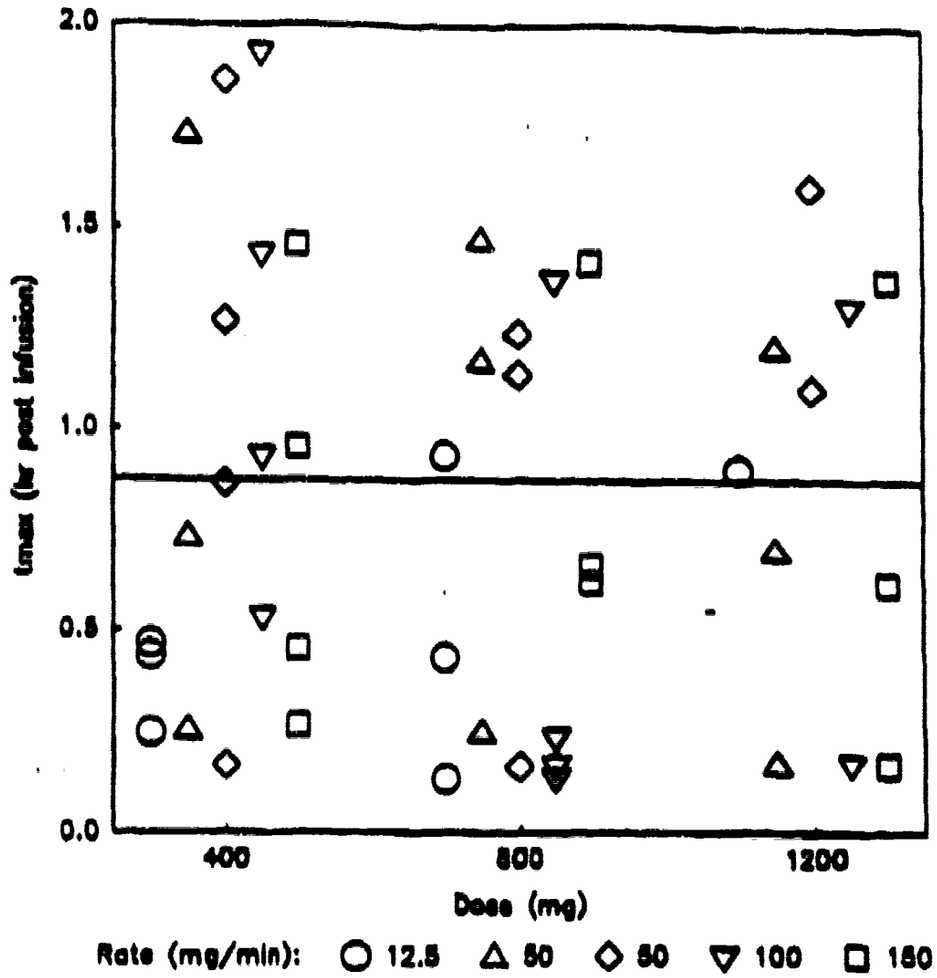


FIGURE G. Individual Phenytoin tmax Values (hour postinfusion) Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Horizontal line depicts mean value. Values may have been shifted slightly along the ordinate to facilitate resolution.

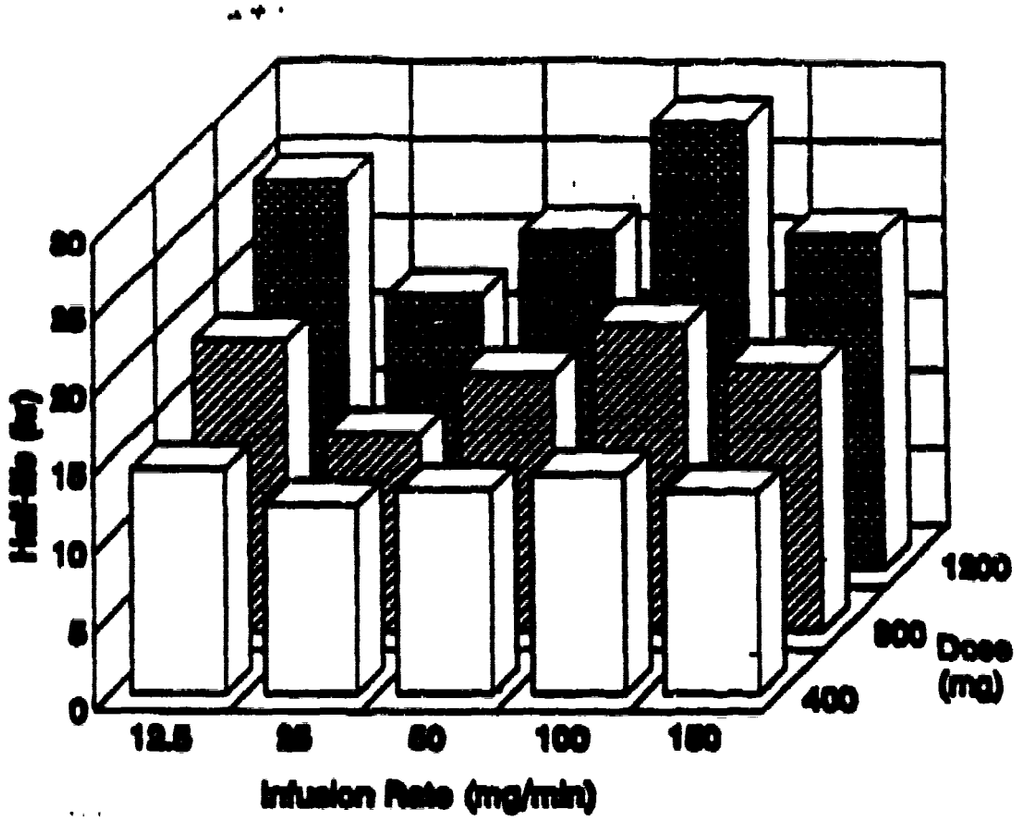


FIGURE H. Relationship Between Mean Phenytoin Half-Life Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

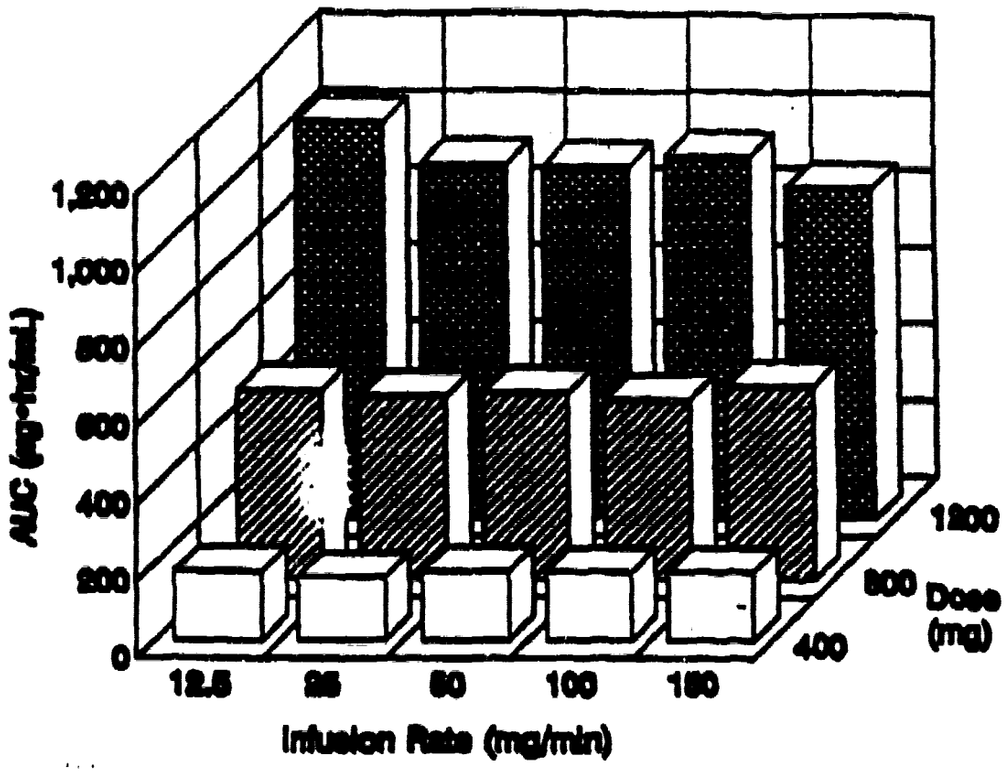


FIGURE I. Relationship Between Mean Phenytoin AUC(0-∞) Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

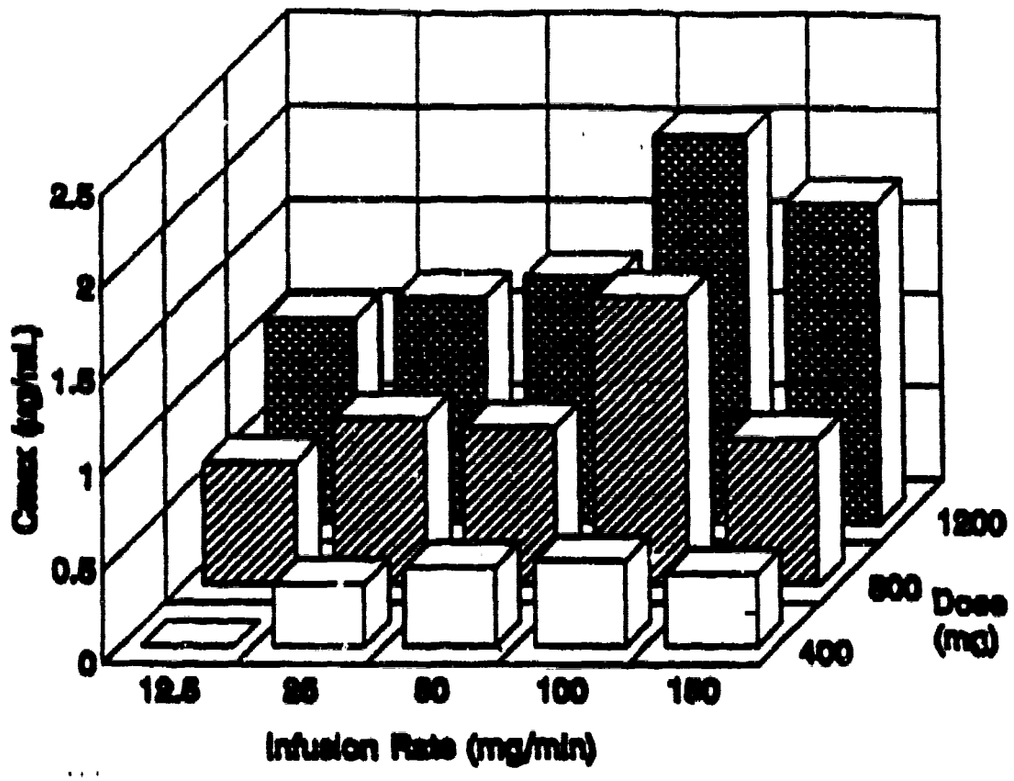


FIGURE J. Relationship Between Mean Free Phenytoin Cmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

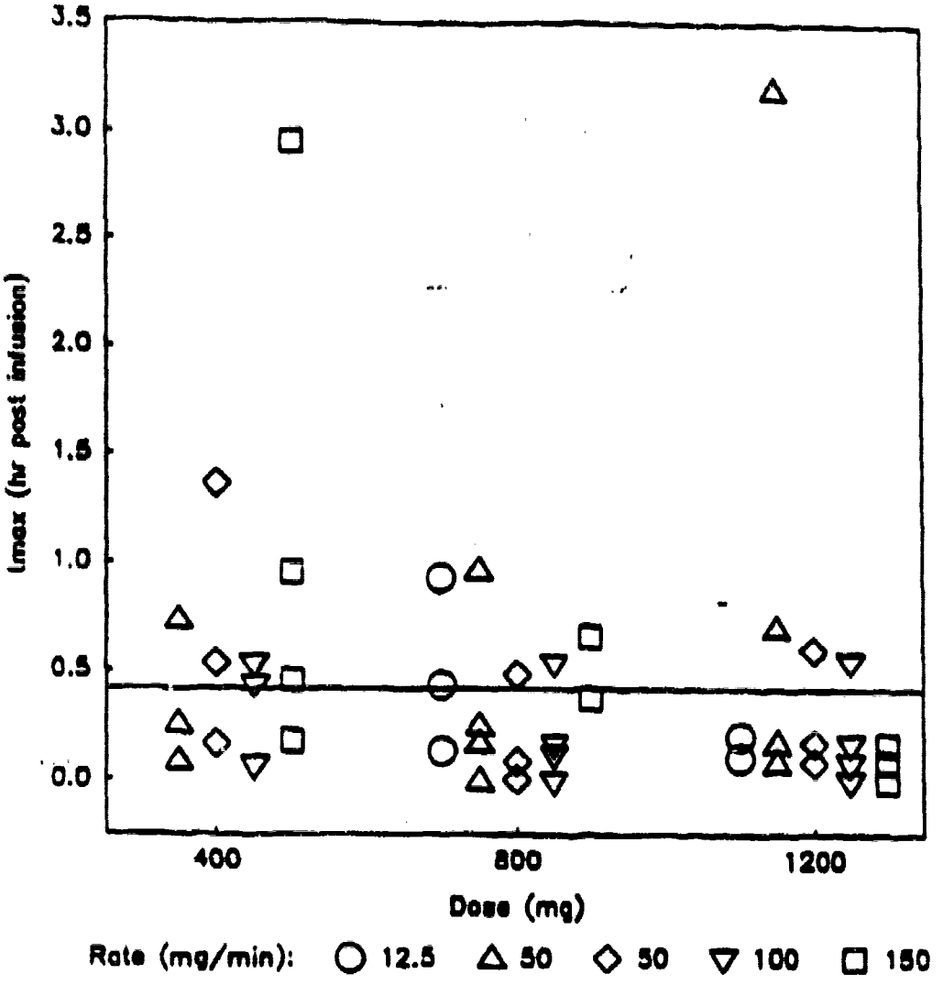


FIGURE K. Individual Free Phenytoin tmax Values (hour postinfusion) Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Horizontal line depicts mean value. Values may have been shifted slightly along the ordinate to facilitate resolution.

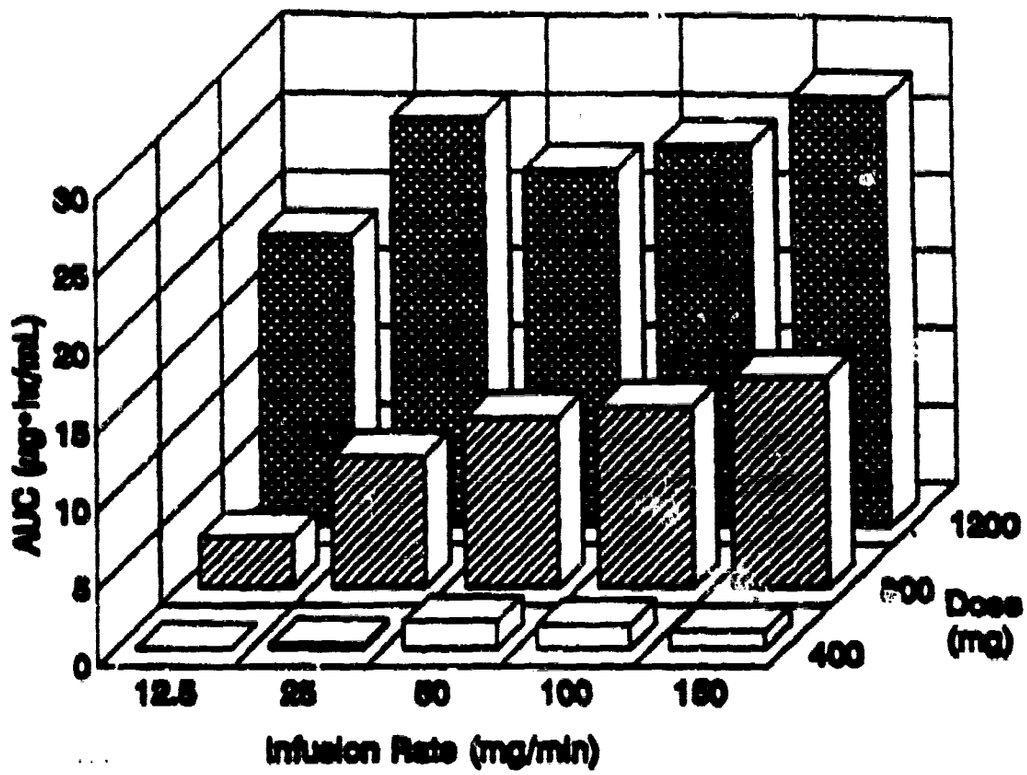


FIGURE L. Relationship Between Mean Free Phenytoin AUC(0-tldc) Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

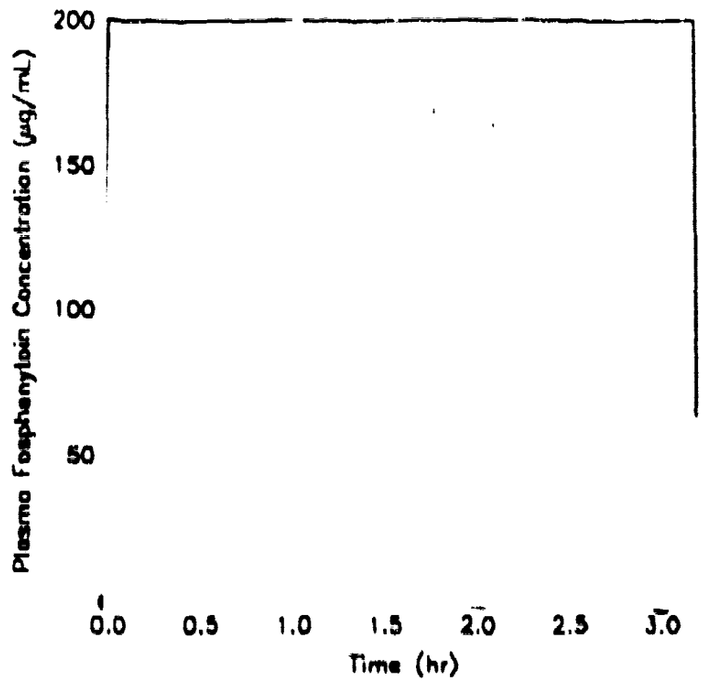


FIGURE O. Mean Plasma Fosphenytoin Concentration Versus Nominal Sample Collection Time Profiles Following Intravenous Administration of 1200 mg Fosphenytoin at 12.5 (○), 25 (●), 50 (▲), 100 (▲), and 150 (□) mg/min to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Values depicted are mean of Period 4 data.

Note: The Y-axis has been rescaled to reflect the adjusted fosphenytoin concentration values.

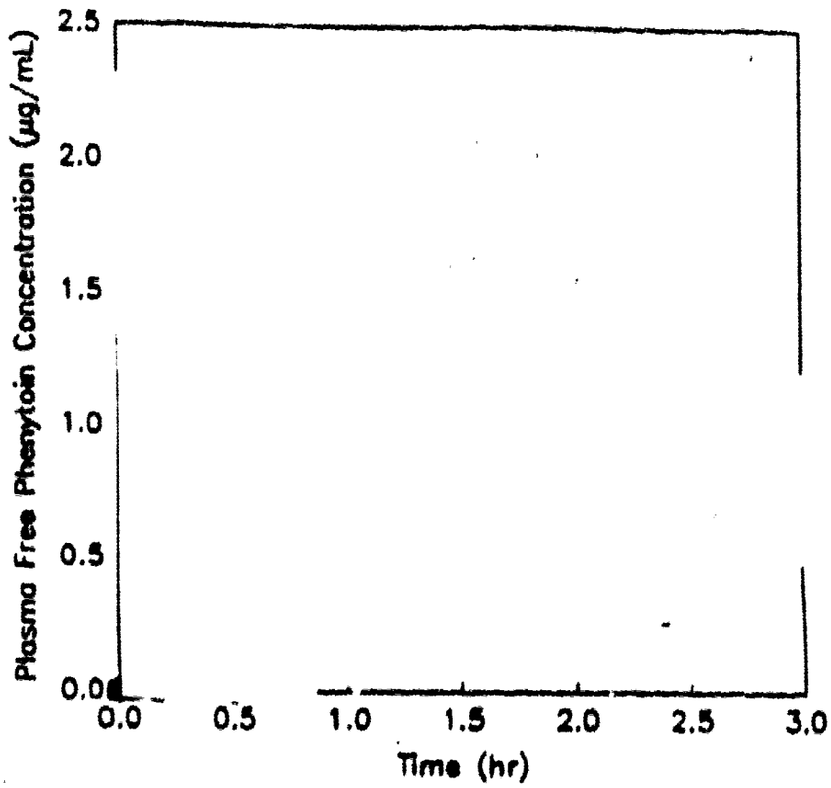
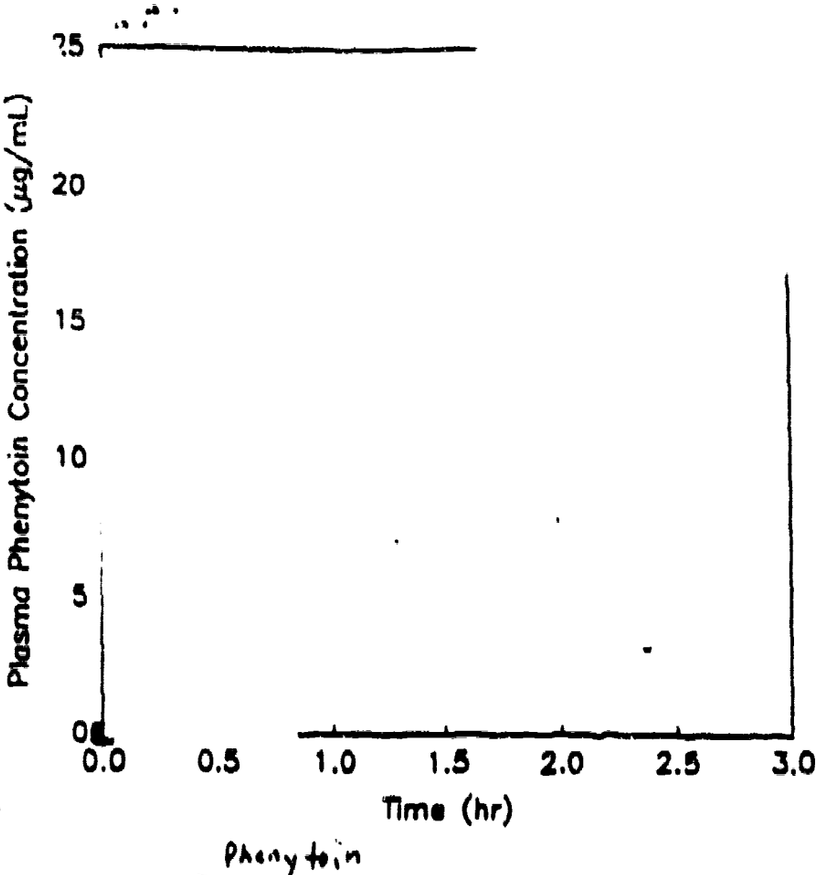


FIGURE Q. Mean Plasma ~~Fosphenytoin~~ Free Phenytoin Concentration Versus Nominal Sample Collection Time Profiles Following Intravenous Administration of 1200 mg Fosphenytoin at 12.5 (○), 25 (●), 50 (▲), 100 (▲), and 150 (□) mg/min to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Values depicted a mean of Period 4 data.



Phenytoin

FIGURE P. Mean Plasma ~~Fosphenytoin~~ Concentration Versus Nominal Sample Collection Time Profiles Following Intravenous Administration of 1200 mg Fosphenytoin at 12.5 (○), 25 (●), 50 (△), 100 (▲), and 150 (□) mg/min to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Values depicted are mean of Period 4 data.

concentrations generally occurred 30 minutes earlier than maximal total phenytoin concentrations. Despite displacement of phenytoin from plasma proteins by fosphenytoin, mean free phenytoin Cmax following fosphenytoin was 35% less th that following Dilantin, with the mean maximum difference occurring at the end o infusion. After conversion of fosphenytoin to phenytoin, plasma free phenytoin concentrations were similar for both treatments. At a molar equivalent dose and r comparable free and total phenytoin AUC values were obtained following fosphenytoin and Dilantin.

SAFETY The nature and frequency of adverse events were similar after fosphen and Dilantin; few adverse events occurred following placebo. The most frequent adverse events after fosphenytoin and Dilantin were nystagmus, dizziness, and tinnitus. Injection-site symptoms (inflammation, pain, and reaction) were experie by fewer subjects following fosphenytoin (33%) than Dilantin (83%). There were deaths, serious adverse events, or withdrawals due to adverse events. No clinical significant changes occurred in clinical laboratory parameters, physical examinatio electrocardiograms, or vital signs.

CONCLUSIONS A molar equivalent dose of fosphenytoin administered at 50 m phenytoin equivalents/min produces comparable free and total phenytoin AUC va but slightly lower and delayed maximal free and total phenytoin concentrations compared to those following Dilantin administered at the same rate. The similar free and total phenytoin concentration-time profiles suggests that fosphenytoin administered at 50 mg phenytoin equivalents/min should be a suitable substitute Dilantin in nonemergent situations. Fosphenytoin has a similar safety profile to Dilantin, but is better tolerated at the injection site.

SYNOPSIS

TITLE A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND DILANTIN®-CONTROLLED, SINGLE-DOSE STUDY OF THE PHARMACOKINETIC AND TOLERANCE PROFILES OF INTRAVENOUS FOSPHENYTOIN SODIUM (CI-982) IN HEALTHY SUBJECTS (PROTOCOL 982-20-0)

INVESTIGATOR

CI-982 ANALYST

OBJECTIVE To compare the pharmacokinetics of phenytoin following single doses of intravenously administered fosphenytoin and Dilantin, and to evaluate the safety and tolerance of fosphenytoin compared with Dilantin and placebo

STUDY DESIGN Randomized, double-blind, 3-way crossover, pharmacokinetic and tolerance study

DRUG TREATMENT Each subject received 1200 mg Dilantin, a molar equivalent dose of fosphenytoin, and placebo; each treatment was separated by a 1-week washout period. Fosphenytoin was infused at 50 mg phenytoin equivalents/min (75 mg/min) and Dilantin at 50 mg/min. Subjects were randomized so that only 2 subjects received each treatment (fosphenytoin, Dilantin, or placebo) at any one time.

SUBJECT CHARACTERISTICS AND DISPOSITION Twelve men ranging in age from 18 to 49 years (median 30) entered and completed this study.

PHARMACOKINETICS Plasma fosphenytoin, total phenytoin, and free phenytoin concentrations were quantified using validated liquid chromatographic methods. Plasma fosphenytoin concentrations peaked near the end of the infusion. Rapid conversion of fosphenytoin to phenytoin was apparent from the short mean fosphenytoin t½ value of 0.29 hour. For the first hour after dosing, total phenytoin concentrations following fosphenytoin were lower than those following Dilantin due to the time required for conversion of fosphenytoin to phenytoin. Mean phenytoin AUC(0-tldc) values following fosphenytoin were approximately 8% less than those following Dilantin, probably due to differences in total phenytoin clearance as a function of plasma phenytoin concentration rather than incomplete conversion of fosphenytoin to phenytoin.

Free phenytoin tmax values after fosphenytoin were influenced by fosphenytoin displacement of phenytoin from plasma proteins as maximal free phenytoin

TABLE 5. Mean (%RSD) Free Phenytoin Pharmacokinetic Values Following Intravenous Administration of 1200-mg Phenytoin Equivalent Doses of Fosphenytoin and Dilantin Infused at 50 mg/min Phenytoin Equivalents

Pharmacokinetic Parameter	Fosphenytoin N = 12		Dilantin N = 11	
Cmax, μg/mL	2.6	(20.4)	4.0	(33.2)
tmax, hr	0.5	(35.2)	0.5	(22.2)
AUC(0-tldc), μg·hr/mL	66.1	(30.9)	74.1	(24.8)
AUC(0-∞), μg·hr/mL	73.1	(34.1)	82.8	(28.9)
AUC_{extrap}, %	8.9	(44.7)	9.8	(51.8)
λz, hr^{-1}	0.034	(22.9)	0.031	(25.6)
t½, hr	21.7	(30.1)	24.3	(32.2)
CL, mL/min	275	(28.9)	238	(26.4)
Vd_{area}, L	484	(13.0)	476	(23.4)

%RSD = Relative standard deviation (% of mean value).

TABLE 6. Comparison of Mean Free Phenytoin Pharmacokinetic Parameters Following Intravenous Administration of 1200-mg Phenytoin Equivalent Doses of Fosphenytoin and Dilantin Infused at 50 mg/min Phenytoin Equivalents

Parameter	Fosphenytoin (Test)			Dilantin (Reference)			Ratio of Least-Squares Means (Test/Reference)	90% Confidence Interval[a]
	Mean	%RSD	N	Mean	%RSD	N		
Cmax, μg/mL	2.58	20.4	12	4.04	33.2	11	64.6[b]	53.8 - 77.8
tmax, hr	0.49	35.2	12	0.46	22.2	11	108.2	94.7 - 121.7
AUC(0-tldc), μg·hr/mL	66.1	30.9	11	74.1	24.8	11	87.2[b]	83.0 - 91.7

Mean = Arithmetic mean of untransformed data.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).
[a] Ninety percent confidence intervals for ratio (test/reference) of treatment least-squares mean values
[b] Ratio represents antitransforms of difference between treatment least-squares means of natural log transformed parameters values (test-reference) expressed as a percentage.

Mean free phenytoin AUC(0-tldc) following fosphenytoin administration was 13% less than that following Dilantin. As previously discussed for total phenytoin, this small difference in AUC(0-tldc) is probably the result of differences in clearance as a function of free phenytoin concentration rather than incomplete conversion of fosphenytoin to phenytoin. Free phenytoin AUC(0-tldc) met commonly used

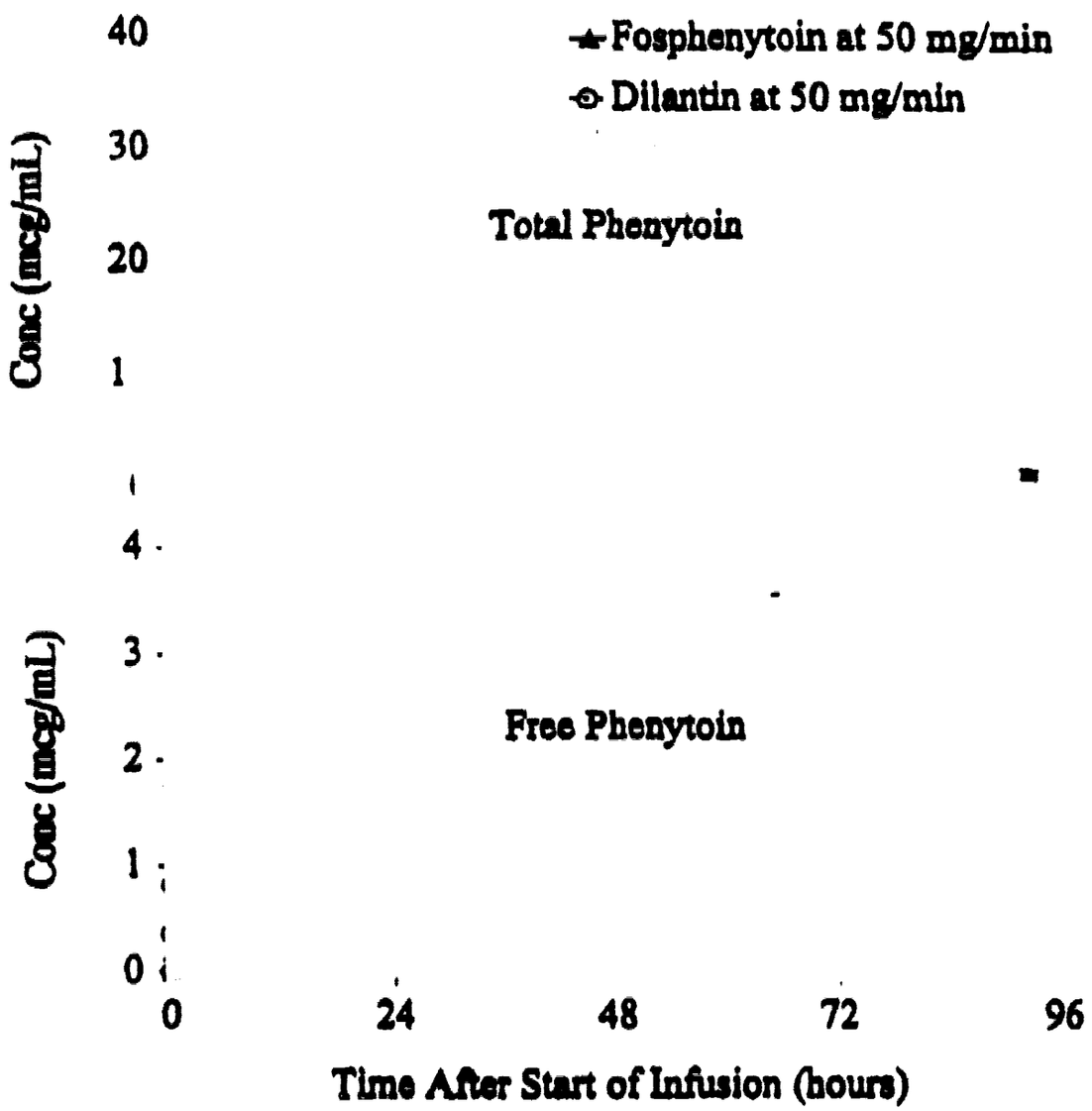


FIGURE 2. **Mean Total and Free Phenytoin Concentrations Following Intravenous Administration of 1200-mg Phenytoin Equivalent Doses of Fosphenytoin and Dilantin Infused at 50 mg/min Phenytoin Equivalents to 12 Healthy Subjects**

3 Pages

Purged

STUDY: A Randomized, Nonblind, Dilantin-Controlled, Single-Dose Study of the Pharmacokinetic Profile and Tolerance of Intravenous Fosphenytoin Sodium (CI-982) in Healthy Subjects

PROTOCOL NUMBER: 982-24-0

RESEARCH REPORT NUMBER: RR 744-00152

STUDY DESIGN: Randomized, nonblind, 3-way crossover study in healthy males between 18 and 50 yrs. of age

TABLE 1. Treatment Sequences for Drug Administration[a]

Sequence		Week 1	Week 2	Week 3
1	Treatment	Fosphenytoin	Fosphenytoin	Dilantin
	Rate	100	150	50
2	Treatment	Fosphenytoin	Dilantin	Fosphenytoin
	Rate	150	50	100
3	Treatment	Dilantin	Fosphenytoin	Fosphenytoin
	Rate	50	100	150

[a] Infusion rates are in milligram phenytoin equivalents per minute for fosphenytoin and milligrams per minute for Dilantin.

SUBJECTS: 12 healthy males (10 white, 2 other), ages 20 - 42

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. EDTA was used as an anti-coagulant and ultrafiltration was performed at 37° C in this study.

PROTOCOL VARIATIONS: There were no protocol variations.

SAFETY RESULTS:

SAFETY The nature of adverse events was similar after fosphenytoin and Dilantin. Nystagmus occurred with similar frequency following both treatments. However, paresthesia and pruritus were noted more frequently following fosphenytoin than Dilantin, and dizziness occurred more often following Dilantin than fosphenytoin. Pruritus increased in frequency as fosphenytoin infusion rate increased. Injection-site symptoms (inflammation, pain, reaction, hypersensitivity) were experienced by fewer subjects following fosphenytoin (42%) than Dilantin (100%). There were no deaths, serious adverse events, or withdrawals due to adverse events. No clinically significant changes occurred in clinical laboratory parameters, physical examinations, electrocardiograms, or vital signs.

PHARMACOKINETIC AND STATISTICAL METHODS:

Fosphenytoin, total phenytoin, and free phenytoin pharmacokinetic parameters were calculated for each subject and each treatment by noncompartmental analysis of plasma concentration-time data.[10] Actual sample collection times were used for pharmacokinetic parameter calculations. Maximum observed plasma fosphenytoin, total phenytoin, and free phenytoin concentrations (Cmax) and the time each occurred (tmax) were recorded as observed. Area under plasma analyte concentration-time curve (AUC) was estimated using the linear trapezoidal method. AUC(0-tldc) was calculated from time zero to the time of the last detectable concentration (ldc). The apparent first-order terminal rate constant (λz) was estimated as the absolute value of the slope of a linear regression of natural logarithm (ln) of plasma analyte concentration on time during the terminal elimination phase of the plasma analyte concentration profile. Apparent terminal half-life ($t\frac{1}{2}$) was calculated as $\ln(2)/\lambda z$. AUC(0-∞) was calculated as the sum of corresponding AUC(0-tldc) and $ldc/\lambda z$ values. Due to the recognized nonlinearity of total and free phenytoin elimination, total and free phenytoin AUC(0-∞), λz, and $t\frac{1}{2}$ values were not reported.

Similarity between treatments observed while qualitatively comparing mean parameter values led to use of the following conventional statistical analysis plan for the assessment of bioequivalence which was performed using a validated computer system.[10] Ln(Cmax) and ln[AUC(0-tldc)] values for free phenytoin were the primary parameters evaluated for pharmacokinetic equivalence using established bioequivalence criteria. Secondary parameters (Cmax, tmax, and AUC[0-tldc]) for free phenytoin were also analyzed. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, subject within sequence, period, and treatment effects. The sequence effect was assessed using the subject within sequence mean square from the ANOVA as the error term to form the appropriate 2-sided F-test. Period effects were tested using residual error variance; a p-value <0.05 was considered significant. Statistical tests were performed using Type III sum of squares from the general linear model (GLM) procedure of SAS (SAS Releases 5.18 and 6.07, SAS Institute Inc, Cary, North Carolina, USA). Least-squares treatment mean values were determined for each parameter. Program code and output are stored in databooks listed in Table 1 in Appendix C.1.

Bioequivalence was concluded if estimates of the 90% confidence interval for the ratio of test (fosphenytoin) to reference (Dilantin) least-squares mean values, based on log-transformed Cmax and AUC(0-tldc) data, were between 80% and 125%.[13] This was equivalent to using the two 1-sided tests procedure.[14]

PHARMACOKINETIC RESULTS: The mean concentration-time profiles for fosphenytoin, total phenytoin and free phenytoin are shown below.

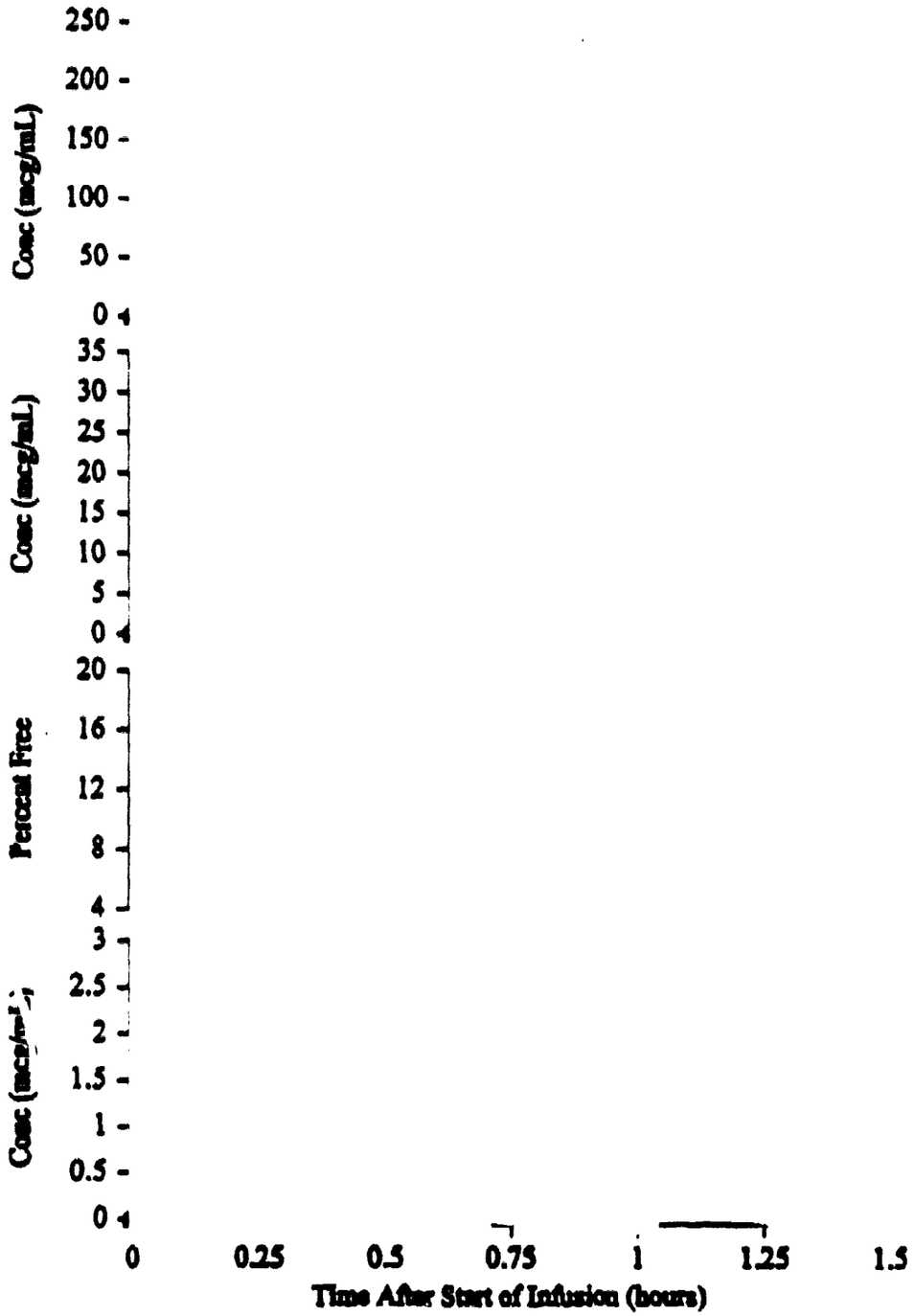


FIGURE 1. **Mean Fosphenytoin (Panel A), Total Phenytoin (Panel B), and Free Phenytoin (Panel D) Concentrations and Mean Phenytoin Free Fraction (Panel C) Following Intravenous Administration of 1200 mg Phenytoin Equivalent Doses of Fosphenytoin Infused at 100 and 150 mg/min Phenytoin Equivalents and Dilantin Infused at 50 mg/min (N = 12)**

The following table demonstrates that using the two one-sided confidence interval approach and the 80 - 125 % confidence interval criteria, fosphenytoin at (phenytoin equivalent) 1200 mg and 150 mg/min is bioequivalent to Dilantin at 1200 mg and 50 mg/min with regard to free phenytoin AUC and Cmax. Fosphenytoin at 100 mg/min is equivalent with regard to extent of exposure (AUC) but not rate (Cmax).

PK PARAMETERS ARE FOR FREE DRUG

Pharmacokinetic Parameter	Fosphenytoin		Dilantin[a]		Ratio	90% CI
	at 100 mg PE/min					
ln(Cmax)[b], μg/mL	2.72		3.21		84.7	72.7 - 98.8
ln[AUC(0-tldc)][b], μg · hr/mL	78.8		85.5		92.2	88.4 - 96.2
Cmax, μg/mL	2.78	(22)	3.30	(26)	84.2	NA
tmax, hr	0.524	(37)	0.526	(17)	99.6	NA
AUC(0-tldc), μg · hr/mL	79.5	(14)	87.1	(22)	91.3	NA
	at 150 mg PE/min					
ln(Cmax)[b], μg/mL	3.08		3.21		96.0	82.1 - 111.7
ln[AUC(0-tldc)][b], μg · hr/mL	84.5		85.5		98.8	94.8 - 103.2
Cmax, μg/mL	3.18	(28)	3.30	(26)	96.4	NA
tmax, hr	0.576	(59)	0.526	(17)	109.5	NA
AUC(0-tldc), μg · hr/mL	85.5	(17)	87.1	(22)	98.2	NA

Ratio = Ratio (test/reference) of treatment least-squares mean values expressed as a percentage.
90% CI = 90% confidence estimate for ratio (test/reference) of treatment least-squares mean values expressed as a percentage.
PE = Phenytoin equivalents.
NA = Not applicable.
[a] At 50 mg/min
[b] Values represent antilogs of log-transformed data

Because extent of exposure at early time points is important in therapy of status epilepticus, the sponsor was asked to evaluate cumulative AUC across time. The results are shown on the following 2 pages.

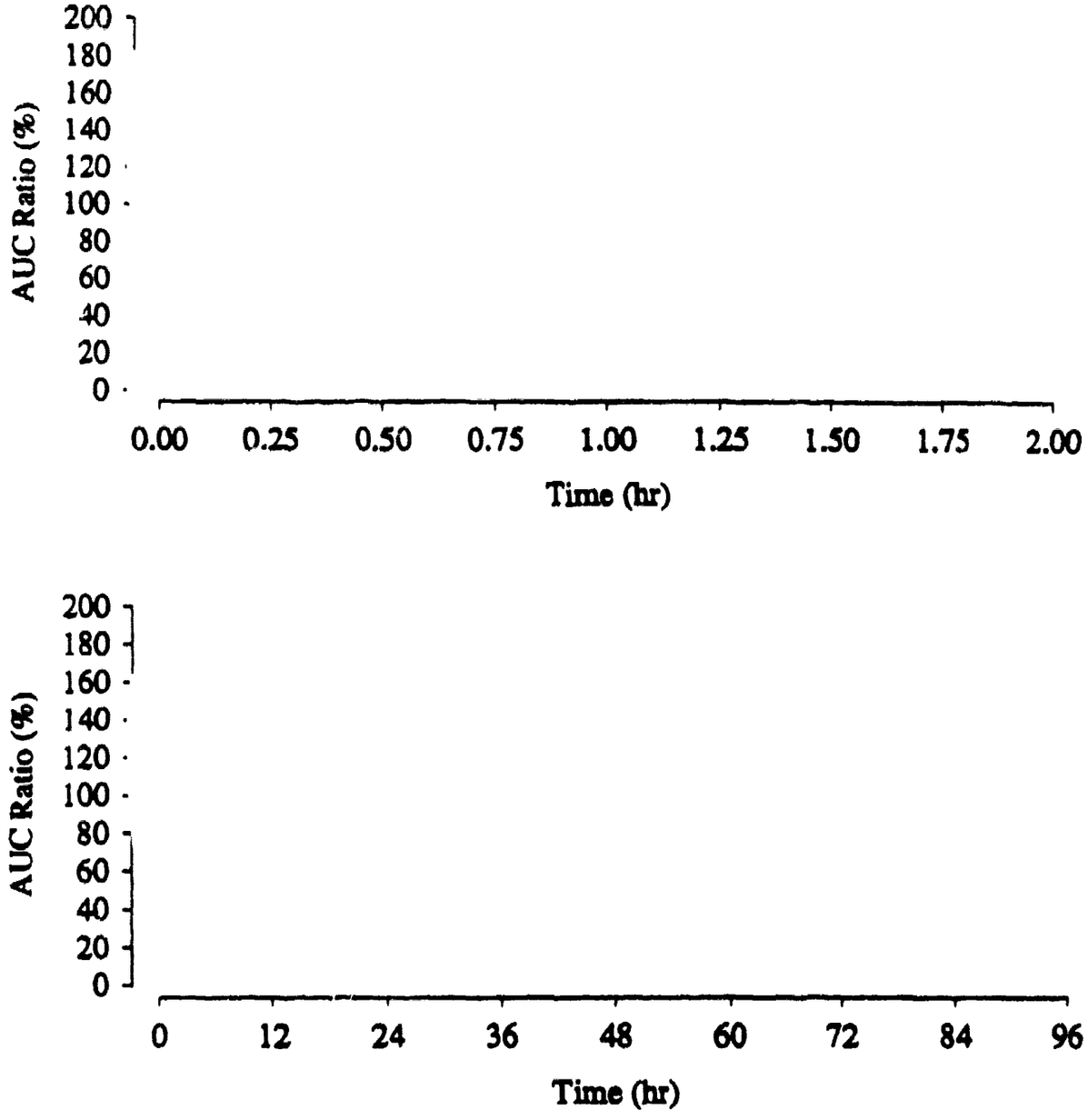


FIGURE 13. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 150 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

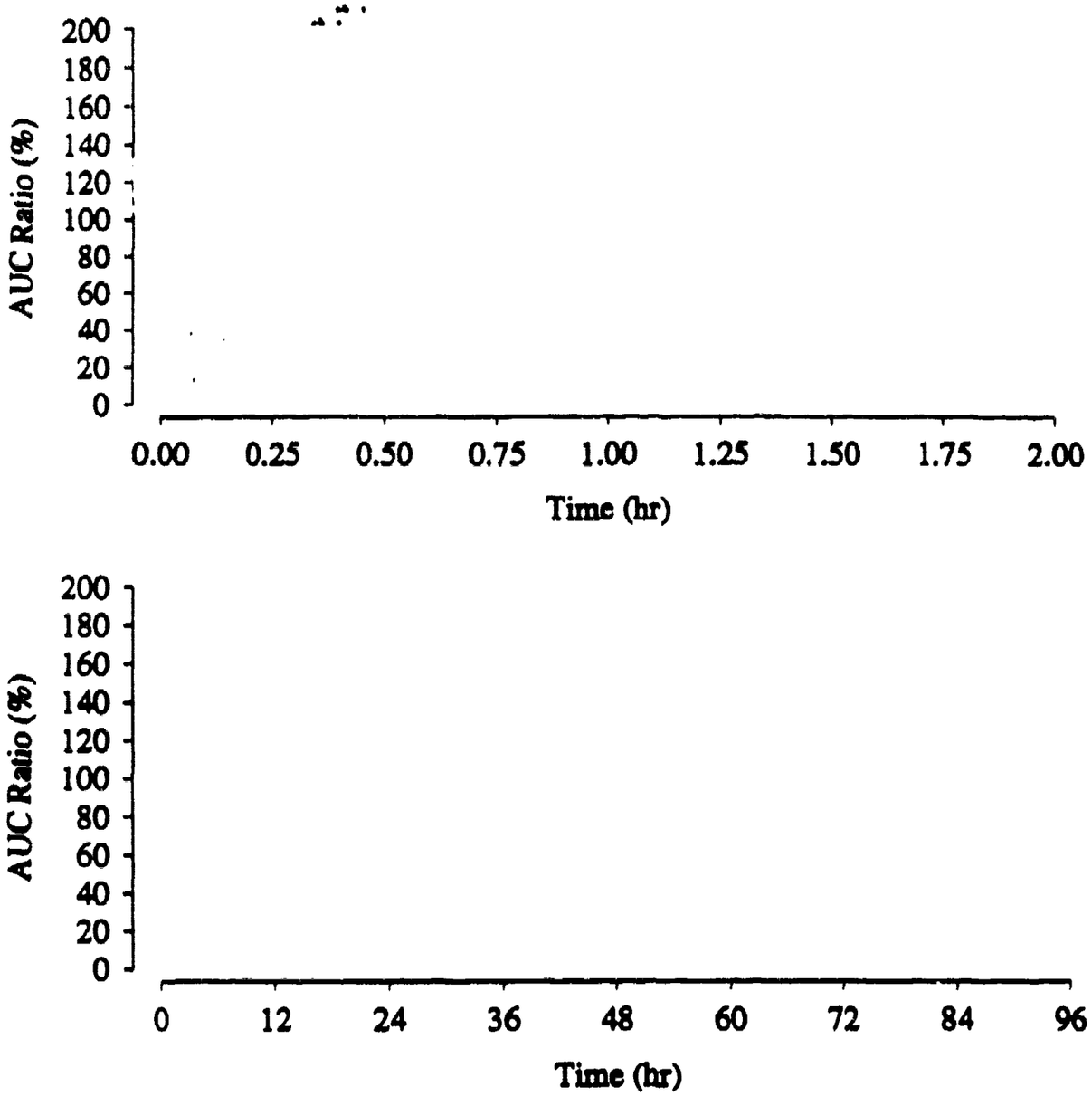


FIGURE 14. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 100 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

The above figures demonstrate that, at the 150 mg/min rate of fosphenytoin, AUC of free phenytoin from fosphenytoin reaches that of free phenytoin from Dilantin at approximately 8 min. post-start-of-infusion., rises above that of Dilantin, and then falls to be approximately equal to that of Dilantin within 30 minutes post-start-of-infusion. This approximate equality is then maintained over the remainder of the time course. At 100 mg/min fosphenytoin, cumulative AUC of free phenytoin takes approximately 1.5 hrs. to reach the 80 - 125 % band.

As forementioned, the cumulative AUC from fosphenytoin is greater than that from Dilantin for approximately 10 - 20 minutes. However, examination of the concentration-time profiles (Panel D -- page 127) shows that the reason for the increased AUC is because fosphenytoin delivers free phenytoin more rapidly than Dilantin, and not because Cmax is increased. An additional point is that the differences in cumulative AUC between the 100 and 150 mg rates is due to the first 15 minutes post-initiation-of-infusion. From that point onward, the differences between the 100 and 150 mg/min infusion rates are minimal.

These analysis' show that, at 100 - 150 mg/min, free phenytoin from fosphenytoin closely approximates, but does not duplicate, free phenytoin from Dilantin at 50 mg/min.

CONCLUSIONS: The concentration-time profile of free phenytoin from 1200 mg of fosphenytoin administered at 100 or 150 mg/min is comparable to that following 1200 mg of phenytoin administered at 50 mg/min. The 150 mg/min rate meets equivalence criteria for Cmax and AUC, whereas the 100 mg/min rate meets criteria for AUC only.

If cumulative AUC is examined, the 150 mg/min rate meets equivalence criteria from 30 minutes onward, the 100 mg/min rate from 90 minutes onward. At time periods longer than 90 minutes the AUC of free phenytoin from fosphenytoin at either administration rate are equivalent to free phenytoin from 50 mg/min Dilantin.

STUDY: Pharmacokinetic meta analysis of fosphenytoin clinical trials

RESEARCH REPORT NUMBER: RR-X 764-02114

OBJECTIVE: To compare systemic exposure of phenytoin, 1) after dosing fosphenytoin and Dilantin®, 2) between patients and healthy subjects, 3) between arterial and venous phenytoin, and 4) the effects of age, gender, and race on the pharmacokinetic profile of fosphenytoin.

STUDY DESIGN: The data from clinical studies 982-13 to 982-16 and healthy volunteer studies 982-18, 982-20 and 982-24 were utilized.
1) Phenytoin population pharmacokinetics was carried out using a nonlinear mixed effect model to evaluate the effects of dosing regimen, body weight, time, age, gender, and serum albumin concentration on phenytoin clearance and distribution in a linear pharmacokinetic model. The studies 982-14 and 982-15 used in the analysis were from routine therapeutic drug monitoring. Only samples collected more than 6 hours after fosphenytoin administration were used (to avoid cross reactivity with immunoassay).
2) Graphical analysis of patient/subject differences were made by subsetting free phenytoin, total phenytoin and fosphenytoin concentration time profiles by dose and infusion rate and visually inspecting for patterns and/or differences among patients and healthy subjects. All the above studies were included.
3) Comparison of arterial and venous plasma concentrations for fosphenytoin, total phenytoin and free phenytoin were made in 6 neurosurgery patients. Plots were visually inspected for trends.
4) Patient sub-populations were graphically analyzed by subsetting plasma concentration profiles by route of administration and then further subsetting by age, gender, and race and visually inspecting for patterns and/or differences among patients.

RESULTS:
1) A linear pharmacokinetic model served as a suitable alternative to the generally applicable non-linear model given the restrictions in the range of doses and plasma phenytoin concentrations available from these clinical trials.

Consistent with previous clinical experience, phenytoin clearance and volume of distribution exhibit a direct relationship with weight. Mean trough phenytoin levels decline over time (Fig 1) and this is also reflected in the individual plots (Fig 2). Modeling suggests this decline in mean plasma phenytoin concentration is most likely explained in terms of an increase in phenytoin clearance in those patients remaining in the studies for more than just a few days rather than a tendency for patients with intrinsically high clearance to remain in the study longer (Fig 2 and Bayes estimates).

Modeling for difference in extent of systemic availability suggests that fosphenytoin delivers 15% less phenytoin than Dilantin, however, this may be due to model misspecification of the i.m. dosage.
2) Graphical presentation of free phenytoin, total phenytoin, and fosphenytoin concentration-time profiles by dose/infusion rate does not suggest the presence of sub-populations or specific individuals for which these levels are atypical.
3) Graphical comparison of plasma arterial and venous concentration time profiles for free phenytoin, total phenytoin and fosphenytoin do not show any differences.

4) Graphical analysis of patient sub-populations did not suggest the presence of sub-populations or specific individuals for which fosphenytoin concentration time profiles were atypical (Fig 3).

CONCLUSIONS: The observed trend for concentrations to drop within individuals suggests a time dependent increase in clearance in phenytoin clearance which has been observed previously in febrile patients and trauma patients. This does not appear to be related to fosphenytoin administration. The observation that intravenous fosphenytoin is 15% less bioavailable than Dilantin is not of concern because the improved fit of the data to the model including this bioavailability term is moderate. No further unusual trends where observed.

Visual inspection of plasma arterial and venous concentration-time profiles for fosphenytoin show no obvious differences which is consistent with the fact that phenytoin is a low extraction ratio drug.

Visual inspection of fosphenytoin concentration time profiles does not show any apparent differences across age, gender, race or in any of the sub-groups. This is consistent with the fact that phosphatase activity is extensive and differences in individuals is unlikely to make much difference in the conversion of fosphenytoin to phenytoin.

The conversion of fosphenytoin to phenytoin is consistent and essentially complete. There is no evidence of atypical phenytoin pharmacokinetics due to differences in fosphenytoin disposition between individuals.

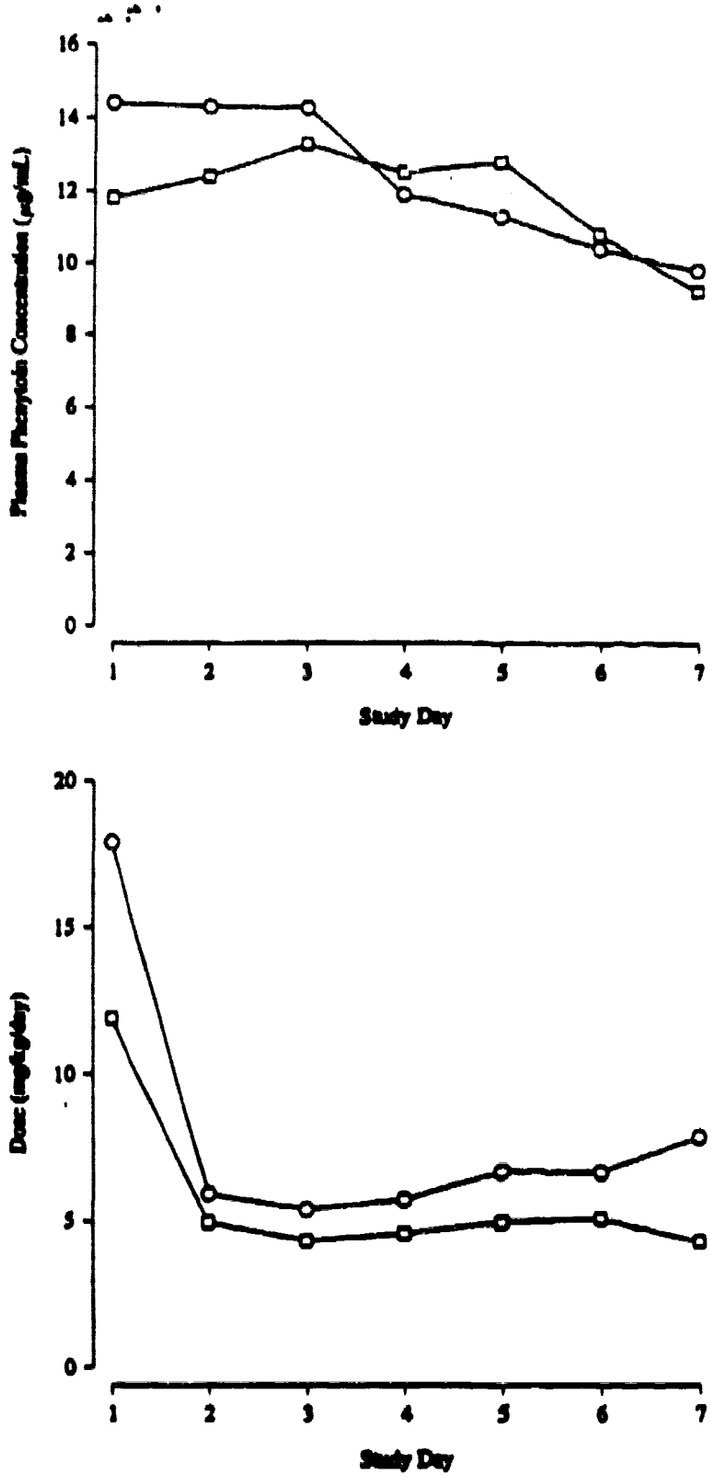
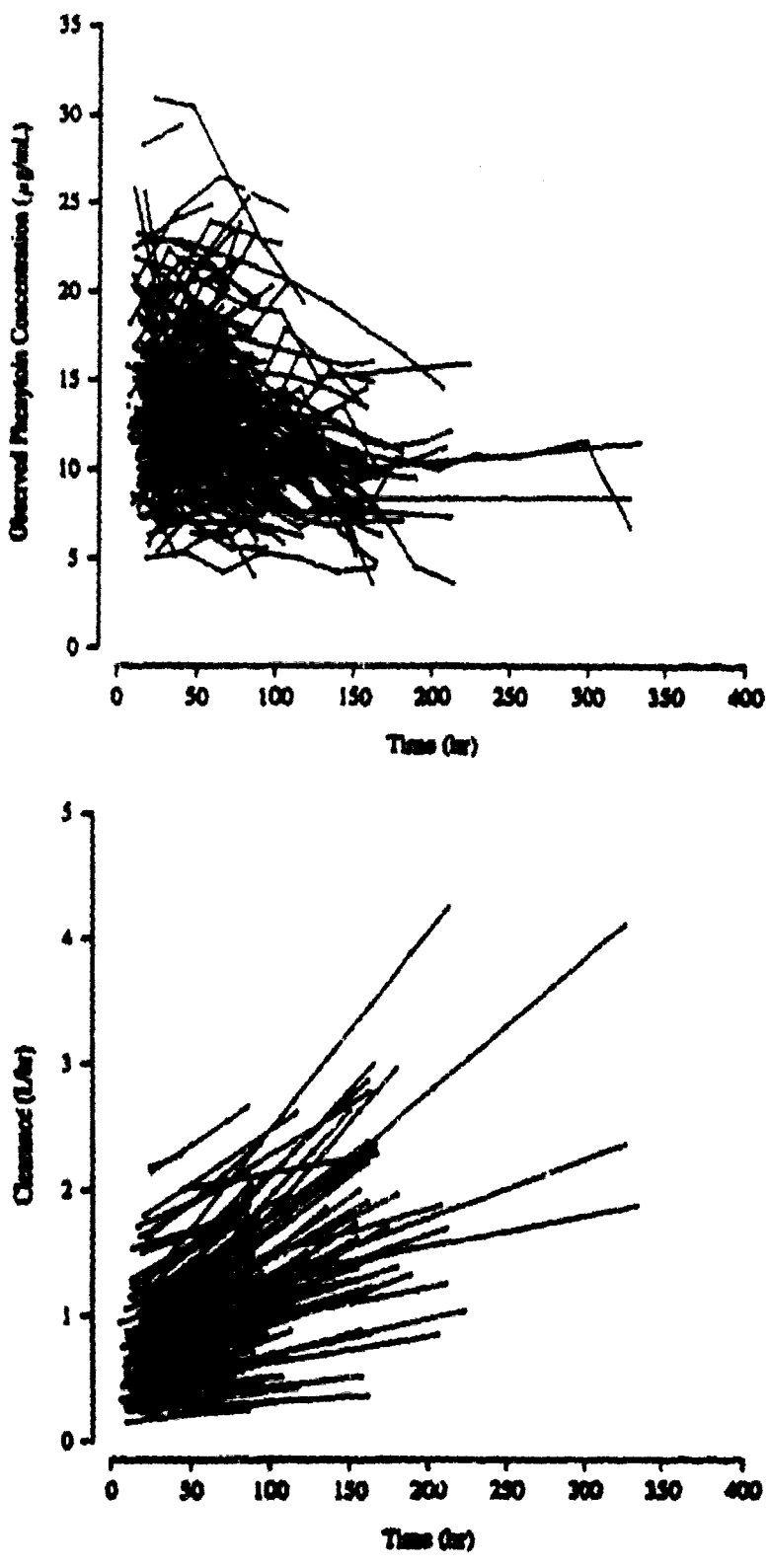


FIGURE 1 Mean Plasma Phenytoin Concentration (Top) and Mean Dose (Bottom) Versus Study Day for (□) Protocol 982-14 (Intramuscular) and (○) Protocol 982-15 (Intravenous)



2.

FIGURE X. **Plasma Phenytoin Concentration (Top) and Post Hoc Estimated Clearance (Bottom) Versus Time for Protocols 982-14 (Intramuscular) and 982-15 (Intravenous). Lines Connect Data by Patient.**

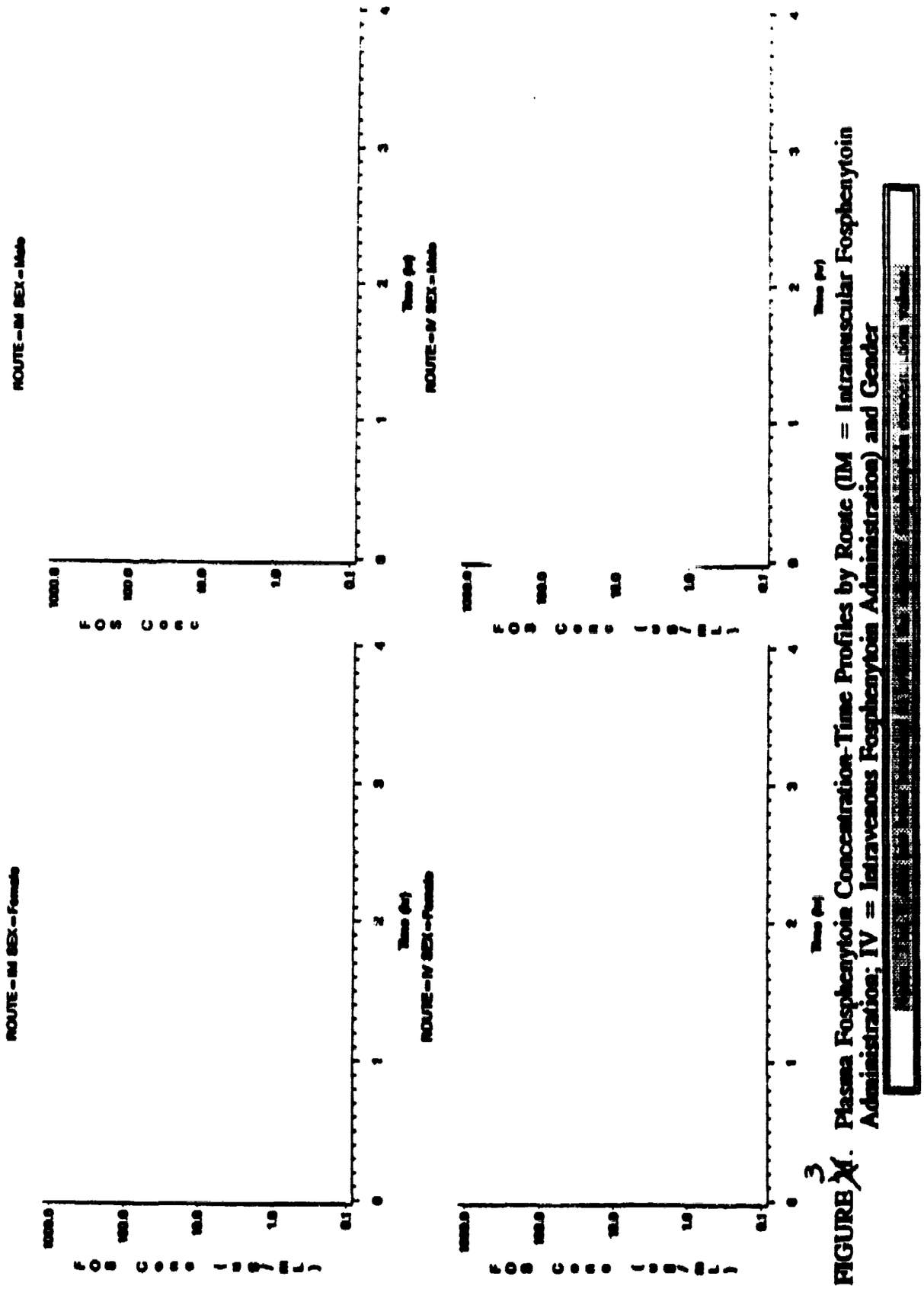


FIGURE 3. Plasma Fosphenytoin Concentration-Time Profiles by Route (IM = Intramuscular Fosphenytoin Administration; IV = Intravenous Fosphenytoin Administration) and Gender

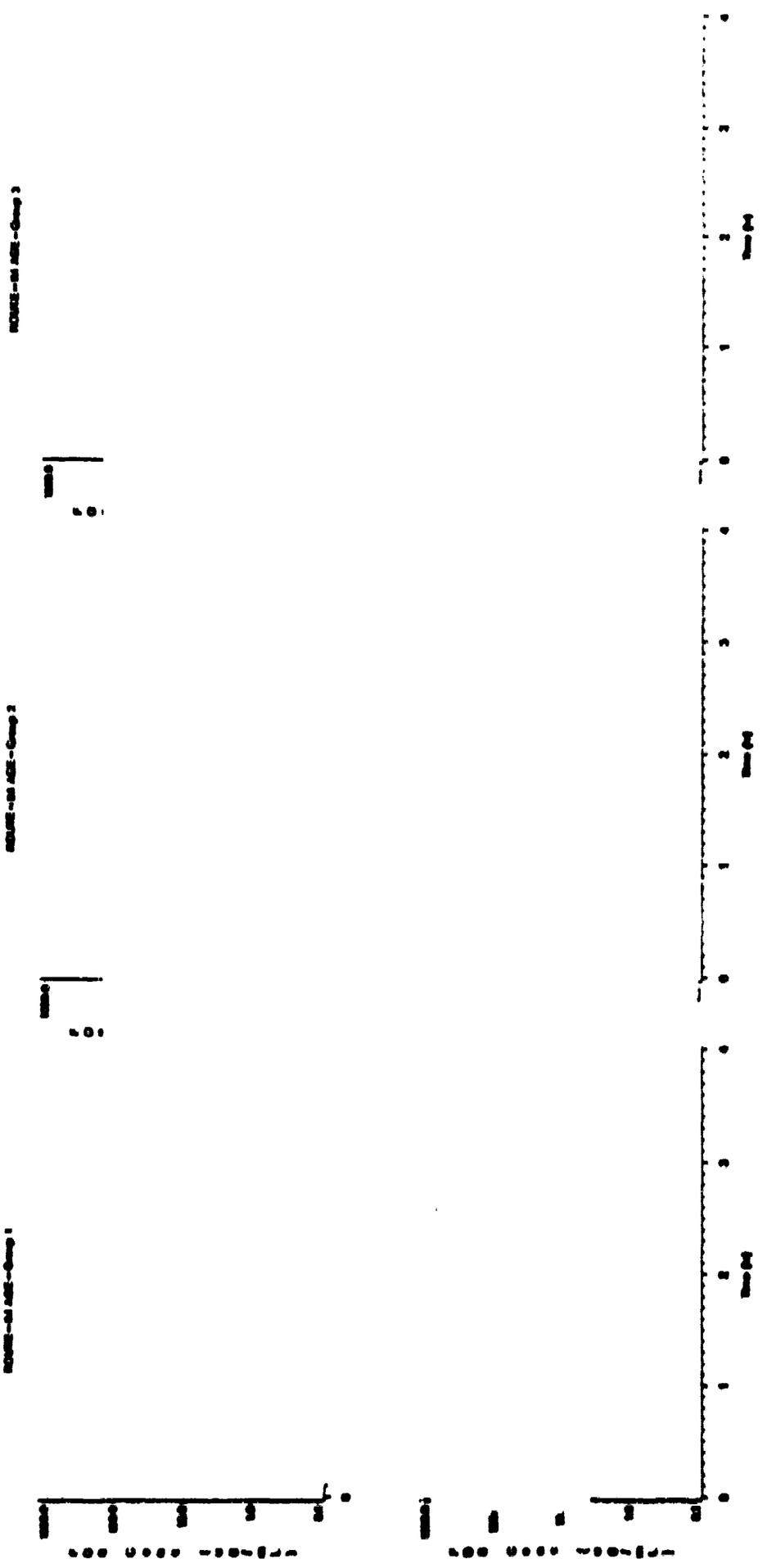


FIGURE 3. Plasma Fosphenytoin Concentration-Time Profiles by Route (IM = Intramuscular Fosphenytoin Administration; IV = Intravenous Fosphenytoin Administration) and Age Group (Group 1 = Age ≤ 40; 2 = 40 < Age ≤ 65; 3 = Age > 65 yr)

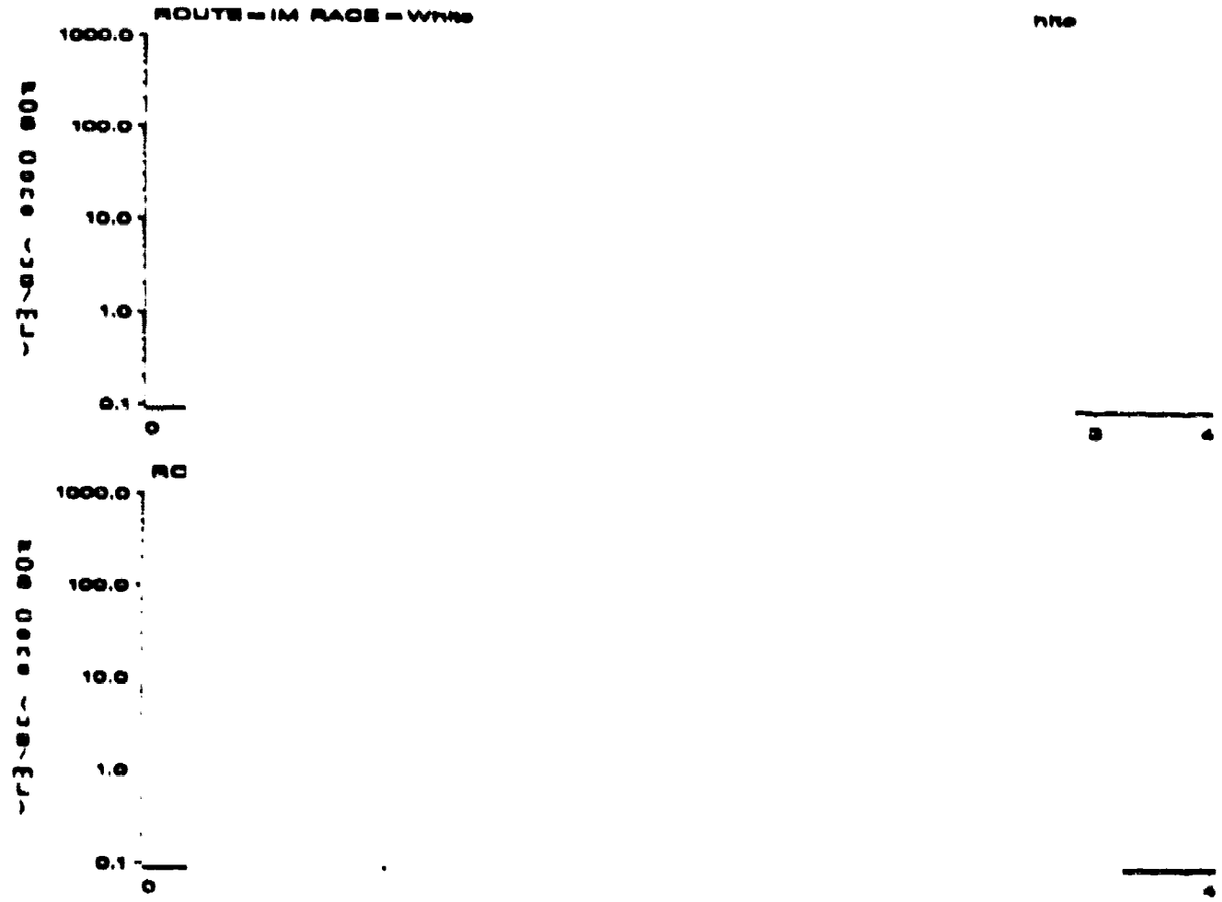


FIGURE 3. Plasma Fosphenytoin Concentration-Time Profiles by Route (IM = Intramuscular Fosphenytoin Administration; IV = Intravenous Fosphenytoin Administration) and Race

[redacted]

note: Fosphenytoin concentrations and parameters reported in the this review have been corrected. They **DO NOT** suffer from the errors detailed in the **Important Note** on p. 3.

STUDY: Characterization of fosphenytoin and phenytoin human plasma protein binding in vitro

RESEARCH REPORT NUMBER: RR 764-02124

OBJECTIVES: To determine the protein binding characteristics of fosphenytoin and phenytoin using standard in vitro methodologies.

STUDY DESIGN: Plasma samples were spiked with fosphenytoin (up to 800 μg/mL) and phenytoin (up to 80 μg/mL) and total and unbound drug concentrations were determined via ultrafiltration and HPLC. NONMEM was used to fit the data to a variety of binding models.

RESULTS: The following pertinent conclusions can be made (see Figures 1 - 5):

1. Fosphenytoin binding is best described by a model which incorporates 2 saturable binding sites. Fosphenytoin binds to the site of highest affinity with a binding constant of approximately 1.1 μg/mL, suggesting that this is the approximate unbound plasma concentration above which nonlinear binding may be observed. The second site has a much lower affinity (Kd > 100 μg/mL) suggesting that binding at this site will be linear at typical in vivo plasma fosphenytoin concentrations.

2. Phenytoin binding is best described by a model which incorporates 1 saturable binding site and 1 linear binding site. The affinity constant for the saturable binding site is approximately 30 μg/mL.

3. Fosphenytoin (at free concentrations above approximately 1.0 μg/mL or total concentrations above approximately 75 μg/mL) is capable of displacing phenytoin from the high affinity binding sights whereas phenytoin (at total concentrations below 80 μg/mL) does not significantly displace fosphenytoin.

4. These results are qualitatively consistent with the results of in vivo studies. However, quantitatively there are some inconsistencies. These inconsistencies are likely due to deficiencies in the in vivo studies (including the performance of ultrafiltration at non-physiological temperatures, the use of heparin as the anticoagulant, and the use of contaminated radiolabeled drugs).

10. FIGURES

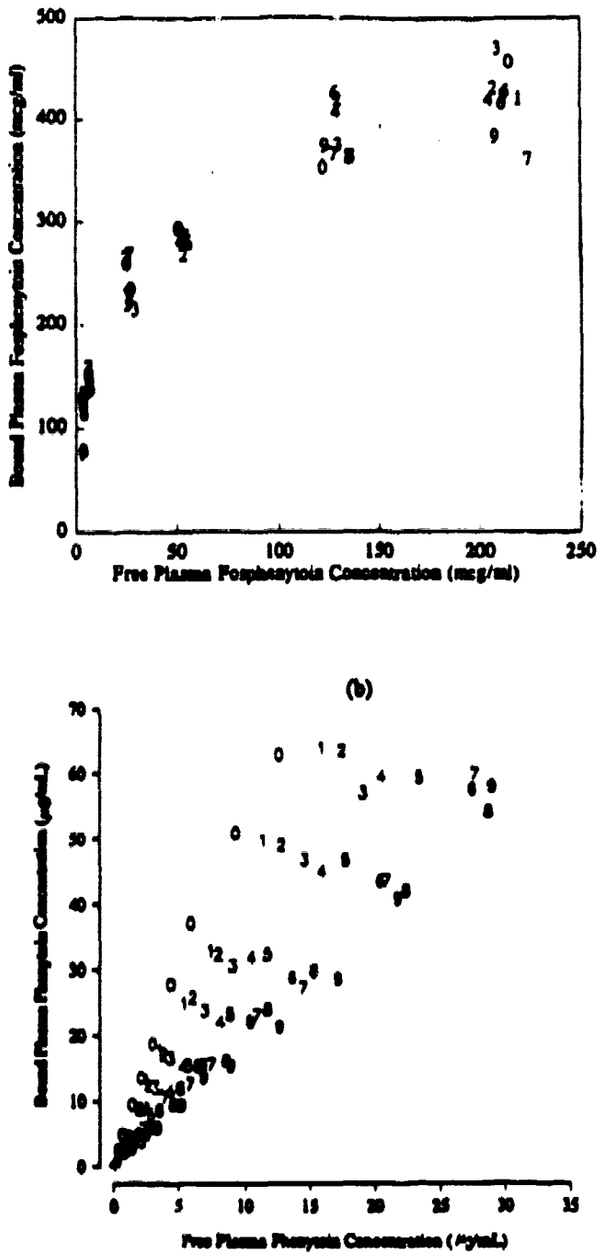


FIGURE 1. **Plasma Protein Binding and Displacement Plots for Fosphenytoin (a) and Phenytoin (b). Symbol references nominal displacer concentration with 0 indicating no displacer present and 9 indicating the maximum amount: 80 µg/mL phenytoin in (a) and 800 µg/mL fosphenytoin in (b). See Table 2 for complete range of nominal concentrations.**

Notes: Panel [illegible] have been rescaled to reflect the adjusted phenytoin concentration values.

4 Pages

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APPENDIX 3

COMPREHENSIVE FORMULATION SUMMARY

The composition of the drug product intended for market is the same as that identified in the attached as Formulation 1 Fosphenytoin Injection 75 mg/ml. Other than the ^{13}C-labeled fosphenytoin (Formulation X) used in Study 982-10, Formulation 1 was the only fosphenytoin formulation used in clinical trials.

List of All Formulations Used in Clinical Studies
(Sorted by Study Number)
(Page 1 of 2)

Study No. 982-	Formulation No.	Formulation Name/Strength	Lot No.	Batch Size	Site of Manufacture
001	1	Fosphenytoin Injection 75 mg/mL	[a]	[a]	PR[b]
001	1P	Placebo for Fosphenytoin	[a]	[a]	PR[b]
002	1	Fosphenytoin Injection 75 mg/mL	Z86-6-8	[a]	PR[b]
002	[c]	Dilantin Injection 50 mg/mL	05726	[c]	[c]
003	1	Fosphenytoin Injection 75 mg/mL	[a]	[a]	PR[b]
003	1P	Placebo for Fosphenytoin	[a]	[a]	PR[b]
005	1	Fosphenytoin Injection 75 mg/mL	[a]	[a]	PR[b]
006	1	Fosphenytoin Injection 75 mg/mL	Z86-1-8	[a]	PR[b]
006	[c]	Dilantin Injection 50 mg/mL	05726	[c]	[c]
007	1	Fosphenytoin Injection 75 mg/mL	Z87-3-1	[d]	PR[b]
010	X	$^{13}C_3$-Fosphenytoin Injection	Z88-5-4	[d]	PR[b]
010	Y	$^{15}N_2$-$^{13}C_3$-Phenytoin Injection	Z88-5-5	[d]	PR[b]
011	1	Fosphenytoin Injection 75 mg/mL	Z87-3-1	[d]	PR[b]
011	[c]	Valium Injection 5 mg/mL	[e]	[c]	[c]
012	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester[e]
012	1P	Placebo for Fosphenytoin	CM 345120	150 L	Rochester
012	[c]	Dilantin Injection 250 mg/5 mL	03060	[c]	Rochester
013	9PA1	Placebo Capsule	CL 002017	500,000 Caps	MOPS[f]
013	11A3	Dilantin Capsule 100 mg	CM 223070	105,000 Caps	PR[b]/MOPS
013	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
013	1P	Placebo for Fosphenytoin	CM 345120	150 L	Rochester
014	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester

[a] Not specified. Study conducted by
[b] Manufactured at
[c] Commercially available product.
[d] Not specified. Study conducted by
[e] Rochester, Michigan
[f] Morris Plains, New Jersey

List of All Formulations Used in Clinical Studies
(Sorted by Study Number)
(Page 2 of 2)

Study No. 982-	Formulation No.	Formulation Name/Strength	Lot No.	Batch Size	Site of Manufacture
015	1	Fosphenytoin Injection 75 mg/mL	CM 0020192	17,000 Amps	Rochester
015	46	Dilantin Injection 250 mg/5 mL	CM 057031	480 L	Rochester
015	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
016	1	Fosphenytoin Injection 75 mg/mL	CM 0020192	17,000 Amps	Rochester
016	1	Fosphenytoin Injection 75 mg/mL	CR 0200193	5,000 Vials	Rochester
017	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
017	[a]	Dilantin Injection 250 mg/5 mL	03060	[c]	Rochester
018	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
020	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
020	1P	Placebo for Fosphenytoin	CM 345120	150 L	Rochester
020	[a]	Dilantin Injection 250 mg/5 mL	03060	[c]	Rochester
021	46	Dilantin Injection 250 mg/5 mL	CM 057031	480 L	Rochester
021	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
021	[a]	Sodium Chloride Injection USP	66-429-DK	[g]	Abbott
022	1	Fosphenytoin Injection 75 mg/mL	CM 0020192	17,000 Amps	Rochester
022	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
024	46	Dilantin Injection 250 mg/5 mL	CM 057031	480 L	Rochester
024	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester

[a] Not specified. Study conducted b
[b] Manufactured a
[c] Commercially available product.
[d] Not specified. Stu
[e] Rochester, Michigan
[f] Morris Plains, New Jersey
[g] Powder blend made

3 Pages
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APPENDIX 4

3 Pages

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APPENDIX 5

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 6, 1995

FROM: Associate Director,
Division of Scientific Investigations (HFD-340)

SUBJ: Review of EIRs Covering
NDA # 20-450, Fosphenytoin Sodium (Cerebyx®) Injection, sponsored by Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co.

TO: Paul D. Leber, M.D.
Director, HFD-120
Division of Neuropharmacological Drug Products

At the request of HFD-120, the Division of Scientific Investigations initiated audits of three pharmacokinetics and bioequivalency studies. These audits were expedited due to the User Fee status of this NDA.

The clinical portion of study 982-014 was performed at the University of Tennessee, Memphis, TN. The clinical portions of studies 982-018 and 982-024 were performed a
The analytical portions of all three studies were performed at] Following the inspections, Forms 483 (attached) were issued. Our evaluation of these findings is as follows:

1. Reported fosphenytoin concentrations were in error since the water content of the fosphenytoin reference standard was not taken into account in calculations.

4 Pages
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protein-binding, unbound phenytoin, and percentage unbound phenytoin, be reviewed for corroboration independent of the data evaluated here.

In light of the nonlinear kinetics for fosphenytoin and phenytoin, a dosing error up to 5% combined with analytical errors up to 10% may need to be considered when interpreting pharmacokinetics.

After you have reviewed the material, we request that this transmittal memo be appended to the original NDA submission. Please forward a copy of your review to HFD-340 for our files.

C.T. Viswanathan

C. T. Viswanathan, Ph.D.

Chemist Review

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-450

Cerebyx®

(Fosphenytoin Sodium Injection)

HFD-120 REVIEW DIVISION

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-102

DATE COMPLETED: August 30, 1994

ENVIRONMENTAL ASSESSMENT

1. **Date:**

EA dated:	06/30/1994
NDA filed:	07/14/1994
Consult to HFD-102	07/27/1994
Assigned:	08/19/1994
Telecon:	08/22/1994
Faxed response:	08/22/1994

2. **Name of applicant/petitioner:**

Warner-Lambert Company

Adequate.

3. **Address:**

201 Tabor Road
Morris Plains, NJ 07950

Adequate.

4. **Description of the proposed action:**

a. **Requested Approval:**

Warner Lambert has filed an NDA for Cerebyx® (Fosphenytoin Scdium).

DEFICIENT. The drug product name and drug substance names are incorrect. This occurs throughout the rest of the document.

b. **Need for Action:**

The product will be used in the treatment and control of seizures in patients with status epilepticus.

Adequate.

c. **Production Locations:**

i. **Proprietary Intermediate(s):**

None

ii. **Drug Substance:**

Address: Parke-Davis Holland Chemical Facility
188 Howard Avenue
Holland, Michigan 49424

Facility Lescription & Adjacent Environment:
A brief facility description is provided. The facility is located in an industrial and commercial area which includes residential, light industry and retail business. It is adjacent to the Macatawa River and is in the Eastern Deciduous Forest Ecoregion (climax forest beech-maple).

Adequate.

iii. **Finished Dosage Form:**

Address: Parke-Davis Rochester Facility
870 Parkdale Avenue
Rochester, Michigan 48307

Facility Description & Adjacent Environment:
A brief facility description is provided. The facility is located adjacent to a city park, residential areas and light manufacturing.

Adequate.

d. **Expected Locations of Use (Drug Product):**

Not discussed. **DEFICIENT.**

e. **Disposal Locations:**

The fate of returned or expired drug product or rejected drug substance is not discussed. **DEFICIENT.**

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance: Fosphenytoin **DEFICIENT.** Should be identified as the sodium salt.

Drug Product: Not listed. Adequate as the drug product is identified elsewhere in the EA.

Chemical Name: 5,5-diphenyl-3-[(phosphonooxy)-methyl]-2,4-imidazolidinedione **DEFICIENT.** Should be identified as the sodium salt.

CAS #: 92134-98-0. The Libra (Roy) confirms that this number is the CAS for Fosphenytoin Sodium.

Molecular Weight: 362.28 g/mole (free acid)
406.24 g/mole (sodium salt)

Molecular Formula: $C_{15}H_{15}N_2O_6P$ (free acid)
$C_{15}H_{13}N_2O_6PNa_2$ (sodium salt)

Structural Formula: Not included. **DEFICIENT.**

Physical Descrip.: fine white solid (drug substance)

Additives: No information provided. **DEFICIENT.**

Impurities: No information provided. **DEFICIENT.**

6. **Introduction of substances into the environment: For the site(s) of production:**

   a. **Potential Emitted substances:**

   A list of raw materials used in the synthesis of the bulk drug and the composition of the drug product is provided in the non-confidential portion of the EA. **Note: the company will be given the opportunity to move this information to a confidential appendix, although they may choose to leave it where it is.**

   The company was requested (telecon 8/22/1994) to provide a flow diagram for the synthesis of the drug substance and the manufacturing process for the drug product. This was faxed on 8/22/1994. An official copy should be provided. **DEFICIENT.**

   b. **Controls (Air, Liquid Effluent, Solid):**

   DEFICIENT. See Attachments 1 and 2.

c. **Compliance with Federal, State and Local Emission Requirements:**

A list of applicable environmental regulations are included and they state that the Rochester and Holland Michigan facilities are substantially in compliance with all applicable regulations (page 28). Adequate. They do not discuss meeting compliance with occupational exposure requirements. **DEFICIENT.**

d. **Effect of Approval on Compliance with Current Emissions Requirements:**

DEFICIENT. See Attachments 1 and 2.

e. **Estimated Expected Emitted Concentration/Quantities:**

DEFICIENT. See Attachments 1 and 2.

The maximum expected environmental concentration for Fosphenytoin has been calculated at 4.6×10^{-5} ppm (46 ppt), based on the 5th year manufacturing estimate of 5,115 pounds. Adequate. The EA document refers to this as the minimum EEC. **DEFICIENT.**

7. **Fate of emitted substances in the environment:**

Parent Compound:	Fosphenytoin Sodium (99.2% conversion to phenytoin)
In vivo:	Phenytoin
Metabolites:	Hydroxyphenytoin

The approximate percent excreted as phenytoin and hydroxyphenytoin should be provided if known. **DEFICIENT.**

The Tier 0 testing provided indicates Tier 1 (aquatic) testing for Fosphenytoin and Hydroxyphenytoin and Tiers 1 (aquatic) and 2 (terrestrial) testing for Phenytoin. See Attachment 3.

No information was provided regarding hydrolytic stability or dissociation constants for the compounds of interest. **DEFICIENT.**

Insufficient information is provided regarding the test methods for water solubility and partition coefficient. **DEFICIENT.** For water solubility information such as the methodology used (e.g., undersaturation/oversaturation), the study site, the temperature at which the solubility was determined and the HPLC method should be provided. For the partition coefficient information such as the test methodology, the study site, concentration at which the study was performed (2 different ones needed) and the HPLC method should be provided.

Although not necessary, the photolytic degradation of Fosphenytoin Sodium was determined. The conclusion (page 17, 1st sentence in second paragraph) should be revised to indicate that photolysis is not a primary removal mechanism of Fosphenytoin Sodium from the environment. **DEFICIENT.**

Fosphenytoin Sodium is aerobically biodegraded in the aquatic compartment to Phenytoin. Phenytoin does not biodegrade in the aquatic compartment and does not to absorb to soil. The company states that Hydroxyphenytoin aerobically biodegrades rapidly in the aquatic compartment and that it has been proven/demonstrated to completely degrade to CO_2. The data provided does not support these statements. **DEFICIENT.** (See Attachments 4 and 5)

8. **Environmental effects of released substances:**

See Attachments 4 and 5.

Neither Fosphenytoin, Phenytoin or Hydroxyphenytoin inhibit microbial growth at concentrations expected in the environment nor are they acutely toxic to *Daphnia magna*. (See Attachment 4).

Adequate.

9. **Use of resources and energy:**

a. **Production:**

Production of the material will result in a 1% or less increase in production levels or energy usage over current levels at both the Holland and Rochester facilitates. Adequate.

b. **Effect on Endangered/Threatened Species:**

None. Adequate.

c. **Effect on Properties Listed/Eligible for National Register of Historic Places:**

None. Adequate.

10. **Mitigation measures:**

The Emergency Plan, Pollution Incident Protection Plan (PIPP) and Spill Prevention Control and Countermeasure Plan (SPCC) for the Holland Facility is provided.

The Emergency Response Plan for the Rochester Facility is provided.

Safe handling guides and MSDS's are provided to personnel.

Material is disposed as indicated under # 6.

Adequate.

11. **Alternatives to the proposed action:**

They state that the proposed action will have no impact on the environment and the one alternative is no action (approval) by the FDA.

DEFICIENT. They can not say it will have no impact, only the FDA can in the FONSI.

12. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

A list is provided. **DEFICIENT.** They state that no consultants were used, but include in the list is a consultant (performed many of the environmental test) for this EA. also did some basic testing is support o. They also state that the *Curricula vitae* for the listed individual are attached. But they were not included.

13. **Certification:**

Provided. Adequate.

14. **References:**

References are provided. Adequate.

15. Appendices:

The appendices are not identified as confidential or non-confidential, although some individual pages are stamped as confidential. **Note: the company will be reminded about the confidentiality issues.**

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 1**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-1995

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: **CEREBYX®**
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

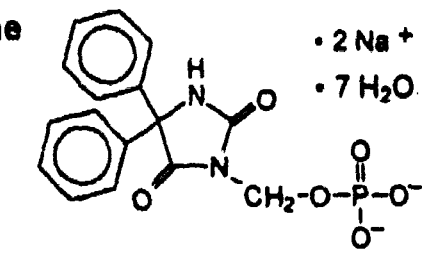
PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx ___ OTC

JUN - 7 1995

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

$C_{16}H_{13}N_2O_6PNa_2 \cdot 7H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

Phenytoin starting material is synthesized under DMF , which is currently under review and contains some major deficiencies. In general, the deficiencies in the NDA appear to be minor, however some control issues need to be resolved. For one intermediate in the fosphenytoin synthesis, there is no data to show that it is not present as an impurity in the drug substance. The proposed impurity limits for the drug product need to be evaluated.

CONCLUSIONS & RECOMMENDATIONS:

Establishment Evaluations, Microbiology and Environmental Assessment are still pending as is Methods Validation [this cannot be initiated until we obtain a satisfactory response to questions about possible impurities in the n.d.s., see item 8 of draft letter]. Due to these issues, and manufacturing deficiencies in both the NDA and DMF the NDA is Not Approvable for Chemistry at this time.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/05-JUN-1995
HFD-120/CSO/RNighswander
HFD-120/SBlum/Init.: 6/7/95

Martha R Heimann 6/7/95
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.001

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Cerebyx®

(fosphenytoin sodium)

Injection

NDA 20-450

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS (HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-250

Cerebyx®

(fosphenytoin sodium)

Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Cerebyx®, Warner-Lambert Company has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fosphenytoin sodium is a synthetic drug which is administered as an injectable solution in the treatment and control of seizures in patients with status epilepticus. The drug substance will be manufactured at Parke-Davis Holland Chemical Facility, Holland, Michigan. The drug product will be manufactured at Parke-Davis Rochester Facility, Rochester, Michigan. The finished drug product will be used in hospitals and clinics.

Fosphenytoin sodium is a prodrug which is rapidly and completely converted to phenytoin *in vivo*. Patient excretions contain a small percentage of the dose as phenytoin (<5%), some dihydrodiol phenytoin (~7-11%) and the major metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) (~67-88%). Small amounts of fosphenytoin sodium may enter the environment due to manufacture. Chemical and physical test results indicate that fosphenytoin sodium, phenytoin and, the major metabolite, p-HPPH will most likely be restricted to the aquatic environment.

Hydrolysis of fosphenytoin and phenytoin and photolysis of fosphenytoin sodium is expected to be slow under environmental conditions. Fosphenytoin is rapidly biotransformed to phenytoin under biodegradation test conditions, phenytoin is not chemically converted and p-HPPH can be completely biodegraded, although the biodegradation is not rapid.

As fosphenytoin and the major metabolites are expected to persist in the aquatic environment for some time, the toxicity of fosphenytoin sodium, phenytoin and p-HPPH to aquatic organisms was characterized. Acute static toxicity studies in water fleas (*Daphnia magna*) indicate that the drug substance is generally not toxic to aquatic organisms at concentrations of at least 5 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Microbial inhibition studies indicate that environmental microorganisms are not inhibited at concentrations of at least 7 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned drug product will be disposed of at a licensed incineration facility. Out-of-specification drug product and drug substance will be reprocessed or disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

6/9/95 Nancy B Sager
DATE

Prepared By
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

6/26/95 Robert A. Jerussi
DATE

Concurred
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment I: Environmental Assessment
Attachment II: Material Safety Data Sheet (drug substance)

ATTACHMENT I

ITEM 3.6.
Freedom of Information Environmental Assessment for
Fosphenytoin Sodium Injection

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TABLE OF CONTENTS
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FREEDOM OF INFORMATION ENVIRONMENTAL ASSESSMENT FOR FOSPHENYTOIN SODIUM INJECTION

1. DATE

November 29, 1994

2. NAME OF APPLICANT

Warner-Lambert Company

3. ADDRESS OF APPLICANT

201 Tabor Road
Morris Plains, New Jersey 07950

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Description of the Proposed Action

Warner-Lambert has filed a New Drug Application for Cerebyx® (Fosphenytoin sodium). The drug substance is Fosphenytoin sodium. The New Drug Application requests approval of Fosphenytoin Injection for the treatment and control of seizures in patients with status epilepticus.

4.2. Need for the Action

Approval of this application will result in production and distribution of Cerebyx® in the United States. Approval will offer patients in the United States an effective therapy for treatment and control of seizures in patients with status epilepticus in hospitals and clinics. Because of the therapeutic benefits associated with its availability and use, approval is sought and preferable to nonapproval. It is estimated

that 1.5 million people are identified as suffering from epilepsy in the United States with an estimated yearly increase of approximately 70,000 to 130,000 patients.

4.3. Locations Where the Products Will be Produced

Bulk drug substance will be manufactured at the following Warner-Lambert facility:

Parke-Davis Holland Chemical Facility
188 Howard Avenue
Holland, Michigan 49424

The Parke Davis Holland Chemical facility is located on approximately 50 acres of land in the Township of Holland (1990 population—17,523), in Ottawa County, Michigan, approximately 30 miles west of Grand Rapids. The site is just north of the city of Holland and consists of approximately 15 buildings and employs an average work force of 300 employees. It is adjacent to the Macatawa River near the river's confluence with Lake Macatawa. Lake Macatawa flows into Lake Michigan approximately 4.5 miles downstream from the facility. The plant is located in an industrial and commercial area which includes residential, light industry, retail business and beech-maple forests.

The Holland facility receives its potable water from Holland Township. Holland Township obtains its potable water from the city of Wyoming, the city of Holland, and in rural areas, from ground water. Wyoming obtains water from Lake Michigan via an intake structure located approximately 6 miles northwest of the facility and about 6 miles north of Lake Macatawa's outlet to Lake Michigan. The city of Holland obtains its potable water from Lake Michigan via an intake located about 0.75 miles off-shore and about 5 miles west of the facility and 2 miles north of Lake Macatawa's outlet to Lake Michigan. The facility pumps its sanitary wastes to the Holland Municipal Waste Treatment Facility.

Process water for noncontact cooling is obtained from an intake located on the channel leading to the Macatawa River on the east side of the facility.

The Holland facility is located on a former beach and associated offshore deposits of a higher stage of Lake Michigan. These areas have locustrine sand and gravel deposits and may include intercalated clay. Eolian sand and organic soils may be present. The area is in the Eastern Deciduous Forest Ecoregion, and the climax forest is beech-maple[1]. The site slopes from a high in the north of 605 feet to the Macatawa River in the south, which has an approximate elevation of 579 feet. The site is mostly paved or covered with buildings.

Drug product formulation, packaging and testing will be performed at the following Warner-Lambert facility:

Parke-Davis Rochester Facility
870 Parkedale Avenue
Rochester, Michigan 48307

The Parke-Davis Rochester facility is located on 80 acres of land in Oakland County, Michigan in the northeast corner of the City of Rochester (1990 population—7,096). It is approximately 30 miles north of Detroit, Michigan. The facility consists of 40 buildings and employs an average workforce of 500 people. The closest neighboring structure is over 800 feet away. The facility is surrounded by a city park to the south, a public roadway and residential area to the north, light manufacturing to the east, and vacant property followed by residential neighborhoods to the west. The site is approximately 35 miles upstream from the confluence of the Clinton River and Lake St. Clair. See Appendix 1 for Site Location Map and Site Plan.

Returned and unused drug product will be returned via the Warner-Lambert Drug Distribution System. Material with inadequate shelf-life for distribution will be sent to the following facilities:

Warner-Lambert Company
400 W Lincoln Avenue
Lititz, PA 17543

Returned products will be destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

Material that does not meet specifications will be either reprocessed at the manufacturing sites specified and submitted as a supplement to the NDA or destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

5.1. Chemical Names

5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

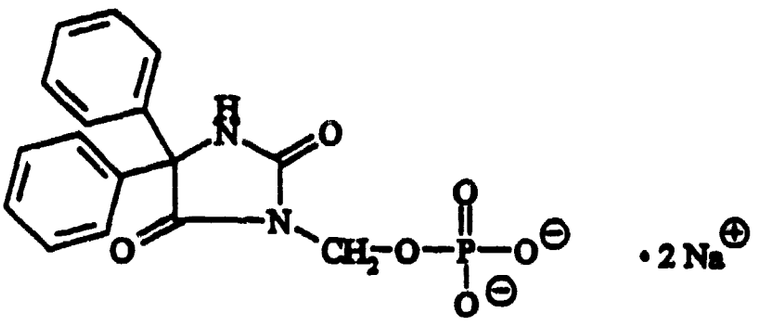
CAS Registry Number 92134-98-0

5.2. Synonym Names

Cerebyx®

Fosphenytoin sodium (USAN)

5.3. Structural Formula



5.4. Description

Fine white solid

5.5. List of Potential Impurities

Phenytoin
Dibenzylphosphate
Diphenylglycine
Diphenylhydantoic Acid
Diphenylimidazolidinone
Diphenylglycinamide
(2,5-dioxo-4,4-diphenyl-2,4-imidazolidinyl-1-yl) methoxy]methoxy]phosphoric acid bis(phenylmethyl)ester
2,4-Imidazoldinedione,3,3'-methylenebis[5,5-diphenyl-(4-cyclohexyl-2,5-dioxo-4-phenyl-1-imidizolidinyl)methyl ester, disodium salt.

A material safety data sheet (MSDS) for Fosphenytoin sodium is provided in Appendix 2.

5.6. Ultraviolet Spectrum

The apparent maximum UV absorbance in water and methanol is 200 and 204 nm, respectively. Spectra are provided in Section 15(a)3.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Fosphenytoin sodium is synthesized in the Holland, Michigan facility. The following chemicals with their corresponding CAS numbers are used in the production of Fosphenytoin sodium.

6.1. Materials Emitted into the Air in Holland, Michigan Plant

Ambient air quality at the Holland, Michigan facility is not routinely monitored. Indoor air quality is monitored. In addition, the facility has a number of other air permits that are not associated with hazardous waste management but are associated

with the specific batch manufacturing processes conducted at the site. Emission permit applications have been submitted for the Fosphenytoin sodium process. The permit (air, liquid, and solid) numbers, requirements, expiration dates, and other pertinent information are summarized in Appendix 3. Refer to Appendix 4 for where emission permits apply in the flow diagrams of synthetic route and manufacturing direction for drug substance and drug product, respectively.

6.2. Materials Disposed as Solid Waste in Holland, Michigan Plant

Solid waste is generated in the bulk pharmaceutical production at the Holland plant in 2 forms. Waste cakes from process solution filtration, and mixed wastewater filtration. The former solids are isolated from Niagara (stacked plate) pressure filters, and are primarily activated carbon and diatomaceous earth filter aid from decolorizing operations. The latter type is a product of process wastewater filtration. Suspended solids present in the wastewater are removed after pH adjustment by passing the water through a rotary precoat filter. Sludge from the wastewater is peeled off the filter along with diatomaceous earth filter aid. Both of these sludges are combined in roll-off hoppers and disposed of in a hazardous waste landfill.

The solid waste and waste solvent for our Holland, Michigan facility are disposed by the following contractors:

Waste Stream	Vendor Name	Address
Waste Solids	Chemical Waste Management	Adam's Center Landfill 4636 Adams Center Road Fort Wayne, IN 46806
Waste Solvent	EWR Inc	PO Box 160 Coal City, IL 60416
Waste Solvent	Systech Environmental Corporation	11397 County Road 176 Paulding, OH 45879
Off-Specification Pharmaceutical Substance	Chemical Waste Management	Trade Waste Incinerator #7 Mobile Avenue Sauget, IL 62201

6.3. Materials Disposed as Liquid in Holland, Michigan Plant

Aqueous emissions are regulated by Michigan Minerals Wells Act, Safe Drinking Water Act, and the Resource Conservation and Recovery Act. Compliance with these statutes has been achieved by obtaining Underground Injection Control permits from US EPA MI-139-1W-0003, MI-139-1W-0004, and MI-139-1W-0005. For noncontact cooling water discharges, NPDES Permit MI-0004715 has been granted. The permit numbers, authorizing agencies, and other pertinent information are also summarized in Appendix 3.

A storm water retention pond is located in the southwest corner of the Holland, Michigan site next to the Macatawa River. This pond receives surface runoff from the west part of the site, except runoff from certain roofs and all secondary containment areas, which is sent to the chemical waste treatment system. The unlined retention pond has no outlet, but water leaves it through the soil. A description of the wastewater treatment system is provided in Appendix 5. Water from this treatment system is disposed of by deepwell injection for which Permits MI-139-1W-0003, MI-139-1W-004, and MI-139-1W-0005 have been granted.

The Fosphenytoin sodium is received in bulk form from the Parke-Davis facility located in Holland, Michigan, and the following chemicals with their CAS numbers are used in the production of Fosphenytoin solutions for injection.

6.4. Material Disposed of as Liquid - Rochester, Michigan

Liquid wastes are containerized and transported after on-site storage to Drug & Laboratory Disposal, Inc (D&L), located in Plainwell, Michigan. D&L is an EPA licensed Treatment and Disposal facility meeting the requirements of 40 CFR Part 265 and is a licensed Michigan Act 136 Liquid Industrial Waste Hauler. D&L treats the waste as follows; the liquid waste is bulked and treated by flocculation to remove all solids, the liquids are decanted and sent to a licensed fuel blender for incineration.

6.5. Materials Disposed of into the Sewage Treatment System in Rochester, Michigan

For the Rochester, Michigan site, mixing tank residues and spent rinsate solutions containing de minimis concentrations of Fosphenytoin sodium will be discharged to the Detroit Wastewater Treatment Plant. Excess bulk Fosphenytoin solution will be containerized and placed into temporary storage in the hazardous waste storage shed prior to transport to a licensed hazardous waste incinerator for destruction. Excess buffer solutions will be neutralized prior to discharge into the sewer system. The application for the wastewater permit has been submitted to Detroit Water and Sewage Department (DWSD). The pertinent information on the liquid emission permit is summarized in Appendix 6. Approval of this product will not exceed the limit for this permit.

6.6. Materials Disposed of as Solid Waste in Rochester, Michigan

The glass vials and ampoules used in the production of Fosphenytoin for injection may become solid wastes due to inspection failures, QC failures, and sterility failures. Filled vials and ampoules which fail inspections and testing will be stored and scheduled for crushing. After crushing, the liquids are separated from the crushed glass and containerized. The separated liquids are sent off-site for incineration. The crushed glass is rinsed and then sent to a licensed Class II landfill located in Michigan. The disposition of solid waste is under a registered hazardous waste generator identification number, MID 005380126. Pertinent information of this registration is also summarized in Appendix 6.

6.7. Materials Disposed of as Hazardous Waste Materials in Rochester, Michigan

Parke-Davis' Rochester facility is a registered generator of hazardous wastes. All solid and hazardous waste associated with production of Fosphenytoin sodium Injection will be managed as hazardous waste utilizing a licensed waste hauler and disposal facility (Drug and Laboratory Disposal, Inc). This contractor is an EPA licensed treatment and disposal facility located at Plainwell, Michigan. There is no compliance issue regarding the generation, hauling, or disposal of this material.

Off-specification (including rejected) and excess Fosphenytoin sodium will be containerized and stored in the Hazardous Waste Storage Shed prior to transport to a licensed hazardous waste incinerator. Storage of this waste shall not exceed 90 days from initial placement in the storage shed. All waste shipments shall be properly manifested using Michigan Department of Natural Resources Uniform Manifests. Manifest copies will be kept and submitted as required by Michigan Public Act 64.

6.8. Materials Emitted into the Air in Rochester, Michigan

Air-borne particulates may be generated during the formulation process, although such an occurrence is unlikely. Bulk Fosphenytoin sodium powder is weighed-out in the Drug & Chemical Dispensing area prior to delivery to the bulk formulation room. The Drug & Chemical area is equipped with several in-line HEPA filtering systems capable of 99% particulate removal efficiencies prior to discharge to the ambient atmosphere. In the bulk formulation room, Fosphenytoin sodium is added directly to the injection solution containing; water for injection; buffer solutions; and tromethamine. The resulting mixture is agitated to completely mix the ingredients. The mixing occurs in an enclosed formulation tank, thus minimizing poteutial air releases. Vapor pressures of all ingredients are very low and none are expected to vaporize during handling and mixing. Nevertheless, application of air emission permits has been granted for HEPA filters in Drug and Chemical Dispensing and solution manufacturing areas. The numbers authorizing agencies, requirements, and other pertinent information are summarized in Appendix 6. All employees working with Fosphenytoin Injection production will adhere to Warner-Lambert's Safe Handling Guideline for Fosphenytoin sodium (Appendix 7) which require the use of personal protective equipment. Additionally, Industrial Hygiene monitoring will be conducted to verify that worker exposures to all Fosphenytoin Injection ingredients are below Occupational Exposure Guidelines (OEGs).

6.9. Compliance With Regulatory Statues and Emission Standards

The Holland, Michigan, Parke-Davis facility maintains compliance with the following federal, state, and local regulations. The increase in waste generation and emissions due to Fosphenytoin sodium production will be negligible and will not adversely impact our ability to comply with these rules.

Federal: Resource Conservation & Recovery Act (RCRA)
Emergency Planning & Community Right To Know Act (EPCRA)
Hazardous Materials Transportation Act (HMTA)
Superfund Amendments & Reauthorization Act (SARA)
Clean Air Act Amendments (CAAA)
Clean Water Act (CWA)

State: MI PA 64 - Hazardous Waste Management Act
MI PA 641 - Solid Waste Act
MI PA 245 - Clean Water Act
MI PA 348 - Clean Air Act
MI PA 368 - Medical Waste Act
MI PA 136 - Liquid Industrial Waste Act

Local: Holland Charter Township Ordinance 106
- Wastewater Discharge Regulations
- These rules cover the discharge of sanitary sewage from the Holland plant.

The Rochester facility has maintained substantial compliance with all of the above regulations, and production of Fosphenytoin Injection will not adversely affect current compliance status. In addition, the Rochester facility has also maintained substantial compliance with the following state and local regulations:

State: MI PA 307 - Environmental Response Act
MI PA 478 - Leaking Underground Storage Tank Act

Local: City of Detroit Industrial Wastewater Discharge Ordinance

Discharges to the sanitary sewer system are expected from mixing tank rinse water, disposal of cleaning solutions, and discarding of excess buffer solutions. The quantities and components reaching the waste water treatment plant are not expected to exceed effluent quality limits as set by the City of Rochester. All buffer solutions will be neutralized prior to discharge, and only hot deionized/distilled water is used as a cleaning agent. The City of Rochester regulates industrial discharges and requires that industry monitor their effluent at least twice per year to demonstrate compliance. The Rochester facility has maintained compliance with this ordinance.

The Rochester waste water treatment plant has a maximum capacity of 2.5 million gallons per day and is a B-rated plant utilizing an activated sludge process. The Rochester plant offers primary and secondary treatment, and disinfects by chlorination followed by dechlorination prior to discharge into the Clinton River. After June 1, 1994, the City of Rochester will be sending its sanitary and industrial discharges to the City of Detroit's waste water treatment plant. The Detroit plant has a maximum capacity of 1.2 billion gallons per day and is currently receiving 800 million gallons per day. The Detroit waste water treatment plant utilizes an activated sludge process and offers primary and secondary treatment, and chlorination for disinfection prior to discharge into the Detroit River.

Finished product waste is expected to be generated. Crushed glass will be sent to an approved Class II landfill. The MDNR Solid Waste Division administers landfill compliance. Finished product liquids are separated from crushed glass and are drummed and stored on-site pending transport to a licensed hazardous waste incinerator. The waste finished product is regulated by MI PA 64 and also administered by the MDNR—Solid Waste Division as hazardous liquid waste. Parke-Davis Sterile Products has been issued EPA Generator ID MID 005380126 as a generator of hazardous wastes.

Applicable exposure and emission limits for the Rochester facility are shown in the Table below.

6.10. Maximum Expected Emitted Concentration

Calculation of a maximum EEC is based on release of the Drug Substance uniformly within the US using the equation presented by the Pharmaceutical Manufacturers Association in their guidance document for preparation of environmental assessments and an estimated fifth-year production of _____ pounds of Fosphenytoin sodium.

ppm (in US environment) = lbs/year x (8.9×10^{-9})
derived from ppm = (A)(B)(C)(D)(E)(F)
where:

A = pounds produced divided by 1 year (fifth-year production estimate).
B = 1 year by 365 divided days (length of year).
C = 1 day-person divided by 150 gallons (average daily water use per person in US).
D = 1 divided by 246,000,000 persons (population of US).
E = 1 gallon divided by 8.34 pounds (weight of a gallon of water).
F = 1,000,000 (conversion to parts per million).

The maximum expected emitted concentration in the US is calculated to be:

ppm (in US environment) =
ppb (in US environment) =
ppt (in US environment) =

Estimated environmental concentrations and exposures as a result of drug product use.

Calculations were performed in order to estimate the worst-case concentration of Fosphenytoin that could possibly be present in the United States. The estimate assumes that all Fosphenytoin Injection produced for sale in the US (based on fifth-year postapproval production estimates, _____ lbs) will be administered to patients and disposed of directly into sewage systems. This calculation overestimates the environmental concentration of Fosphenytoin sodium in at least 2 ways: (1) It assumes that all the Fosphenytoin produced will be sold and used by patients, and that none will be left unsold, unused by patients, or will expire or be returned for disposal outside sewage treatment systems, and (2) It assumes that all of the Fosphenytoin sodium Injection administered to patients will be excreted into sewage treatment systems. Patient metabolism will obviously reduce the quantity of Fosphenytoin sodium reaching the environment, as will discharge into private septic systems. Nonetheless, 46 parts per trillion is calculated to be the "maximum" expected environmental concentration in the US following the estimate presented above.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Fosphenytoin sodium is a prodrug which is readily converted quantitatively to phenytoin (dilantin) by patients. Based on a review article on the metabolism of

phenytoin (Appendix 8), it is expected that Fosphenytoin sodium to be largely metabolized to hydroxylated phenytoin. The major metabolite, 5-(4-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) excreted in urine, accounted for 67% to 88% of administered dose. The other urinary metabolite is dihydrodiol phenytoin which only accounted for about 7% to 11% of the dose. Less than 5% of the dose is expected to be excreted in urine as unchanged phenytoin. Accordingly, data were developed on Fosphenytoin, phenytoin and p-hydroxyphenytoin (HPPH).

7.1. Hydrolysis of Fosphenytoin Sodium

Hydrolytic stability: Hydrolysis of Fosphenytoin disodium had been studied at various pHs and buffer concentrations by V. J. Stella (Appendix 9). The rate constant is contained in the table below:

Effect of Buffer Concentration on the Rate of Hydrolysis of Fosphenytoin Sodium at Various pH Values[a]

Buffer	Buffer Conc, M	Apparent First-Order Rate Constant (κ), x $10^4 h^{-1}$	κ_{obs} at Zero Buffer Conc, x $10^4 h^{-1}$
Acetate			
pH 3.9	0.025	50.1	
	0.05	50.7	
	0.1	52.1	44.4
Phosphate			
pH 6.5	0.02	13.4	
	0.03	15.2	
	0.04	18.3	8.3
pH 7.4	0.01-0.04	2.9[b]	2.9
pH 8.1	0.02-0.04	1.1[b]	1.1

[a] μ = 0.5, 70°C.
[b] No buffer catalysis

Studies of the hydrolysis of phenytoin was described in the Analytical Profiles of Drug Substances Volume 13, Page 429 (Appendix 10). After refluxing phenytoin in 2.5 N HCL for 7 hours, essentially complete recovery of starting material was obtained. Phenytoin heated 24 hours at 170°C to 18°C in 20% NaOH(5 N) gave 82% yield of diphenylglycine. Stability study of phenytoin injection had shown the

presence of dihenylhydantoic acid as a decomposition product along with diphenylglycine.

7.2. Dissociation Constants

The ionization constant (pKa) for Fosphenytoin sodium, phenytoin and p-hydroxyphenytoin is listed below:

Compound	pKa
Fosphenytoin sodium	6.2 ± 0.017 (n = 3)
Phenytoin[a]	8.31, 8.33
HPPH	8.22

[a] Reported in Analytical Profile of Drug Substances Vol 13, P 426 (1984) (Appendix 10).

The study report is provided as Appendix 11.

Physico-Chemical Data Summary Table

Fosphenytoin sodium

Molecular Formula and Weight: $C_{16}H_{15}N_2O_6P$, 362.28 g/mole, free acid
$C_{16}H_{13}N_2O_6PNa_2$, 406.24 g/mole, sodium salt

Phenytoin

Molecular Formula and Weight: $C_{15}H_{12}N_2O_2$, 252.27 g/mole, free acid
$C_{15}H_{11}N_2O_2Na$, 274.25 g/mole, sodium salt

Hydroxyphenytoin (HPPH)

Molecular Formula and Weight: $C_{15}H_{12}N_2O_3$, 268.27 g/mole

7.3. Solubility

Solutions of Fosphenytoin sodium were mixed on a rotary wheel for 1 hour at 24 rpm. Samples were filtered and quantified by HPLC yielding the following results.

Buffer System	pH	Solubility (mg/mL)	Final pH
0.25 M $NaC_2H_3O_2$	4.0	78.5	4.37
	5.0	140.2	6.39
0.05 M Na_2HPO_4	6.0	148.7	7.04
	7.0	134.5	7.60
	8.0	137.2	8.50
0.05 M $Na_2B_4O_7$	9.0	141.3	9.35
	10.0	121.7	10.28

The complete test report including the HPLC procedure, study site, and temperature is provided in Appendix 12.

The water solubility of phenytoin has been published in Analytical Profiles of Drug Substances, edited by Klaus Flory, Volume 13, Page 417 (1984). Information presented below for phenytoin was taken from this reference (Appendix 10). Information regarding buffer composition and final pH were not available, however, the relatively low solubilities observed suggest that the final pH values were similar to the pH of the buffers.

pH	Solubility (mg/mL)
1.6	0.02
4.4	0.02
5.0	0.01
5.9	0.02
6.9	0.02
8.0	0.01
9.0	0.10
10.0	0.96
11.0	9.6
12.0	96

Solubility: Solutions of Hydroxyphenytoin were mixed on a rotary wheel for 1 hour at 24 rpm. Samples were filtered and quantified by HPLC yielding the following results.

The complete test report including HPLC method, study site, and temperature is provided in Appendix 11.

Buffer System	pH	Solubility (mg/mL)
0.05 M NaH_2FO_4	4.0	0.013
	5.0	0.014
	6.0	0.014
0.05 M Na_2HPO_4	7.0	0.014
	7.5	0.016
	8.0	0.022
0.05 M $Na_2B_4O_7$	9.0	0.104
	10.0	1.19

7.4. Partition Coefficient

Fosphenytoin sodium, phenytoin and hydroxyphenytoin were equilibrated with equal volumes of octanol and aqueous buffer. An internal standard, acetophenone, was added to each container and mixed on a rotary wheel for 30 minutes at 24 rpm. Each phase was analyzed by HPLC with the following results.

Buffer System	$\log(K_{ow})$ Fosphenytoin	$\log(K_{ow})$ Phenytoin	$\log(K_{ow})$ Hydroxyphenytoin
0.05 M Phosphate, pH 4.0	-1.10	2.48	1.96
0.05 M Phosphate, pH 7.4	-2.03	2.40	1.91
0.05 M Borate, pH 9.1	-3.06	1.34	0.82

The complete test reports are provided as Appendices 11 and 12.

7.5. Vapor Pressure

The vapor pressures of Fosphenytoin sodium, phenytoin, and hydroxyphenytoin were determined following the procedures in FDA Environmental Assessment Technical Assistance Handbook Section 3.07. The gas saturation method was used for each compound, and for each compound the vapor pressure was determined to be less than 1.3×10^{-5} Pa (1.0×10^{-7} torr). The complete final report on the vapor pressure of Fosphenytoin, Study Number 10320-0993-6129-740, Report Number 94-6-5318 is attached as Appendix 13. The complete final report on the vapor pressure of phenytoin, Study Number 10320-0394-6140-740, Report Number 94-6-5308 is attached as Appendix 14. The complete final report on the vapor pressure of hydroxyphenytoin, Study Number 10320-0394-6144-740, Report Number 94-6-5307 is attached as Appendix 15.

7.6. Sorption/Desorption

The propensity for human drug substances to be transported from disposal sites is determined by factors contributing to their distribution, mobility, and persistence in the environment. Partitioning between solid and aqueous phases influences mobility by controlling sorption and leaching rates. A measure of a compound's tendency to sorb and desorb readily can predict the ultimate disposition of residues as either bound to soil/sludge, or as freely soluble material.

Fosphenytoin sodium, phenytoin, and hydroxyphenytoin were studied to determine their sorption and desorption properties following the FDA Environmental Assessment Technical Assistance Handbook Section 3.08. Three soil types were used with both reagent water to mimic "soft" water, and 0.01 M $CaCl_2$ to approximate "hard" water.

For Fosphenytoin sodium, at a solution to soil ratio of 5:1, results showed that the mean percent sorbed for all 3 soil types ranged from 19.0% to 42.4% in $CaCl_2$ and from 8.68% to 29.9% in reagent water. When desorption was tested, none of the sorbed Fosphenytoin sodium could be removed from reagent water or $CaCl_2$. This indicated that Fosphenytoin sodium was strongly bound to the 3 types of soils tested, but the low desorption was probably due to rapid degradation occurring in the samples. Since radiolabeled Fosphenytoin sodium was not available for this study,

water and soil concentrations were determined by using HPLC with UV detection. The preliminary screening portion of the study demonstrated that minor differences in sorption occurred between reagent water and $CaCl_2$ solution for all 3 soil types. Results of the preliminary study are summarized below.

	K_d		K_{oc}	
Soil Type	$CaCl_2$	Water	$CaCl_2$	Water
Washington	6.29	9.60	972	1480
Kansas	149	42.8	1010	2910
Wisconsin	46.9	23.5	1450	727

Washington soil: 46% sand, 47% silt, 7% clay, 1.1% organic matter, pH 7.8, cation exchange capacity 23.6 meq/100 g.

Kansas soil: 10% sand, 47% silt, 43% clay, 2.5% organic matter, pH 5.5, cation exchange capacity 34.4 meq/100 g.

Wisconsin soil: 48% sand, 37% silt, 15% clay, 5.5% organic matter, pH 7.1, cation exchange capacity 17.2 meq/100 g.

Consistent with the FDA Handbook, advanced isotherm testing was conducted with all 3 soils in both water types, since binding at a 5:1 ratio would have demonstrated greater than 25% sorption. Due to the relatively high sorption observed in the screening phase, solution to soil ratios of 50:1 and 100:1 were used in the advanced isotherm test (50:1 for Washington, 100:1 for Kansas and Wisconsin). Results of the definitive test conducted at concentrations ranging from 50.7 to 3.02 mg/L are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	11.8	1820	1.25	0.997
Kansas	43.2	2940	1.59	0.976
Wisconsin	6.10	183	0.953	0.801

Results of the definitive test conducted at concentrations ranging from 49.4 to 3.80 mg/L in 0.01 M $CaCl_2$ are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	23.1	3,570	1.85	0.866
Kansas	315	21,400	1.99	0.995
Wisconsin	51.2	1,580	71.75	0.941

The complete final report on the sorption/desorption of Fosphenytoin sodium, Study Number 10320-0993-6128-710, Report Number 94-6-5352 is attached as Appendix 16.

For phenytoin, the same testing was performed using soils from the same lots. At a solution to soil ratio of 5:1, results showed that the mean percent sorbed for all 3 soil types ranged from 10.1% to 43.0% in $CaCl_2$ and from 2.04% to 45.0% in reagent water. When desorption was tested, 51.6 to 87.4% and 63.4 to 100% of the sorbed phenytoin could be removed from reagent water and $CaCl_2$, respectively. This indicated that phenytoin was only slightly bound to the 3 types of soils tested. The preliminary screening portion of the study demonstrated that no significant difference in sorption occurred between reagent water and $CaCl_2$ solution for all 3 soil types. Results of the preliminary study are summarized below.

	K_d		K_{oc}	
Soil Type	$CaCl_2$	Water	$CaCl_2$	Water
Washington	0.604	0.303	93.3	46.8
Kansas	1.16	1.01	78.5	68.8
Wisconsin	3.61	3.41	112	105

Consistent with the FDA Handbook, advanced isotherm testing was only conducted with the Wisconsin soil in $CaCl_2$ since desorption was greater than 75% for the other

2 soils. Results of the definitive test conducted at concentrations ranging from 10 to 0.6 mg/L are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	NA	NA	NA	NA
Wisconsin	3.46	107	1.06	0.996

The complete final report on the sorption/desorption of phenytoin sodium, Study Number 10320-0394-6141-710, Report Number 94-6-5314 is attached as Appendix 17.

For hydroxyphenytoin, the same testing was performed using the soil from the same lots. At a solution to soil ratio of 5:1, results showed that the mean percent sorbed for all 3 soil types ranged from 13.7% to 53.3% in $CaCl_2$ and from 3.54 to 43.8% in reagent water. When desorption was tested, 45.8% to 61.2% and 30.5% to 100% of the sorbed hydroxyphenytoin could be removed from reagent water and $CaCl_2$, respectively. This indicated that hydroxyphenytoin was only slightly bound to the 3 types of soils tested. The preliminary screening portion of the study demonstrated that no significant difference in sorption occurred between reagent water and $CaCl_2$ solution for all 3 soil types. Results of the preliminary study are summarized below.

	K_d		K_{oc}	
Soil Type	$CaCl_2$	Water	$CaCl_2$	Water
Washington	0.851	0.487	131	75.3
Kansas	1.92	2.09	130	142
Wisconsin	4.81	3.55	149	110

Consistent with the FDA Handbook, advanced isotherm testing was only conducted with the Kansas and Wisconsin soils in $CaCl_2$ since desorption was greater than 75%

for the other soil. Results of the definitive test conducted at concentrations ranging from 1.2 to 0.08 mg/L are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	1.85	124	1.20	0.993
Wisconsin	3.33	103	1.19	0.998

The complete final report on the sorption/desorption of hydroxyphenytoin, Study Number 10320-0394-6145-710, Report Number 94-5-5286 is attached as Appendix 18.

7.7. Photolysis

Fosphenytoin sodium was studied to determine its potential for photolysis following the FDA Environmental Assessment Technical Assistance Handbook Section 3.10. Photolysis as a pathway for degradation can be important from an environmental perspective since most pharmaceuticals will enter the environment in a dissolved form, whether from discharge from the site of production or from patient use. Photolysis occurs when a dissolved compound absorbs light and degrades through energy transfer.

Photolysis was investigated at 3 pHs, 5.0, 7.0, and 9.0 for a 30-day period. Results demonstrated that Fosphenytoin sodium is relatively resistant to photolysis. The half-lives were determined to be 112 days at pH 5, 193 days at pH 7, and 86 days at pH 9. Correlation coefficients ranged from 0.586 to 0.654 and are consistent with half lives 3 to 6 times longer than the experimental period. These data indicate, that photolysis in aqueous solution is not a primary removal mechanism for Fosphenytoin sodium in the environment.

The complete final report on the photodegradation of Fosphenytoin sodium, Study Number 10320-0394-6138-720, Report Number 94-6-5328 is attached as Appendix 19.

7.8. Biodegradation in Water

Biodegradation is a process by which organic chemicals may be significantly reduced in their structural complexity in the environment through biological means. Knowledge of the potential for biodegradation of a chemical is often critical in the assessment of environmental exposure and impact of the chemical. The objective of the study was to determine the potential for biodegradation of Fosphenytoin sodium under standard laboratory conditions. The biodegradation studies were conducted according to modified methods and procedures based in part on the information published in the FDA Technical Assistance Handbook, Section 3.11.

Aerobic biodegradation studies in water were performed with Fosphenytoin sodium, [^{14}C]phenytoin and [^{14}C]hydroxyphenytoin. Test flasks were incubated at 22°C in the dark to minimize the potential for photolysis, and inoculated with a bacterial population obtained from a publicly owned sewage treatment plant. The study design was a batch activated sludge simulation in which activated sludge was removed from a local waste water treatment works and used in a concentration similar to that found in most treatment plants, 3,000 mg solids per liter of solution. (The study design recommended in the handbook is based on a solids concentrations several orders of magnitude lower). The studies were conducted in triplicate with glucose as a positive reference control, and negative blank controls. The quantity of carbon dioxide ($^{14}CO_2$) released as a result of microbial degradation in the sludge/water was measured. HPLC measurements were performed periodically to determine whether partial degradation of Fosphenytoin sodium, had occurred.

From the Fosphenytoin sodium flasks, the cumulative CO_2 collected over 28 days was negligible relative to the dose initially applied. Volatile organic products also were not detected from these flasks. From the glucose flasks, greater than 60% of the dosed radioactivity was collected as CO_2. While these results showed no evidence for the complete biodegradation of Fosphenytoin sodium to carbon dioxide, analysis of the test solutions containing Fosphenytoin sodium were performed using HPLC

throughout the study. Results of these analyses indicated complete biotransformation to phenytoin occurred in the first day.

The complete final report on the aerobic aquatic biodegradation of Fosphenytoin sodium, Study Number 10320-1093-6136-731, Report Number 94-6-5349 is attached as Appendix 20.

From the [^{14}C]phenytoin flasks, the cumulative $^{14}CO_2$ collected over 42 days was negligible relative to the dose initially applied. ^{14}C-volatile organic products also were not detected from these flasks. From the ^{14}C-glucose flasks, greater than 60% of the dosed radioactivity was collected as $^{14}CO_2$. Analysis of the test solutions containing [^{14}C]phenytoin were performed using HPLC-RAM throughout the study and indicated that no chemical conversion occurred during the study.

The complete final report on the aerobic aquatic biodegradation of phenytoin, Study Number 10320-0394-6142-731, Report Number 94-6-5337 is attached as Appendix 21.

From the [^{14}C]hydroxyphenytoin flasks, the cumulative $^{14}CO_2$ collected over 42 days was approximately 10% of the dose initially applied. ^{14}C-Volatile organic products were not detected from these flasks. From the ^{14}C-glucose flasks, greater than 60% of the dosed radioactivity was collected as $^{14}CO_2$. These results demonstrated conclusively that the complete biodegradation of [^{14}C]hydroxyphenytoin to carbon dioxide can occur using organisms commonly found in publicly owned treatment plants. However, this biodegradation is not rapid. Analysis of the test solutions containing [^{14}C]hydroxyphenytoin were performed using HPLC-RAM throughout the study and indicated that approximately 30% of the applied test substance had degraded to more polar products. This characterization of polarity was made by comparison of HPLC retention times.

The complete final report on the aerobic aquatic biodegradation of hydroxyphenytoin, Study Number 10320-0394-6146-731, Report Number 94-6-5323 is attached as Appendix 22.

The environmental distribution of Fosphenytoin sodium should place in the aquatic phase. The low vapor pressure demonstrates that the atmospheric compartment will not be significantly affected by release of Fosphenytoin. With the extremely low solids level of sewage treatment plants, Fosphenytoin and its degradation products will be present primarily in the hydraulic phase. The ultimate fate of Fosphenytoin is determined in part by the metabolism in patients and the biodegradation in water. Metabolism data indicates that Fosphenytoin is completely modified by patients to the hydroxy derivative, hydroxyphenytoin. Biodegradation data shows that hydroxyphenytoin will easily degrade when exposed to common bacteria indigenous to sewage treatment plants. Therefore, fosphenytoin and its degradation products will not persist in the environment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Production, use and discharge of Fosphenytoin sodium into the environment will pose no adverse effect on humans, animals, plants or environmentally significant organisms. All organisms tested indicated that no threat to any of them are possible at concentrations at or near those calculated to occur upon approval of this NDA.

As a measure of the toxicity of any chemical, the determination of the lowest concentration that inhibits microbial growth is important because of possible ramifications if that concentration is exceeded in the environment. Three microbial growth inhibition studies were conducted according to the methods and procedures published in the FDA Technical Assistance Handbook, Section 4.02. The microbial inhibitory concentrations (MICs) of Fosphenytoin sodium, phenytoin and hydroxyphenytoin were determined for each of 5 species. For all 3 compounds, preliminary tests using concentrations of 0.1 to 1000 ppm (0.1 mg/L to 1000 mg/L) showed no effects to all 5 species investigated at all concentrations tested including 1000 mg/L. Based on the results of the preliminary exposure, definitive tests were not conducted. The MICs reported were defined as the lowest concentrations of these materials that completely inhibited the growth of the test organism.

Species	Fosphenytoin MC (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	> 1000
Nostoc	> 1000

The complete final report on the microbial growth inhibition of Fosphenytoin sodium, Study Number 10320-0594-6155-770, Report Number 94-6-5293 is attached as Appendix 23.

Species	Phenytoin MC (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	> 1000
Nostoc	> 1000

The complete final report on the microbial growth inhibition of phenytoin, Study Number 10320-0594-6156-770, Report Number 94-6-5294 is attached as Appendix 24.

Species	Hydroxyphenytoin MC (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	> 1000
Nostoc	> 1000

The complete final report on the microbial growth inhibition of hydroxyphenytoin, Study Number 10320-0594-6157-770, Report Number 94-6-5295 is attached as Appendix 25.

The acute toxicities (concentration at which 50% of the organisms are affected or EC_{50}) of Fosphenytoin sodium, phenytoin and hydroxyphenytoin to *Daphnia magna* (a freshwater invertebrate), were investigated. This organism is often tested and considered to be 1 of the most sensitive aquatic species available for standardized aquatic studies. The no observed effect concentration (NOEC) was determined as well as the EC_{50}. The NOEC is defined as the highest concentration at or below which there was no toxicant-related immobilization, or physical or behavioral abnormalities when compared to the control. The study was conducted according to the methods and procedures published in the FDA Technical Assistance Handbook, Section 4.08.

During the *Daphnia magna* acute toxicity study with Fosphenytoin sodium, immobilization or sublethal effects were observed among daphnids exposed to several of the measured concentrations (0% at 23, 48 and 94 mg/L, 10% at 190 mg/L, 75% at 380 mg/L, and 100% at 760 mg/L) following 24-hours of exposure. After 48-hours' exposure, 75% were immobilized at 190 mg/L, 95% at 380 mg/L, and 100% at the highest concentration, 760 mg/L. No immobilization was observed at lower concentrations or in the control solutions (some erratic behavior was noted at 94 mg/L). The outcome of the study was a calculated 48-hour EC_{50} for daphnids exposed to Fosphenytoin of 170 mg/L. The 48-hour NOEC for this study was determined to be 48 mg/L.

The complete final report on the *Daphnia magna* Static Acute Toxicity of Fosphenytoin sodium, Study Number 10320-0594-6154-110, Report Number 94-5-5273 is attached as Appendix 26.

During the *Daphnia magna* acute toxicity study with phenytoin, no immobilization or sublethal effects were observed among daphnids exposed to any of the measured concentrations (39, 23, 14, 8.3, and 4.9 mg/L) following 24-hours of exposure. The functional limit of solubility in the hardened freshwater used for this study was 39 mg/L, determined by stirring a saturated solution of phenytoin for 24 hours. After

48-hours' exposure, 20% were immobilized at the highest concentration, 39 mg/L. No immobilization was observed at lower concentrations or in either the solvent control or the control solutions. The outcome of the study was a calculated 48-hour EC_{50} for daphnids exposed to phenytoin of greater than 39 mg/L. The 48-hour NOEC for phenytoin was determined to be 23 mg/L.

The complete final report on the *Daphnia magna* Static Acute Toxicity of phenytoin, Study Number 10320-0993-6134-110, Report Number 94-6-5321 is attached as Appendix 27.

During the *Daphnia magna* acute toxicity study with hydroxyphenytoin, no immobilization or sublethal effects were observed among daphnids exposed to any of the measured concentration (28, 17, 10, 6.2, and 3.6 mg/L) following 24-hours of exposure. The functional limit of solubility in the hardened freshwater used for this study was 28 mg/L, determined by stirring a saturated solution of hydroxyphenytoin for 24 hours. After 48-hours' exposure, no immobilization was observed at any concentration or in either the solvent control or the control solutions. The outcome of the study was a calculated 48-hour EC_{50} for daphnids exposed to hydroxyphenytoin of greater than 28 mg/L. The 48-hour NOEC for hydroxyphenytoin was determined to be 28 mg/L.

The complete final report on the *Daphnia magna* Static Acute Toxicity of hydroxyphenytoin, Study Number 10320-0494-6153-110, Report Number 94-5-5271 is attached as Appendix 28.

The narrowest margin of safety for Fosphenytoin sodium is based on the NOEC for *Daphnia magna* (the most sensitive species tested) and is calculated by dividing 48 mg/L by [redacted] (the minimum expected concentration based on distribution of all Fosphenytoin over the entire United States). This calculation results in a safety margin of 1,067,000. Similar safety margins for phenytoin and hydroxyphenytoin using the NOECs determined and [redacted]. The safety margin for phenytoin is 500,000 and for hydroxyphenytoin, 609,000.

Based on the documented rapid degradation pathways and the large safety margins (greater than 100,000), Fosphenytoin sodium has been shown to have no effect on the

external aquatic environment. Fosphenytoin sodium was shown to degrade in water with a half life of less than 1 day under microbially populated conditions similar to those seen in wastewater treatment plants. This clearly demonstrates that Fosphenytoin sodium will not persist in the environment. Furthermore, Fosphenytoin sodium was shown to have no effect on a wide variety of microorganisms at concentrations as high as 1000 mg/L. The LC_{50} to Daphnia magna was determined to be 170 mg/L and the no observed effect concentration was calculated to be 48 mg/L. Thir lowest risk concentration is more than 1,000,000 times higher than that which would occur if all the produced Fosphenytoin were used and discharged over the entire United States.

Metabolism data produced by Parke-Davis indicates that the entire quantity of Fosphenytoin sodium taken by patients is excreted as hydroxyphenytoin. Hydroxyphenytoin has been proven to biodegrade to more polar compounds and ultimately to carbon dioxide. Furthermore, no toxicity was observed for hydroxyphenytoin at the limit of solubility. Therefore, degradation pathways were determined for the parent drug substance Fosphenytoin, and the ultimately discharged metabolite, hydroxyphenytoin. The intermediate in degradation, phenytoin, which is formed *in vivo* transiently, was not observed to degrade under the laboratory conditions employed. Nonetheless, no environmental effects were observed at concentrations within 100,000-fold of the predicted environmental concentration.

9. USE OF RESOURCES AND ENERGY

In 1993, the Holland, Michigan manufacturing site used 19,643,113 kilowatts of electricity and 34.62×10^{10} BTU of steam to produce 1,085,153 kg of drug substances. The fifth-year production estimate for Fosphenytoin is pounds (11,253 kg) and represents an increase of 1.04%, on a kg basis.

The production of Fosphenytoin sodium represents less than 1% of the total pharmaceutical production at the Rochester facility. The proposed action will not alter land use since production will take place on premises currently owned by Parke-Davis and utilized for the manufacture of pharmaceutical products. The use of natural resources and energy for the manufacture of Fosphenytoin sodium is 0.1% of

the present total plant usage and can be accommodated by the existing infrastructure. The Rochester facility generates its own electricity via a gas-fired turbine. In 1993, the total natural gas use was 465,098 billion cubic feet and the increase in consumption due specifically to the production of Fosphenytoin Injection is estimated to be less than 1%.

No impact will occur to endangered or threatened species. Since this activity does not involve the alteration, demolition, or construction of building or earth projects, approval will have no impact on property listed in the National Register of Historic Places.

10. MITIGATION MEASURES

The following measures are taken to prevent potential adverse environmental impacts:

- Use of MDNR permitted air purifying equipment to prevent air emissions from exceeding established Federal and State levels;

- Disposal of neutralized buffer solutions and wash/rinse water into the City of Rochester municipal sewer system which is treated by their tertiary wastewater treatment facility;

- Disposal of crushed glass wastes into a MDNR licensed Class II landfill;

- Destruction of all solid waste Fosphenytoin in a licensed hazardous waste incinerator;

- Material Safety Data Sheets for hazardous or potentially hazardous materials are made available to employees of Parke-Davis Company. These documents provide information on potential hazards, personal protective equipment, safe handling practices, and emergency procedures. Additionally, Parke-Davis distributes Safe Handling Guidelines for all new pharmaceuticals which describes the precautions which must be taken when handling these compounds.

Parke-Davis has a comprehensive occupational health and safety program. This includes conducting preplacement physical examinations of employees and periodic health surveillance examinations of all employees in manufacturing areas. Additionally, the company operates a health clinic to address any employee illness and/or injury occurring during the work day. The above procedures will serve to monitor employees for the development of conditions attributable to exposure.

The Rochester facility has an established Emergency Response Plan and Spill Prevention, Control & Countermeasure Plan and has conducted employee training in these procedures to effectively control and respond to releases of hazardous materials. Spill control stations equipped with absorbent materials and personnel protective equipment are located throughout the facility. A facility-wide Waste Management Plan has also been prepared and employees trained on their respective responsibilities. The Waste Management Plan includes procedures for hazardous, nonhazardous, pathological, flammable, and liquid industrial waste handling.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on the data summarized in this environmental assessment, the proposed action will have no impact on the environment. One alternative to the proposed action (drug approval) is no action by FDA. This will deprive humanity of potentially beneficial therapy, and also will have no impact on the environment.

12. LIST OF PREPARERS OF THE ENVIRONMENTAL ASSESSMENT

The following is a list of persons and respective qualifications, that participated in preparation of this Environmental Assessment document. Springborn Laboratories, Inc, was utilized as the consultant in the completion of this document.

M. K. Lemon CHMM Environmental Engineer
BS - Environmental Sciences
Certified Hazardous Materials Manager
Professional Experience - 13 years

A. Sommers	Industrial Hygienist MS - Occupational Health & Safety Professional Experience - 3 years
M. Nickolaus	Senior Associate Scientist - Technical Services BS - Management Professional Experience - 24 years
P. Fackler	Director, Environmental Chemistry PhD - Analytical Chemistry Professional Experience - 16 years
T. Bauer	Environmental Manager, B. S. Chemical Engineering Professional Experience - 15 years

Curricula vitae for these individuals are attached as Appendix 29.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of his knowledge for the preparation of the environmental assessment.

Date: November 29, 1994

Signature: Sean Brennan Sean Brennan

Title: Senior Director, Worldwide Regulatory Affairs

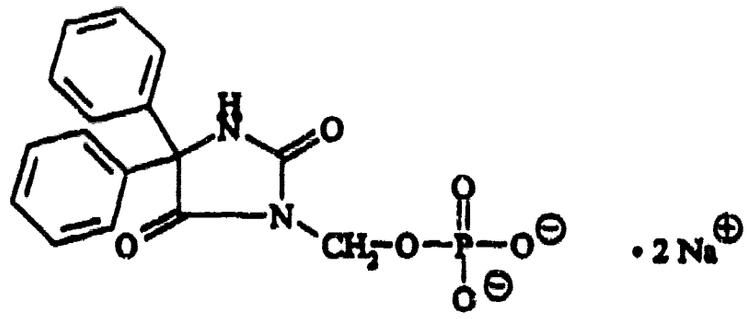
14. REFERENCES

1. Jose Philip, et al. Analytical Profiles of Drug Substances, edited by Klaus Florey, 1984;13:417.

15. APPENDICES

(a) Data Summary Tables

1. Structural Formula:



Chemical Names: 5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

CAS Registry Number 92134-98-0

Synonym Names: Cerebyx®
Fosphenytoin sodium (USAN)

2. Vapor Pressure:

Compound	Vapor Pressure
Fosphenytoin	Less than 1.3×10^{-5} pascal (1.0×10^{-7} torr)
Phenytoin	Less than 1.3×10^{-5} pascal (1.0×10^{-7} torr)
Hydroxyphenytoin	Less than 1.3×10^{-5} pascal (1.0×10^{-7} torr)

3. Ultraviolet Spectra

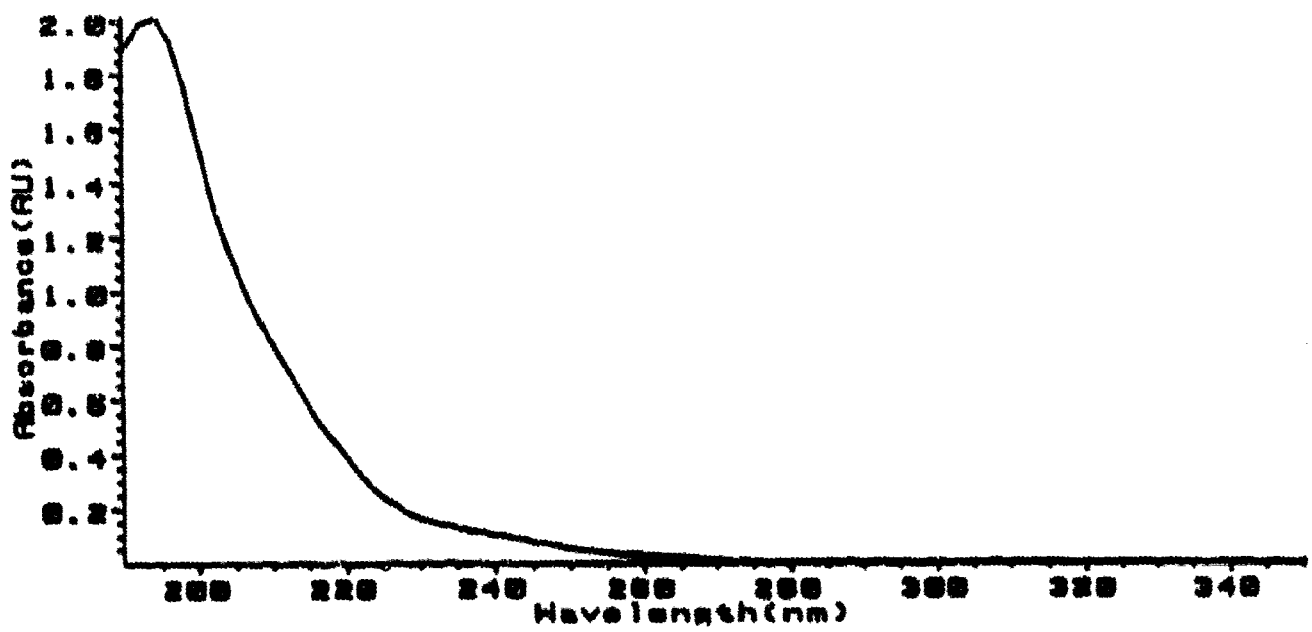


FIGURE 1. Ultraviolet Spectrum of Fosphenytoin Reference Standard II in Water (0.0165 mg/mL)

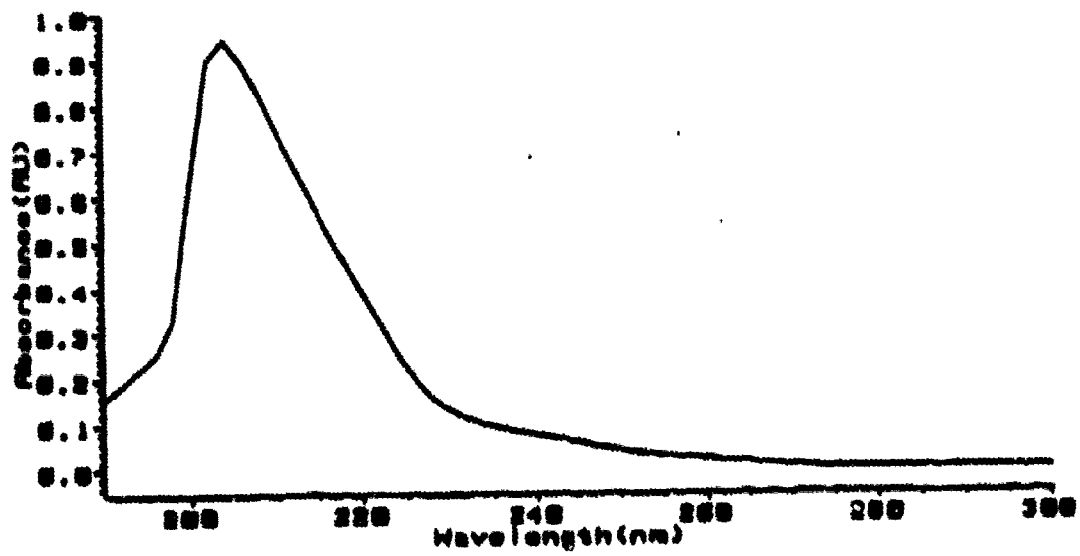


FIGURE 2. Ultraviolet Spectrum of Fosphenytoin Reference Standard II in Methanol, (0.0165 mg/mL)

4. Water Solubility:

Fosphenytoin Sodium

Buffer System	pH	Solubility (mg/mL)	Final pH
0.25 M $NaC_2H_3O_2$	4.0	78.5	4.37
	5.0	140.2	6.39
0.05 M Na_2HPO_4	6.0	148.7	7.04
	7.0	134.5	7.60
	8.0	137.2	8.50
0.05 M $Na_2B_4O_7$	9.0	141.3	9.35
	10.0	121.7	10.28

Phenytoin

pH	Solubility (mg/mL)
1.6	0.02
4.4	0.02
5.0	0.01
5.9	0.02
6.9	0.02
8.0	0.01
9.0	0.10
10.0	0.96
11.0	9.6
12.0	96

Hydroxyphenytoin (HPPH)

Buffer System	pH	Solubility (mg/mL)
0.05 M NaH_2PO_4	4.0	0.013
	5.0	0.014
	6.0	0.014
0.05 M Na_2HPO_4	7.0	0.014
	7.5	0.016
	8.0	0.022
0.05 M $Na_2B_4O_7$	9.0	0.104
	10.0	1.19

5. Partition Coefficient:

Buffer System	log(K_{ow}) Hydroxyphenytoin	log(K_{ow}) Fosphenytoin	log(K_{ow}) Phenytoin
0.05 M Phosphate, pH 4.0	-1.10	2.48	1.96
0.05 M Phosphate, pH 7.4	-2.03	2.40	1.91
0.05 M Borate, pH 9.1	-3.06	1.34	0.82

6. Sorption/Desorption:

For Fosphenytoin sodium at concentrations range from 50.7 to 3.02 mg/L.

Soil Type	K_f	K_{oc}	n	r^2
Washington	11.8	1820	1.25	0.997
Kansas	43.2	2940	1.59	0.976
Wisconsin	6.10	188	0.953	0.861

Results at concentrations ranging from 49.4 to 3.8 mg/L in 0.0/M $CaCl^2$

Soil Type	K_f	K_{oc}	n	r^2
Washington	29.1	3,570	1.85	0.866
Kansas	315	21,400	1.99	0.995
Wisconsin	51.2	1,580	71.75	0.941

For phenytoin, advanced isotherm testing was only conducted at concentrations ranging from 10 to 0.6 mg/L with the Wisconsin soil in $CaCl_2$ since desorption was greater than 75% for the other 2 soils.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	NA	NA	NA	NA
Wisconsin	3.46	107	1.06	0.996

For Hydroxyphenytoin, advanced isotherm testing was conducted with Kansas and Wisconsin soils at concentrations ranging from 1.2 to 0.08 mg/L in $CaCl_2$ since desorption was greater than 75% for the Washington soil.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	1.85	124	1.20	0.993
Wisconsin	3.33	103	1.19	0.998

7. **Photolysis:**

Photolysis for Fosphenytoin Sodium

pH	Half-Lives (Days)
5.0	112
7.0	193
9.0	86

8. Toxicology Studies of Fosphenytoin Sodium

Tabular Summary of Toxicology Studies
(Page 1 of 19)

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	 Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	 NDA Location Volume	 Page
Acute Toxicity Studies								
Mouse (CD-1)	IV Infusion[c]	SAL		Fosphenytoin[a]	ACC	745-01722	1.12	114
5M + 5F, 120	(20 mL/kg)[d]	VC[e]		NOED = 33.3				
6 Weeks	14 Days	33.3	33	MNLD = 63.3				
		63.3	63	MLD = 156				
		120	120	Phenytoin				
		230	233	NOED = ND				
		433	440	MNLD = 63				
				MLD = 192				
Rat (SD)	IV Bolus	SAL		Fosphenytoin[a]	ACC	745-01726	1.12	147
5M + 5F, 120	(10 mL/kg)[f]	VC[g]	VC	NOED = 50				
7 Weeks	14 Days	50	45	MNLD = 153				
		73.3	65	MLD = 213				
		107	95	Phenytoin				
		153	145	NOED = ND				
		233	210	MNLD = 45				
		333	300	MLD = 90.4				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[d] Fosphenytoin dosing solution concentrations ranged from 2.50 to 32.5 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 22.0 mg/mL.

[e] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[f] Fosphenytoin dosing solution concentrations ranged from 7.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 4.50 to 30.0 mg/mL.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	Study Report NDA Location Volume	Study Report NDA Location Page
Acute Toxicity Studies (continued)								
Rat (SD)	IV Infusion[c]	SAL		Fosphenytoin[a]	ACC	745-01727	1.12	180
5M + 5F, 130	(10 mL/kg)[d]	50[e]	45	NOED = ND				
7 Weeks	14 Days	73.3	65	MNLD = 153				
		107	95	MLD = 242				
		153	145	Phenytoin				
		233	210	NOED = ND				
		333	300	MNLD = 210				
				MLD = 275[h]				
Rat (SD)	IV Infusion[c]	SAL		Fosphenytoin[a]	ACC	745-01725	1.12	214
5M + 5F, 120	(10 mL/kg)[f]	VC[g]		NOED = 33.3				
4 Weeks	14 Days	33.3	33	MNLD = 120				
		63.3	63	MLD = 258				
		120	120	Phenytoin				
		230	233	NOED = 33				
		433	440	MNLD = 120				
				MLD = 297				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[d] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[e] Fosphenytoin dosing solution concentrations ranged from 7.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 4.50 to 30.0 mg/mL.

[f] Vehicle = Tris buffer, pH adjusted to 8.8.

[g] Estimate; value could not be calculated using Moving Average Interpolation or Probit Analysis Method.

[h] Fosphenytoin dosing solution concentrations ranged from 5.0 to 65 mg/mL. Phenytoin dosing solution concentrations ranged from 3.3 to 44 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	 Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	 NDA Location Volume	 Page
Acute Toxicity Studies (continued)								
Rat (SD) 5M + 5F, 72 7 Weeks	IM (5 mL/kg)[j,k] 14 Days	SAL 33.3[l] 76.7 167 247[l] 333[l]	 34 169 250 337[l]	Fosphenytoin[a] NOED = 33.3 MNLD = 167 MLD = 278 Phenytoin NOED = 34 MNLD = 337 MLD = >337	ACC	745-01738	1.12	248
Rat (SD) 5M + 5F, 160 6 Weeks	IP (10 mL/kg)[m] 14 Days	SAL VC[c] 33.3 60 100 177 300 500 850	 33 60 102 178 305 500 868	Fosphenytoin[a] NOED = 60 MNLD = 177 MLD = 352 Phenytoin NOED = 60 MNLD = 178 MLD = 339	ACC	745-01723	1.12	328

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[d] Vehicle = Tris buffer, pH adjusted to 8.8.

[j] Dose volume for 337 mg/kg phenytoin group was 6.74 mL/kg.

[k] Fosphenytoin dosing solution concentrations ranged from 10 to 100 mg/mL. Phenytoin dosing solution concentrations ranged from 6.8 to 50 mg/mL.

[l] N = 5 rats/sex.

[m] Fosphenytoin dosing solution concentrations ranged from 5.0 to 75 mg/mL. Phenytoin dosing solution concentrations ranged from 3.3 to 50 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	 Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	 NDA Location Volume	 Page
Acute Toxicity Studies (continued)								
Rat (SD)	IP	SAL		Fosphenytoin[a]	ACC	745-01720	1.12	358
5M + 5F, 140	(20 mL/kg)[c]	VC[c]		NOED = 100				
7 Days	14 Days	33.3	33	MTD = 100				
		60	60	MLD = 181				
		100	102	Phenytoin				
		177	178	NOED = 102				
		300	305	MTD = 102				
		500	509	MLD = 224				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[a] Fosphenytoin dosing solution concentrations ranged from 2.50 to 37.5 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 25.0 mg/mL.

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Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Day	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	NDA Location Volume	NDA Location Page
Escalating-Dose Toxicity Studies									
Rabbit (NZW)	IV Infusion[c]	1	6.7[p]	6.8	Fosphenytoin[q]	ACC	745-01721	1.12	386
6M + 6F, 24	(10 mL/kg)[p]	3	13.3	13.5	NOED = 40				
NA		6	20	20.2	MTD = 40				
		9	26.7	27	No Deaths				
		13	40	40.5	Phenytoin				
		15[p]	53.3	54	NOED = 27				
					MTD = 40.5				
					No Deaths				
Dog (beagle)	IV Bolus	1	6.7[g]	6	Fosphenytoin[q]	ACC	745-01728	1.12	412
2M + 2F, 8	(2 mL/kg)[d]	3	13.3	12	NOED = 13.3				
10 Months		5	26.7	24	MTD = 26.7				
		8[p]	40	36	No Deaths				
					Phenytoin				
					NOED = 6				
					MTD = 24				
					No Deaths				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligrams/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[d] Vehicle = l-arginine HCl, pH adjusted to 8.8.

[e] Vehicle = Tris buffer, pH adjusted to 8.8.

[g] Fosphenytoin dosing solution concentrations ranged from 1.0 to 8.0 mg/mL. Phenytoin dosing solution concentrations ranged from 0.68 to 5.40 mg/mL.

[p] Animals observed for 14 days after last dose.

[q] Fosphenytoin dosing solution concentrations ranged from 5.0 to 30 mg/mL. Phenytoin dosing solution concentrations ranged from 3.0 to 18 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Day	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	NDA Location Volume	NDA Location Page
Escalating-Dose Toxicity Studies (continued)									
Dog (beagle)	IV infusion[c]	1	6.7[g]	6	Fosphenytoin[a]	ACC	745-01725	1.12	471
2M + 2F, 8	(2 mL/kg)[d]	3	13.3	12	NOED = 13.3				
10 Months		5	26.7	24	MTD = 26.7				
		9[e]	40	36	No Deaths				
					Phenytoin				
					NOED = 12				
					MTD = 24				
					No Deaths				
Dog (beagle)	IM	1	6.7[g]	6.7	Fosphenytoin[a]	ACC	745-01742	1.12	527
3M + 3F, 12	(0.13-1.00 mL/kg)[f]	3	16.7	16.9	NOED = 33.3				
10 Months		7	33.3	33.7	MTD = 33.3				
		9[e]	50	50	No Deaths				
					Phenytoin				
					NOED = 6.7				
					MTD = >50				
					No Deaths				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[d] Vehicle = Tris buffer, pH adjusted to 8.8.

[e] Animals observed for 14 days after last dose.

[f] Fosphenytoin dosing solution concentrations ranged from 5.0 to 30 mg/mL. Phenytoin dosing solution concentrations ranged from 3.0 to 18 mg/mL.

[g] Fosphenytoin dosing solution concentration = 75 mg/mL. Phenytoin dosing concentration = 50 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Multidose Toxicity Studies						
Rat (SD) 5M + 5F, 60 6-7 Weeks	IV Bolus (10 mL/kg)[b] 7 Days	VC[c] 20 40 66.7 107 160	Deaths at 107 and 160 mg/kg. Dose-related lethargy, ataxia, and head tremors at ≥66.7 mg/kg. Decreased body weight gain and food consumption, glucosuria, and increased ALT, ALP, and BUN at 107 and 160 mg/kg. No pathologic findings. (ACC)	745-01730	1.13	001
Rat (SD) 10M + 10F, 100 8 Weeks	IV Bolus (10 mL/kg)[d] 2 Weeks	SAL VC[e] 13.3 33.3 100	Death, hypoactivity, dyspnea, dilated pupils, prostration, ataxia, hypothermia, decreased body weight gain in males, transient decreases in food consumption, increased urine volumes, and glucosuria in both sexes at 100 mg/kg. No pathologic findings. (IRDC)	745-01732	1.13	106
Rat (Wistar) 15M + 15F, 144[f] 6-7 Weeks	IV Bolus (2 mL/kg)[g] 4 Weeks[w]	VC[e] 20 40 100	No deaths. Ataxia, hypoactivity, and salivation at 40 and 100 mg/kg. Decreased body weight gain in males at 100 mg/kg. Reversible increases in ALT and ALP at 100 mg/kg. Increased liver:body weight in males at 100 mg/kg and females at all doses; reversible at 20 and 40 mg/kg. Reversible dose-related injection site irritation at ≥20 mg/kg and vacuolation of hepatocytes at 100 mg/kg. (BP)	250-01648	1.14	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Vehicle = Tris buffer, pH adjusted to 8.8.

[c] Fosphenytoin dosing solution concentrations ranged from 3.0 to 24 mg/mL.

[d] Fosphenytoin dosing solution concentrations ranged from 2.0 to 15 mg/mL.

[e] Three additional animals per sex included in control and/or drug-treated groups and utilized only for determination of drug concentrations.

[f] Fosphenytoin dosing solution concentrations ranged from 15 to 75 mg/mL.

[w] Five animals per sex per group were euthanized after a 4-week withdrawal period (Week 8).

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Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Multidose Toxicity Studies (continued)						
Rat (SD) 5M + 5F, 90[w] 7-9 Weeks	IM (0.7-3.3 mL/kg)[x] 2 Weeks	SAL 33.3 66.7 100 133 167	Deaths at 133 and 167 mg/kg. Dose-related lethargy, prostration, ataxia, and/or tremors at ≥66.7 mg/kg. Decreased body weight gain, transient decreases in food consumption, and increased urine volumes in males at ≥100 mg/kg. Injection-related gross pathologic changes in muscle in 1 animal each at 100 and 167 mg/kg. (DCC)	745-01745	1.14	338
Rat (SD) 10M + 10F, 150[y] 7 Weeks	IM (0.4-2.0 mL/kg)[x] 13 Weeks	SAL PHT[z] 20 40 100	Increased liver weights in females at all doses. Deaths, dilated pupils, hypoactivity, excessive salivation, decreased body weight, increased AST, ALT, and ALP, hyperglycemia, glucosuria, and intracytoplasmic hepatocellular vacuolation with fosphenytoin at 100 mg/kg. Similar findings were noted with phenytoin. Local irritation with both compounds. (SDC)	745-01744	1.15-16	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligrams/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[w] Three additional animals per sex included in control and/or drug-treated groups and utilized only for determination of drug concentrations.

[x] Fosphenytoin dosing solution concentration = 75 mg/mL.

[y] Five additional animals per sex per group utilized only for determination of drug concentrations.

[z] Phenytoin Sodium Injection, USP, administered at 100 mg/kg, dosing solution concentration = 50 mg/mL; group terminated at Week 9.

Tabular Summary of Toxicology Studies
(Page 9 of 19)

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Multidose Toxicity Studies (continued)						
Dog (beagle) 2M + 2F, 24 11-12 Months	IV Bolus (2.8 mL/kg)[m] 7 Days	VC[c] 6.7 13.3 20 26.7 33.3	No deaths. Dose-related diarrhea, salivation, and emesis at ≥13.3 mg/kg. In addition, ataxia at 26.7 and 33.3 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings. (ACC)	745-01731	1.16	292
Dog (beagle) 4M + 4F, 40 7-8 Months	IV Bolus (2.8 mL/kg)[nb] 2 Weeks	SAL VC[c] 10 20 33.3	No deaths. Hypoactivity, emesis, excessive salivation, and ataxia at 20 and 33.3 mg/kg. In addition, tremors at 33.3 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings. (IRDC)	745-01733	1.17	001
Dog (beagle) 4M + 4 F, 24 10-12 Months	IV Bolus (0.67 mL/kg)[oo] 4 Weeks[dd]	VC[c] 10 20 33.3	No deaths. Dose-related incidence of emesis at ≥10 mg/kg and transient salivation, ataxia, and erythema of gums at ≥20 mg/kg. Tremors and hypoactivity at 33.3 mg/kg. Increased ALP at 33.3 mg/kg at Weeks 4 and 8. Increased salivary gland weights in both sexes at 33.3 mg/kg and females at 20 mg/kg at Week 4. Increased liver:body weight in males at 20 and 33.3 mg/kg; reversible at 20 mg/kg. Hypertrophy of salivary glands in males at 33.3 mg/kg at Weeks 4 and 8. (AA)	745-01970	1.18	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[c] Vehicle = Tris buffer, pH adjusted to 8.8.

[m] Fosphenytoin dosing solution concentrations ranged from 5.0 to 25 mg/mL.

[nb] Fosphenytoin dosing solution concentrations ranged from 7.5 to 25 mg/mL.

[oo] Fosphenytoin dosing solution concentrations ranged from 22.4 to 75.0 mg/mL.

[dd] One animal per sex per group was euthanized after a 4-week withdrawal period (Week 8).

Tabular Summary of Toxicology Studies
(Page 10 of 19)

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Multidose Toxicity Studies (continued)						
Dog (beagle) 2M + 2F, 24 9-10 Months	IM (0.2-1.0 mL/kg)[x] 2 Weeks	SAL 10 20 33.3 40 50	No deaths. Dose-related incidence of emesis and ataxia at ≥33.3 mg/kg. Sporadic convulsions, diarrhea, and/or tonic stance at 40 and 50 mg/kg. In addition, prostration and excessive salivation at 50 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings. (DCC)	745-01739	1.18	311
Dog (beagle) 4M + 4F, 40 7-9 Months	IM (0.2-0.8 mL/kg)[x] 13 Weeks	SAL PHT[xx] 10 20 40	No deaths. Emesis and excessive salivation at all doses. In addition, ataxia, hyperactivity, diarrhea, increased ALP, increased liver weights, and intracytoplasmic hepatocellular vacuolation with fosphenytoin at 40 mg/kg. Similar findings were noted with phenytoin. Local irritation with fosphenytoin at 20 and 40 mg/kg and with phenytoin. (HDC)	745-01740	1.19	001

Abbreviations are defined on Page 19 of the Tabular Summary

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[x] Fosphenytoin dosing solution concentration = 75 mg/mL.

[xx] Phenytoin Sodium Injection, USP, administered at 40 mg/kg, dosing solution concentration = 50 mg/mL.

Tabular Summary of Toxicology Studies
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Test Species (Strain) Sex/Group, Total	Study Design[ff]	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Special Toxicity Studies					
Venous and Peri-vascular Irritation[ss] Rabbits (NZW) 6 M, 6[6]	Dosing: Single 30-minute IV infusion or SC injection FOS(mg/mL):VC[a], 10, 25, 50, 75 PHT[b](mg/mL):VC, 6.7, 16.9, 33.7, 50 Observation: 24 hours Parameters: Gross and microscopic examinations	No significant differences in perivascular or venous irritation between fosphenytoin and saline controls. Significant venous and perivascular irritation and high incidence of thrombus formation with phenytoin. (ACC)	745-01724	1.20	001
Intramuscular Irritation[ss] Rabbits (NZW) 12 M, 12	Dosing: Single IM injection FOS(mg/mL):VC[a], 25, 50, 75, 100 PHT[b](mg/mL):VC, 50 Observation: 24 hours Parameters: Gross and microscopic examinations	Fosphenytoin less irritating than saline or phenytoin. Trace to mild hemorrhage, acute inflammation and necrosis with saline, phenytoin vehicle, and phenytoin. (ACC)	745-01737	1.20	055
Rabbits (NZW) 4 M, 28	Dosing: 5 daily IM injections FOS(mg/mL):VC[a], 50, 75, 100 PHT[b](mg/mL):VC, 50 Observation: 5 days Parameters: Serum CPK, gross and microscopic examinations	Hemorrhage in all control and treatment groups. Necrosis with phenytoin; less severe with fosphenytoin at 75 and 100 mg/mL. Increased CPK with phenytoin vehicle, phenytoin, and fosphenytoin. (ACC)	745-01741	1.20	094

Abbreviations are defined on Page 19 of the Tabular Summary.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Vehicle = l-arginine HCl, pH adjusted to 8.8.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[ff] All in vivo studies included saline (0.9% NaCl) control group.

[ss] Concentrations based on the weight of the sodium salt of fosphenytoin or phenytoin.

Tabular Summary of Toxicology Studies
(Page 12 of 19)

Test Species (Strain) Sex/Group, Total	Study Design[ff]	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Special Toxicity Studies (continued)					
Glucosuria[a] Rats (SD) 10 M, 30	Dosing: Single 30-minute IV infusion FOS[b](mg/kg): 100 PHT[b](mg/kg): 100 Dose Volume: 10 mL/kg[hh] Observation: 48 hours Parameters: Clinical signs, serum and urine glucose concentrations	Similar increases in serum and urinary glucose concentrations with fosphenytoin and phenytoin. (DCC)	745-01734	1.20	140
CNS Safety Screen[a] Mice (CD-1) 6 M, 90	Dosing: Single IP injection FOS[b](mg/kg): VC[c], 33.3, 66.7, 133, 333, 667 PHT[b](mg/kg): VC[d], 33, 69, 134, 337, 675 Dose Volume: 20 mL/kg[ii] Observation: Approximately 4 hours Parameters: Clinical signs and behavioral changes	Deaths at 333 and 667 mg/kg fosphenytoin and 337 and 675 mg/kg phenytoin. Similar incidence and severity of CNS effects observed with fosphenytoin and phenytoin. (ACC)	745-01736	1.20	170

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Vehicle = Tris buffer, pH adjusted to 8.8.

[ff] All in vivo studies included saline (0.9% NaCl) control group.

[hh] Fosphenytoin dosing solution concentration = 15 mg/mL. Phenytoin dosing solution concentration = 10 mg/mL.

[ii] Vehicle was tested in 3 groups of animals at 100% or diluted to 66% or 32% with saline (0.9% NaCl).

[jj] Fosphenytoin dosing solution concentrations ranged from 2.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 33.75 mg/mL.

Tabular Summary of Toxicology Studies
(Page 13 of 19)

Test Species (Strain) Sex/Group, Total	Study Design[a]	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Special Toxicity Studies (continued)					
Cardiovascular Safety Screen[b] Dogs (Beagle) 4 F, 20	Dosing: Single IV injection FOS[mg/kg]: VC[c], 18 PHT[b][mg/kg]: VC, 18 Dose Volume: 1 mL/kg[bk] Observation: 60 minutes Parameters: Cardiovascular, blood drug concentrations	No deaths. Gradual decrease in HR, LVdP/dt, and MABP with fosphenytoin and immediate decrease in these parameters with phenytoin. Significant increase in LVEDP with phenytoin. Minimum plasma phenytoin concentrations were 22.1 *µg/mL* 5 minutes postdose and 49.4 *µg/mL* 30 seconds postdose following administration of fosphenytoin and phenytoin, respectively. (ACC)	745-01735	1.20	193
Human Blood Compatibility[bl] In Vitro	Concentrations: FOS[mg/mL]: 0.15 to 75 PHT[b][mg/mL]: 0.10 to 50 Parameters: Hemolysis, plasma protein flocculation	No hemolysis or plasma protein flocculation with fosphenytoin. Hemolysis at 5.0 to 50 mg/mL and mild plasma protein flocculation with phenytoin at 20 mg/mL. (DCC)	745-01746	1.20	279

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Vehicle = Tris buffer, pH adjusted to 8.8.

[d] All in vivo studies included saline (0.9% NaCl) control group

[bl] Concentrations based on the weight of the sodium salt of fosphenytoin or phenytoin.

[bk] Fosphenytoin dosing solution concentration = 27 mg/mL. Phenytoin dosing solution concentration = 18 mg/mL.

Tabular Summary of Toxicology Studies
(Page 14 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Dose[1] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report		
					RR Number	NDA Location	
						Volume	Page
Reproductive Toxicity Studies							
Fertility							
Male							
Rat (SD) 40, 200 12-13 Weeks	IM (Tris Buffer) [2 mL/kg]	UC VC 16.7 50 100	75 Days Prior to and through Mating	Paternal toxicity at 50 and 100 mg/kg. No effects on fertility or reproduction. (AA)	745-02042	1.21-22	001
Female							
Rat (SD) 40, 200 15 Weeks	IM (Tris Buffer) [2 mL/kg]	UC VC 16.7 50 100	15 Days Prior to Mating through Lactation Day 21	Maternal and reproductive toxicity at 50 and 100 mg/kg. Developmental toxicity at all doses, including teratogenicity at 16.7 and 100 mg/kg. (AA)	745-02092	1.23-24	017
Teratology							
Exploratory							
Rat (SD) 3F, 9 NA	IV Bolus (Tris Buffer) [2.3,10 mL/kg]	100	10 Days	All animals euthanized moribund by Day 4. No trauma at injection site. (AA)	745-01843	1.24	276

Abbreviations are defined on Page 19 of the Tabular Summary.

[1] Doses expressed as milligrams/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

Tabular Summary of Toxicology Studies
(Page 15 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Dose[1] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Reproductive Toxicity Studies (continued)							
Teratology (continued)							
Dose Range-Finding							
Rat (SD) 5F, 35 20 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	VC 6.7 16.7 33.3 50 66.7	Gestation Days 7 through 17	Maternal toxicity at 16.7, 33.3, and 66.7 mg/kg. Developmental toxicity at 50 and 66.7 mg/kg. No adverse effects at 6.7 mg/kg. MTD = 66.7 mg/kg. (AA)	745-01859	1.25	001
Definitive							
Rat (SD) 40F, 200 12-13 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	UC VC 6.7 33.3 66.7	Gestation Days 7 through 17	Four deaths, decreased maternal body weight gain and food consumption, decreased birth and male offspring weights at Week 13 at 66.7 mg/kg. No teratogenicity or behavioral toxicity. (AA)	745-01973	1.25-26	124

Abbreviations are defined on Page 19 of the Tabular Summary.

[1] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

Tabular Summary of Toxicology Studies
(Page 16 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Dose[1] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report		
					RR Number	NDA Location	
						Volume	Page
Reproductive Toxicity Studies (continued)							
Teratology (continued)							
Exploratory							
Rabbit (NZW) SP, 6 NA	IV Bolus (Tris Buffer) [1,2 mL/kg]	33.3	13 days	No clinical signs or effects on body weight or food consumption. No trauma at injection site. (AA)	745-01844	1.27	014
Dose Range-Finding							
Rabbit (NZW) SP, 35 7-8 Months	IV Bolus (Tris Buffer) [1-2 mL/kg]	VC 3.3 16.7 33.3 50 66.7	Gestation Day 6 through 18	Maternal toxicity at 33.3, 50, and 66.7 mg/kg. Developmental toxicity at 66.7 mg/kg. No adverse effects at 3.3 mg/kg. MTD = 33.3 mg/kg. (AA)	745-01871	1.27	021

Abbreviations are defined on Page 19 of the Tabular Summary.

[1] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

Tabular Summary of Toxicology Studies
(Page 17 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Dose[1] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report kR Number	NDA Location Volume	NDA Location Page
Reproductive Toxicity Studies (continued)							
Teratology (continued)							
Definitive							
Rabbit (NZW) 20F, 1[0]0 7-8 Months	IV Bolus (Tris Buffer) [1 mL/kg]	UC VC 6.7 16.7 33.3	Gestation Day 6 through 18	No deaths. Decreased body weight gain and food consumption at 33.3 mg/kg. No maternal reproductive or fetal toxicity, and no teratogenicity. (AA)	745-01931	1.27	155
PERINATAL-POSTNATAL TOXICITY							
Rat (SD) 25 F, 125 12 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	UC VC 16.7 33.3 66.7	Gestation Day 15 through Lactation Day 20	Maternal and perinatal-postnatal toxicity at 33.3 and 66.7 mg/kg. Subtle behavioral toxicity at 33.3 and 66.7 mg/kg. (AA)	745-02071	1.28-30	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[1] Dose expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

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Tabular Summary of Toxicology Studies
(Page 18 of 19)

Test	Concentration Range or Dose	Results (Laboratory)	Study Report		
			RR Number	NDA Location	
				Volume	Page
Genetic Toxicity Studies					
Mutagenicity					
Mutagenesis in *Salmonella typhimurium*	312.5-5000 µg/plate[mm]	Nonmutagenic in the absence or presence of S9. (AA)	745-01958	1.31	016
Point mutation assay in V79 Chinese hamster lung cells	500-4000 µg/mL[mm]	No mutation at HGPRT locus in the absence or presence of S9. (AA)	745-01935	1.31	083
Clastogenicity					
Structural chromosome aberration assay in V79 Chinese hamster lung cells	500-4000 µg/mL[mm](-S9) 125-4000 µg/mL[mm](+S9)	Clastogenic at ≥3000 µg/mL only in the presence of S9. (AA)	745-82101	1.31	145
Micronucleus assay	33.3, 66.7, 133 mg/kg[m]	No increase in micronucleus frequency. (AA)	745-01898	1.31	248

Abbreviations are defined on Page 19 of the Tabular Summary.

[mm] Concentrations based on the weight of fosphenytoin.

[m] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 20 mg/mL; dose volume = 10 mL/kg. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

Tabular Summary of Toxicology Studies
(Page 19 of 19)

ABBREVIATIONS:

AA	=	Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan
ACC	=	American Critical Care, McGaw Park, Illinois
ALP	=	alkaline phosphatase
ALT	=	alanine aminotransferase
AST	=	aspartate aminotransferase
BUN	=	blood urea nitrogen
CNS	=	central nervous system
CPK	=	creatine phosphokinase
DCC	=	Du Pont Critical Care, Waukegan, Illinois
F	=	female
FOS	=	fosphenytoin
HGPRT	=	hypoxanthine-guanine phosphoribosyltransferase
HR	=	heart rate
IM	=	intramuscular
IP	=	intraperitoneal
IRDC	=	International Research and Development Corporation, Mattawan, Michigan
IV	=	intravenous
LVEDP	=	left ventricular end diastolic pressure
LVdP/dt	=	left ventricular contractility
M	=	male
MABP	=	mean arterial blood pressure
MLD	=	median lethal dose
MNLD	=	maximum nonlethal dose
MTD	=	maximum tolerated dose
NA	=	not available
ND	=	not determined
NOED	=	no observed effect dose
NZW	=	New Zealand White
PHT	=	phenytoin
S9	=	postmitochondrial supernatant from livers of rats induced by Aroclor 1254
SAL	=	saline (0.9% NaCl) control
SC	=	subcutaneous
SD	=	Sprague-Dawley
SP	=	Parke-Davis Research Institute, Sheridan Park, Mississauga, Ontario, Canada
UC	=	untreated control
VC	=	vehicle control

9. Microbial Growth Inhibition

The Microbial Inhibitory Concentrations (MC) for Fosphenytoin Sodium

Species	Fosphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

The Microbial Inhibitory Concentrations (MC) for Phenytoin

Species	Fosphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

The Microbial Inhibitory Concentrations (MC) for Hydroxyphenytoin

Species	Hydroxyphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

10. The Acute Toxicity Studies with *Daphnia magna*

Compound	EC_{50} (mg/L)	NOEC (mg/L)
Fosphenytoin Sodium	170	48
Phenytoin	39	23
Hydroxyphenytoin	28	28

EC_{50}: Concentration at which 50% of the organisms are affected.
NOEC: The no-observed effect concentration for 48 hours.

ATTACHMENT II

MATERIAL SAFETY DATA SHEET

THIS MATERIAL SAFETY DATA SHEET IS DIRECTED PRINCIPALLY TO PROCESSORS, FORMULATORS, AND USERS OF THIS MATERIAL. THE DESCRIPTION OF PHYSICAL, CHEMICAL AND TOXICOLOGICAL PROPERTRIES AS WELL AS THE ADVICE ON HANDLING IS BASED ON PAST EXPERRIENCE AND CURRENTLY AVAILABLE INFORMATION. IF YOU HAVE ANY QUESTIONS REGARDING THE HAZARDS ASSOCIATED WITH THE USE OF THIS MATERIAL PLEASE CONTACT THE PERSON NAMED IN SECTION I.

1. MATERIAL IDENTIFICATION

Product Name: 5,5-DIPHENYL-3-PHOSPHONOOXYMETHYL 2,4-IMIDAZOLIDINEDIONE DISODIUM SALT

Formula: C16H13N2O6P Na2
Process #: CI-982
W.L. ID #: PD 135711-00153
NDC ID #: ND
UPC #: NA

MSDS #: ND
Date of Issue: 06/10/94
Supersedes: 03/18/93
Revision No: 3

Manufacturing Division:
Parke-Davis
188 Howard Avenue
Holland, MICHIGAN 49424
USA

PERSON TO CONTACT:

Chris Pfeiffer
(616)392-2375

NIOSH RTECS No: ND

Common Name: NA
Chemical Family: ND

Synonyms:
5,5-DIPHENYL-3-PHOSPHONOOXYMETHYL 2,4-IMIDAZOLIDINEDIONE DISODIUM SALT
FOSPHENYTOIN SODIUM
CI-982

Comments: none

2. INGREDIENTS AND EXPOSURE LIMITS

INGREDIENT NAME	CAS #	
5,5-DIPHENYL-3-PHOSPHONOOXYMETHYL 2, 4-IMIDAZOLIDINEDIONE DISODIUM SALT	ND	99

OSHA PEL: ND
ACGIH TLV: ND
Other Exposure: ND
Regulatory: ND
Cancer: No
Synonym/Common: ND
Vapor Pressure: NA
Lower Explosive Limit (LEL): NA
Comments: NONE

PRODUCT Exposure Limits: NONE

MATERIAL SAFETY DATA SHEET

Issued: 06/10/94 MSDS # ND

3. PHYSICAL DATA

Appearance: Crystalline solid.
Odor Threshold: ND
Characteristic Odor: ND

Physical State: Solid
Specific Gravity (H_2O = 1): ND
Acidity (pH) @ 25°C: ND
Boiling Point °C (760 mmHg): NA
Melting Point °C: 220 + Decomp.
Percent Volatile by volume: ND
Water Solubility: Yes
Other Solubility: NO
Vapor Pressure (@ 20°C): ND
Vapor Density (Air = 1): ND
Evaporation Rate (H_2O = 1): ND
Molecular Weight: 406.23

4. FIRE AND EXPLOSION DATA

FLAMMABLE LIMITS IN AIR
LEL: NA
UEL: NA

AUTOIGNITION TEMPERATURE
ND

Flash Point (Method): NA

Extinguishing Media: CO_2, Dry Chemical, Foam, Water Spray

Special Fire Fighting Procedures: Use approved self-contained breathing apparatus.

Unusual Fire Hazards: ND

Unusual Explosion Hazards: ND

Harmful Combustion Products: HCN & Nitrogen Oxides

5. REACTIVITY DATA

Stability: Stable
Hazardous Polymerization: No

Conditions to Avoid: NA
Conditions to Avoid: NA

Chemical Incompatibilities: ND

6. HEALTH HAZARD INFORMATION

TOXICITY INFORMATION: ND

EFFECTS OF OCCUPATIONAL OVEREXPOSURE: ND

MATERIAL SAFETY DATA SHEET

Issued: 06/10/94 MSDS # ND

7. FIRST AID PROCEDURES

THERAPEUTIC CLASS: NA

Eyes: Flush with water for 15 minutes.

Skin: Wash with soap and water until free of residue.

Inhalation: Remove from exposure. Seek medical attention.

Ingestion: Seek medical attention.

8. WORKPLACE PRECAUTIONS / CONTROLS

Handling/Storage Precautions: Store in a cool, dry location, isolated from oxidizing agents. If unusual exposures are expected, an Industrial Hygiene review of work practices and controls is recommended.

Ventilation: General ventilation; local exhaust ventilation.

PERSONAL PROTECTIVE EQUIPMENT

Respirator: Negative pressure, full face, dust filter.
Eye Protection: Safety glasses
Gloves: Coveralls, Gloves

Work Practices: The above personal protective equipment represents the minimum protection recommended. Use appropriate handling methods to minimize dust generation. Avoid skin contact or inhalation of dusts. Wash face, hands and forearms before leaving work area.

9. SPILL & LEAK / ENVIRONMENT / SHIPPING

Procedures for Spill or Leak: Wear self-contained breathing apparatus and appropriate protective clothing.
Collect and place in a suitable container for future disposal.

Waste Management/Disposal: Dispose of in accordance with local, state and federal regulations or the authority having jurisdiction. Incineration in a permitted incinerator is the preferred disposal method. (Advise incinerator of the presence of chlorine, bromine, fluorine, sulfur, heavy metals, etc.)

SHIPPING REQUIREMENTS AND LIMITATIONS

ID/UN No: ND

DOT Hazard Class: ND
DOT Shipping Name: ND
DOT Labels/Placards: ND

Packaging Group: ND
Marking: ND
Container Specifications: ND
Shipping Limitations: ND

Storage Area Temperature Requirements: No restrictions.

MATERIAL SAFETY DATA SHEET

Issued: 06/10/94

MSDS # ND

10. LABELS / SUPPLEMENTAL / OTHER REGULATORY

Hazard Communication Labels: Intermediate - No Toxicity Data

SARA Hazard Classification(s): None

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 2**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-95
AMENDMENT	21-JUL-95	24-JUL-95		16-AUG-95

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:
Proprietary: CEREBYX®
Nonproprietary/Established/USAN: fosphenytoin sodium, injection OCT 13 1995
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

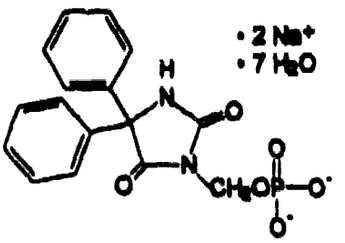
PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx __ OTC
SUPPORTING AND RELATED DOCUMENTS:

CONSULTS: Environmental Assessment: FONSI letter issued and signed by Dr. Jerusal 26-JUN-95
Microbiology / Sterilization Validation, sent to Dr. Cooney, HFD-160 13-APR-95.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

$C_{15}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

The 21-JUL-95 amendment was a response to 16-JUN-95 deficiency letter. A stability update for the drug product is included. CMC review issues are resolved, with the exception of Microbiology and DMF Inspections and methods validation are still outstanding.

CONCLUSIONS & RECOMMENDATIONS:

As inspections, Microbiology review are not yet completed and manufacturing deficiencies in DMF have not been corrected the application is Not Approvable for Chemistry at this time.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/16-AUG-95
HFD-120/RNighswender
HFD-120/SBlum/Init.: MMB 10/12/95

Martha R. Heimann 8/16/95
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 3**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	-
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-95
AMENDMENT	21-JUL-95	24-JUL-95		16-AUG-95
AMENDMENT No. 15	27-SEP-95	28-SEP-95		02-FEB-96
AMENDMENT No. 17	27-OCT-95	30-OCT-95		02-FEB-96
AMENDMENT No. 18	27-OCT-95	30-OCT-95		02-FEB-96
AMENDMENT No. 22	04-JAN-96	05-JAN-96		02-FEB-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH

Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: **CEREBYX®**
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

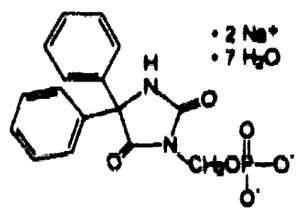
DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx ___ OTC
SUPPORTING AND RELATED DOCUMENTS:

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr. Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95. Minor deficiencies will be included in action letter to sponsor.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{16}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

Several minor amendments were submitted after completion of Review #2. Change in expiration date from 18 months to 24 months (01-JAN-96 amendment)will require adjustment of the post-approval stability protocol. Site inspections are complete and a copy of the EER is attached. DM[illegible] was revised on 18-SEP-95 and is satisfactory for use of phenytoin in synthesis of fosphenytoin. Methods Validation is not complete.

CONCLUSIONS & RECOMMENDATIONS:

Recommend APPROVABLE for Chemistry. The firm should increase stability sterility testing to ensure the product remains sterile through a 24 month expiration date [Draft letter attached] and correct microbiology deficiencies. Letter to sponsor should contain standard methods validation paragraph.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/02-FEB-96
HFD-120/RNighswander
HFD-120/SBlum/Init.: A'N'B 2/8/96

Martha R Heimann 2/2/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.003

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 4**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	N/A
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-95
AMENDMENT	05-SEP-95	06-SEP-95		22-FEB-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:
Proprietary: CEREBYX®
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,926,860, expiration date May 15, 2007, (drug product)

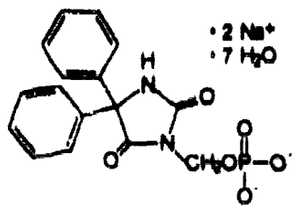
PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx ___ OTC

SUPPORTING AND RELATED DOCUMENTS:

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95. Minor deficiencies will be included in action letter to sponsor.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{15}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

The 05-SEP-95 amendment contained additional copies of the sponsor's Methods Validation package and sample identification (lot #'s etc). Methods validation was performed by the DDA laboratory in St. Louis and by the Detroit District laboratory. Both analysts were able to reproduce the methods and found them generally satisfactory with some comments [see review notes].

CONCLUSIONS & RECOMMENDATIONS:

Methods validation is completed and methods validation paragraph in action letter is not necessary. The NDA remains APPROVABLE for Chemistry with minor deficiency noted in Review No. 3 (02-FEB-96).

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/22-FEB-96
HFD-120/RKnighton/Init.:
HFD-120/SBlum/Init.: SWB 2/29/96

Martha R Heimann 2/22/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.003

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: #5**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
New Correspondence	13-MAR-96	14-MAR-96		10-MAY-96
Amendment	12-APR-96	19-APR-96	15-APR-96	10-MAY-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road, Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: CEREBYX®
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx __ OTC

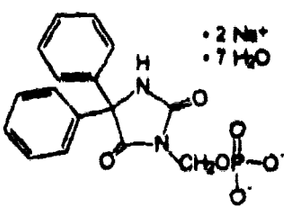
JUL 10 1996

SUPPORTING AND RELATED DOCUMENTS: DMF

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr. Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95 with deficiencies.
Microbiology portion of 13-MAR-96 response reviewed by Dr. Hussong, returned to HFD-120 on 19-APR-96 with approval recommendation.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{15}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

Two submissions dated 13-MAR-96 were a partial to the 23-FEB-96 approvable letter. The CMC and microbiology responses (with some typographical corrections to the microbiology section) are repeated in the 12-APR-96 amendment. All CMC issues have been resolved. Draft labeling expressing fosphenytoin content of the drug product as 'phenytoin equivalents' was submitted in response to the Agency's request [refer to review notes]

CONCLUSIONS & RECOMMENDATIONS:

Chemistry information is correct with minor revisions suggested Medical Reviewer's concurrence with Labeling is necessary.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/10-MAY-96
HFD-120/RNighswander
HFD-120/SBlum/Init.: S.N.B. 5/10/96

Martha R. Heimann 5/10/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-450.005

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: #6**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
Amendment	14-MAR-96	15-MAR-96		18-JUL-96
Amendment	12-JUL-96	15-JUL-96	18-JUL-96	18-JUL-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road, Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary:	**CEREBYX®**
Nonproprietary/Established/USAN:	fosphenytoin sodium, injection
Code Name/#:	CI-982
Chem. Type/Therapeutic Class:	1S

DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

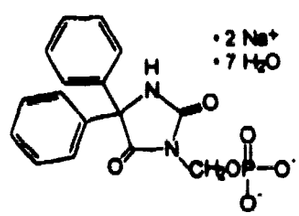
PHARMACOLOGICAL CATEGORY / INDICATION:	Anti-epileptic
DOSAGE FORM:	Injection
STRENGTHS:	75 mg/mL
ROUTE OF ADMINISTRATION:	IV / IM
DISPENSED:	XX Rx ___ OTC

SUPPORTING AND RELATED DOCUMENTS: DMF

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr. Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95 with deficiencies.
Microbiology portion of 14-MAR-96 response reviewed by Dr. Hussong, returned to HFD-120 on 19-APR-96 with approval recommendation.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{16}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

The 12-JUL-96 submission contains final printed labeling for the package insert, vials and cartons. At the request of the clinical review division, the labeling was revised to show both the actual weight of fosphenytoin contained and the equivalent weight of phenytoin sodium. The labeling is acceptable to chemistry and there are no CMC issues outstanding.

CONCLUSIONS & RECOMMENDATIONS:

Recommend Approval for Chemistry.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/18-JUL-96
HFD-120/RNighswander
HFD-120/SBlum/Init.: JWB 7/24/96

Martha R. Heimann 7/18/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-450.006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-450

SEP 12 1994

Parke-Davis Pharmaceutical Research
Division of the Warner-Lambert Company
Attention: Irwin G. Martin, Ph.D
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Dr. Martin:

Reference is made to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosphenytoin Sodium Injection (Cerebyx®).

On the basis of our initial review of your New Drug Application referred to above, received on July 15, 1994 and acknowledged on July 28, 1994, we have determined that the application is not acceptable for filing under 21 CFR 314.101 (d)(3).

The application is incomplete because it does not on its face contain information required under section 505(b) and 21 CFR 314.50(d)(5).

Clinical Safety Data:

1. Inadequate studies to show that the product will be safe for use under the conditions of use recommended in the proposed labeling.

   The application contains reports of only 4 patients with status epilepticus who have been treated with fosphenytoin at rates of infusion at or above 225 mg/min. Experience in normals at this dose and rate combination is also limited; although the application does not supply a precise number, preliminary review estimates that no more than 20 normals may have been so exposed.

   Accordingly, the information submitted is inadequate to permit a substantive assessment of whether or not fosphenytoin will be safe for use when administered under the conditions of use recommended in the Dosage and Administration Section of the proposed labeling which recommends, for the treatment of Status Epilepticus, that an intravenous dose of 22.5 to 30 mg/kg given *"At least 150 mg/min up to 225 mg/min"* be administered as a single dose. Additionally, the section recommends, for the treatment or prophylaxis of seizures, that an IM

or IV administration of 15 to 30 mg/kg fosphenytoin be given *"up to 225 mg/min"* as a single dose.

2. Lack of tests and/or reports on tests to show that the drug will be safe for use; a lack of information on the plasma concentrations of formaldehyde:

   The application does not provide reports on the concentration of formaldehyde formed in plasma during the administration of your product when used as recommended in product labeling. Formaldehyde is a toxin and is formed during the conversion of fosphenytoin to phenytoin.

   Your firm has been advised repeatedly for the need to provide this information, and has, nevertheless, failed to do so.

   We note that your NDA SUMMARY;NDA Overview subsection (Item 2.2, page 106) discusses this and states that a complete discussion of this issue could be found under NDA Item 5, section 5.5.4.6, Tab 55. Our preliminary review of the cited reference to clinical data (RR 744-00024, Study 9653-86-01) reveals, however, that NO data regarding formate levels in human trials is included in the cited study report.

Environmental Assessment

Although not reasons for this Refuse to File Action, our environmental assessment staff has completed a preliminary review of your EA and has asked that the following comments be forwarded.

1. General issues:

   a. The drug substance and drug product are incorrectly identified throughout the environmental assessment (e.g., the drug substance is identified as Fosphenytoin instead of the sodium salt). Please correct the environmental assessment (pages 3-28) to reflect the correct terminology.

   b. The information in the Environmental Assessment is releasable under the Freedom of Information Act. Any proprietary information should be provided in Appendices and be clearly marked as confidential. Some of the information included in your environmental assessment may be confidential (e.g., the list of raw materials used in the synthesis of Fosphenytoin Sodium or the fifth year production estimates). If you wish you may move this information to an appendix and provide only summary information in the actual environmental assessment.

c. A flow diagram for the synthesis of the drug substance and the manufacturing process for the drug product was provided by FAX on August 22, 1994. Please provide an official copy to the file.

2. Please describe the locations where the drug product is expected to be used (Section IV).

3. What is the disposition of returned or expired drug product and rejected drug substance (Section IV)?

4. The Identification of Chemical Substance (Section V) should be revised to include:

a. The correct Chemical Name; i.e., the sodium salt;

b. An appropriate synonym (i.e., sodium salt) with a reference (IUPAC, USAN, etc.,);

c. A structural formula;

d. A list of the additives used or lack thereof; and

e. A list of the impurities or lack thereof.

5. A Material Safety Data Sheet for Fosphenytoin Sodium should be provided (Section V).

6. Incomplete information (except for HEPA/air handling at Rochester) is provided regarding the introduction of substances in the environment, specifically the controls, effect of compliance with current emissions requirements, and estimate of the quantities and concentrations of substances expected to enter the environment (Section VI).

a. For air, liquid and solids emissions originating at both the Holland and Rochester facilities the following should be provided:

i. Emission permit numbers, authorizing Agencies and permit expiration dates;

ii. Applicable emission requirements (both qualitative and quantitative);

iii. An estimate, through use of calculations or direct measure, of the possible quantities and concentrations of substances expected to enter the environment (fifth year production estimates); and

iv. Effect of the quantities/concentrations (from 6.a.iii.) on meeting both the qualitative and quantitative emission requirements.

Inclusion of actual permits is not required. For ease of review it is preferred that this information be presented in a table format.

Any of the requested information that is not applicable to a specific permit/emission (e.g., permit expiration date, quantitative emission requirement) should be clearly indicated/explained.

If Warner Lambert does not have direct control (permits) over the waste disposal (e.g., solid waste), the contractors and/or facilities involved should be identified.

b. There are three air permits pending approval at the Holland facility for this product. Please update the status of these permits and indicate when approval is expected.

c. A discussion of the disposal of solid waste generated by the production of the material at the Holland facility should be included.

d. On pages 10 and 11 the expected environmental concentrations should be identified as "maximum" not "minimum".

7. Citation of and a statement of compliance with any appropriate Federal, State and Local occupational exposure requirements should be provided (Section VI).

8. The following are in regards to the fate of the emitted substances in the environment (Section VII)

a. The estimated percent excreted as phenytoin and hydroxyphenytoin should be provided if available.

b. No information was provided regarding hydrolytic stability or dissociation constants for the compounds of interest.

c. For the water solubility determination, a complete test report which includes information such as the methodology used, study site, temperature at which the solubility was determined and the HPLC method should be provided. If the HPLC method is the one included in the NDA it need only be referenced by number.

d. For the partition coefficient determination a complete test report which includes information such as the test methodology, the study site, concentrations at which the study was performed (Note: FDA methodology requires that 2 different concentrations be used) and the HPLC method should be provided. If the HPLC method is the one included in the NDA it need only be referenced by number.

e. The conclusion regarding the aquatic photolytic degradation of Fosphenytoin Sodium (page 17, last sentence in second paragraph) should be revised to indicate that photolysis is not a primary removal mechanism of Fosphenytoin from the environment.

f. You have indicated that aerobic aquatic biodegradation of Hydroxyphenytoin is rapid and that it has been proven/demonstrated to completely degrade to CO_2 (pages 17 and 21) The data provided does not support these conclusions. The appropriate statements should be revised to state that the data indicates that this biodegradation will occur, but that it is not rapid.

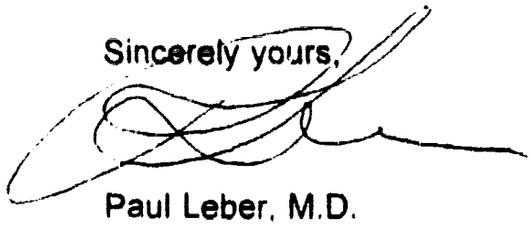
9. Please revise Section XI to state that based on the data you believe that there will be no impact on the environment (or similar wording).

10. You state that no consultants were used (Section XII), but have used the services of at least . Please revise as needed. The *Curricula vitae* cited were not included in Appendix 26.

Within 30 days of the date of this letter, you may request in writing an informal conference about FDA's refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

Should questions arise regarding this application, please contact Mr. Robbin Nighswander, Project Manager, at (301) 594-2777.

Sincerely yours,



Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Microbiologist Review

REVIEW FOR HFD-120
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

19 December 1995

A. 1. NDA 20-450

SPONSOR Parke-Davis Pharmaceutical Research
Division of Warner Lambert
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

2. PRODUCT NAMES: Cerebyx® (fosphenytoin sodium)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A sterile solution containing 75 mg/mL of 10 mL (in 10 mL vials) and 2 mL (in 3 mL vials), for injection

4. METHOD(S) OF STERILIZATION: Aseptic filling of filtered solution

5. PHARMACOLOGICAL CATEGORY: Neuropharmaceutical for treatment of epilepsy

6. DRUG PRIORITY CLASSIFICATION: 1S

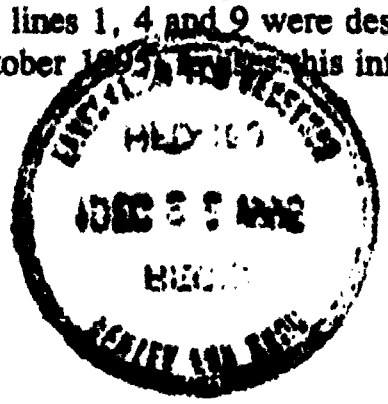
B. 1. DATE OF INITIAL SUBMISSION: 22 February 1995 (Subject of this review)

2. DATE OF AMENDMENT: 27 October 1995 (Also the subject of this review)

3. RELATED DOCUMENTS: DMF
DMF

4. ASSIGNED FOR REVIEW: 2 May 1995 (original) and 15 November 1995 (amendment)

C. REMARKS: The applicant provides a rather comprehensive sterility assurance document in the original submission. Originally, fill lines 1, 4 and 9 were described for this product's manufacture. The amendment (27 October 1995) [illegible] this information, deleting fill line 9, and correcting minor details.



D. CONCLUSIONS: The application is not recommended for approval for reasons of sterility assurance. Specific comments are provided in section in the "Microbiolog st's Draft of Letter to the Applicant". Stability information was not part of the consultative review package but was shown in the NDA index, so the review chemist should assure conformance of the testing schedule with Center policy. Labelling was not provided, and this product is not suitable for multiple dose use.

12-19-95

David Hussong, Ph.D.

12/22/95

cc:

HFD-850/Consult File
HFD-120/CSO
HFD-120/M. Heimann
HFD-805/Consult File
HFD-805/D. Hussong

Drafted by: D. Hussong, 12/19/95
R/D initialed by: P. Cooney, 12/ /95

Filename, c:\d\nda\20-450.rv1

MAY 15 1996

REVIEW FOR HFD-120
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #3 OF NDA

9 May 1996

RETURN

MAY 10 1996

A. 1. NDA 20-450

SPONSOR Parke-Davis Pharmaceutical Research
Division of Warner Lambert
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

2. PRODUCT NAMES: Cerebyx® (fosphenytoin sodium)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A sterile solution containing 75 mg/mL of 10 mL (in 10 mL vials) and 2 mL (in 3 mL vials), for injection

4. METHOD(S) OF STERILIZATION: Aseptic filling of filtered solution

5. PHARMACOLOGICAL CATEGORY: Neuropharmaceutical for treatment of epilepsy

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: 22 February 1995 (subject of Microbiologist's Review #1, 19 December 1995)

2. DATE OF AMENDMENTS: 27 October 1995 (also the subject of Microbiologist's Review #1, 19 December 1995); 14 March 1996 (subject of Microbiologist's Review #2, 9 April 1996); and 12 April 1996 (subject of this review)

3. RELATED DOCUMENTS: DMF
DMF

4. ASSIGNED FOR REVIEW: 22 April 1996

C. REMARKS: The applicant provided a rather comprehensive sterility assurance document in the original submission, and addressed 5 deficiency items in the 14 March 1996 amendment. These were acceptable in Microbiologist's Review #2, but some typographical errors were detected. The applicant chose to correct these errors by resubmitting the information from the 14 March 1996 amendment. The typographical

errors were annotated and corrected in this submission. No deficiencies were offered in Microbiologist's Review #2, and no further review is provided here.

D. CONCLUSIONS: The application is recommended for approval for reasons of sterility assurance.

5-9-96

David Hussong, Ph.D.

5/14/96

cc:

HFD-850/Consult File
HFD-120/CSO
HFD-120/M. Heimann
HFD-805/Consult File
HFD-805/D. Hussong

Drafted by: D. Hussong, 05/09/96
R/D initialed by: P. Cooney, 05/ /96

Filename, c:\d\nda\20-450.rv3

END

BT

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

20450

Cerebyx

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-450

AUG - 5 1996

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Ms. Janeth L. Turner
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Ms. Turner:

Please refer to your July 14, 1994 new drug application and your resubmission dated February 22, 1995 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerebyx® (fosphenytoin sodium) Injection 75 mg/mL (50 mg/mL PE).

We also acknowledge receipt of your additional correspondence and amendments dated:

February 27, 1996	April 12, 1996	May 8, 1996
March 13, 1996	May 1, 1996	July 12, 1996
March 14, 1996	May 2, 1996 (2)	July 30, 1996

This new drug application provides for the following:

> Cerebyx® is indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. The safety and effectiveness of Cerebyx® in this use has not been systematically evaluated for more than 5 days.
>
> Cerebyx® can be used for the control of generalized convulsive status epilepticus and prevention and prevention and treatment of seizures occurring during neurosurgery. It can also be substituted, short-term, for oral phenytoin.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated July 12, 1996 with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. The revisions are as follows:

1. Please correct the legend to Figure 1 to read "...1200 mg PE Cerebyx infused..." rather than "...1200 mg Cerebyx infused...."

2. WARNINGS: Usage in Pregnancy: *Clinical:* section

B. *Risks to the Fetus.*

Paragraph 1, last sentence: please change "contribution" to "contributions".

3. WARNINGS: Usage in Pregnancy: *preclinical:* section

The wording of dose comparisons and plasma level data should be made consistent as follows:

Para 1, sentence 2: ... (approximately 30% of the maximum human loading dose or higher on a mg/m^2 basis), which produced peak maternal plasma phenytoin concentrations of approximately 20 μg/mL or greater.

Para 1, sentence 4: ... (approximately 10% of the maximum human loading dose on a mg/m^2 basis) ....

Para 2, sentence 1: ... (approximately 50% ....

Para 2, sentence 2: ... (approximately 120% ....

4. PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility; section

Para 3, last sentence: ... at doses of 50 mg PE/kg or higher (approximately 40 % of the maximum human loading dose or higher on a mg/m^2 basis).

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-450. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Phase IV Commitment

We remind you of your Phase 4 commitment specified in your submission dated April 12, 1996 and amended on July 12, & 30, 1996. This commitment is listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment." Your commitment is as follows:

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact: Robbin Nighswander, R.Ph.
Regulatory Management Officer
(301) 594-2777

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-450

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Ms. Janeth L. Turner
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

FEB 23 1996

Dear Ms. Turner:

Please refer to your July 14, 1994 new drug application (and your resubmission dated February 22, 1995) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerebyx® (fosphenytoin sodium) Injection 75 mg/ml.

We acknowledge the following additional correspondence and amendments:

September 2, 1994	July 21, 1995	October 31, 1995
September 14, 1994	September 5, 1995	November 3, 1995
October 6, 1994	September 14, 1995	November 20, 1995
December 16, 1994	September 27, 1995	January 4, 1996
March 29, 1995	October 19, 1995	January 8, 1996
June 8, 1995	October 27, 1995	February 9, 1996
June 22, 1995	(2 submissions)	

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to adopt as labeling for Cerebyx®, the draft package insert attached to this letter, modified as requested (i.e., as per this letter and the notes embedded within the text of the attached package insert).

Phase IV Commitment

We also ask that you submit the following information:

1. **Labeling:**

   Package Insert: Should additional information relating to the safety and effectiveness of Cerebyx® become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

   Product and Container Labeling: Please revise all product and container labeling to appropriately convey that dosage conversion calculations do not need to be performed when converting patients between fosphenytoin and phenytoin (i.e., all labeling should clearly convey that 50 mg/ml of phenytoin is being delivered and that NO dosage conversion factor need be applied).

2. **Microbiology:**

   The following microbiological issues concerning sterility assurance and other issues have not been completely addressed:

   a. Bulk solution bioburden limits (prior to filtration) should be specified and the methods to test this, including sample points, should be described. Historical data may be provided in support of the established limit. We prefer the sample collection point be identified in the manufacturing instructions.

   b. The frequency of requalifying sterilizers (autoclaves and tunnels) was specified as every 2 years. We generally recommend more frequent evaluation of the instrument and process.

c. The operating parameters for sterilization of filters and filling equipment were not provided and their validation was not discussed.

d. Validation of the integrity of the container and closure systems' barrier to microbial ingress was not discussed. Please provide a summary of the methods and results demonstrating the integrity of this system.

e. Your amendment dated October 27, 1995 describes specifications for media fills (Tab 5, Appendix 1, page 19). The stated Alert Limit permits no investigation of any kind when as many as 2 containers are contaminated in a batch of 5000. We encourage some investigation of any evidence of contamination in product (simulated or otherwise) manufactured by a process for sterile product.

3. Manufacturing and Controls:

Safety Update

Submit a safety update report as provided for under 21 CFR 314.50(d)(5)(vi)(b). This may be limited to deaths, serious adverse events, other adverse events that led to discontinuation of the drug, and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels. Please also include any serious adverse events reported since your last safety update in the final draft version of product labeling you submit in response to this approvable action.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Robbin Nighswander, R.Ph., M.S.
Regulatory Management Officer
Telephone: (301) 594-2850

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachment (1)

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 9, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Cerebyx® [fosphenytoin injection] NDA 20-450 Approvable Action

TO: Robert Temple, MD, Director, ODE 1
&
File NDA 20-450

This memorandum provides a discussion of several factors affecting the regulatory action that might be taken in regard to Parke-Davis' pending NDA 20-450 for Cerebyx® [fosphenytoin].

Several options, ranging from approval to disapproval are defensible. As a matter of tactics, however, the action letter being forwarded declares the NDA approvable, albeit under a number of conditions that are enumerated both within the text of the letter and within a version of product labeling developed by the division (i.e., in 'notes to the firm' embedded within the text) that would be attached to the letter, if issued. If the Office were to choose an alternative action, the draft approvable letter may be modified accordingly.

Introductory Comments and notes about the administrative strategy applied in the evaluation of this NDA

The structure of the arguments supporting approval

Although Cerebyx® [fosphenytoin] is a new chemical entity, an approval of the NDA for Cerebyx® is only possible, given the type of the information provided in the NDA, because Dilantin®, Parke Davis' innovator brand of phenytoin, is an approved anti-epileptic drug product [AED].

The conclusion that Cerebyx® is effective in use, in particular, turns not on reports of adequate and well controlled clinical investigations, but upon 1) the knowledge that phenytoin is an effective AED, 2) that fosphenytoin is completely converted within minutes of injection to phenytoin and 3) evidence adduced by the sponsor in biopharmacokinetic and clinical trials showing that when Cerebyx® is administered under the directions provided in the proposed Cerebyx® product labeling, the resulting plasma levels of phenytoin approximate those that are obtained when Dilantin injection is administered under its recommended conditions of use for the same claimed use.

Although the agency's earlier determination that the benefits of Dilantin® injection outweigh the risks of its use is a necessary element in the chain of argument and evidence that can be used to support a conclusion that Cerebyx® will be safe for use under its proposed labeling, the determination involving Dilantin® is, in and of itself, insufficient to support the conclusion about Cerebyx®'s safety. Not only is fosphenytoin a different molecular species than phenytoin (and, therefore, may pose an entirely distinct panoply of risks unrelated to its conversion to phenytoin), but fosphenytoin injection yields two/three molecular species, phosphate and formaldehyde/formate that are not produced when Dilantin is administered. How these differences affect the regulatory decision, and how well I believe they have been addressed by the firm, are discussed in a later section of this memorandum.

An administrative issue affecting labeling of both Cerebyx® and Dilantin®

Cerebyx® labeling can be viewed as addressing both fosphenytoin specific (e.g., fosphenytoin, formate, phosphate) and phenytoin related issues. The latter, to the extent that they represent information not currently included in Dilantin® labeling pose a problem in that, with the marketing of Cerebyx®, there would be in existence different, arguably contradictory, statements about the same drug substance (phenytoin) in the labeling of two different approved drug products (Dilantin® and Cerebyx®).

While we do not propose to resolve the problem by linking the approval of

the Cerebyx® NDA to full revision of Dilantin® product labeling, we do recommend, if the Cerebyx® NDA is declared approvable, asking the firm to revise the content of those sections of Dilantin® product labeling (both oral and injectable) that differ substantively from Cerebyx® product labeling (e.g., phenytoin specific matters vis a vis pregnancy, teratogenicity, etc.) and to submit labeling supplements to all[1] their Dilantin product NDAs at the same time as they make a response to a Cerebyx® approvable action letter.

Effectiveness in Use.

As noted in the preceding section, although the Cerebyx® NDA contains no reports of adequate and well controlled clinical investigations that document fosphenytoin injection's capacity to suppress seizures, the effectiveness of the product as an anti-epileptic drug [AED] can be deemed established on the grounds that 1) fosphenytoin is a prodrug for phenytoin[2] and 2) under the conditions of use recommended in the labeling proposed by the Division, Cerebyx® injection will yield plasma levels of free phenytoin that are sufficiently close[3] to those that would be produced

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[1] The firm might not choose to revise Dilantin® injection because they intend that it be replaced by Cerebyx®; I would recommend that we insist that they do, however, in part to ensure that generic labeling for injectable phenytoin is consistent with Cerebyx®.

[2] Each molar unit of administered fospheytoin is converted to an equimolar quantity of phenytoin.

[3] It is acknowledged that 'close' has no clinically defined or generally recognized meaning The word is intended to convey a judgment by the review team that the rate and extent of free phenytoin delivery to the systemic circulation that follows the administration of Cerebyx® do not differ from the rate and extent of free phenytoin delivery that follows the administration of Dilantin® injection to a degree that will a cause a clinically significant difference in treatment response. This judgment, admittedly, cannot be supported by reference to empirical findings; there is no established quantitative relationship between changes in the rate and extent of phenytoin delivery and changes in the percent of patients experiencing a satisfactory anti-epileptic response in any of the clinical settings in which parenteral phenytoin is recommended. While such a judgment is, therefore, undeniably arbitrary, it is

when Dilantin® injection is administered for the same indication[4] under Dilantin® injection's recommended conditions for use to allow Cerebyx® injection to be used in place of Dilantin® injection.

As noted, the bioequivalence of Cerebyx® and Dilantin® injection have not been demonstrated under every possible set of doses and routes of administration being recommended in Cerebyx® labeling. It is our judgment, however, that the products are 'fungible' when given in equimolar doses in settings where the extent, but not the rate, of phenytoin delivery controls its effectiveness.

In the one situation in which rate of phenytoin availability is deemed of critical clinical importance, that is, intravenous loading for the treatment of status epilepticus, the firm has been able to develop a regimen of use under which the pharmacokinetic performance of Cerebyx® and Dilantin® injection are bioequivalent by ordinary agency criteria (i.e., the 90% CL limits on the ratio of the realized values of the estimates for the usual PK parameters of the new to the old product are ≥ 0.8 and ≤ 1.25).

> A digression concerning the doses of phenytoin and fosphenytoin studied may be helpful at this point. The molecular weight of fosphenytoin is approximately 1.5 times that of phenytoin; accordingly a dose of phenytoin only 0.67 that of fosphenytoin is equimolar to the latter. Unfortunately, it is sometimes difficult to be certain whether or not the dose of fosphenytoin

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every bit as reasonable as the one that allows the agency to declare products that differ in their biopharmacokinetic performance 'bioequivalent' as long as the difference in their performance falls within some arbitrary tolerance limits (e.g., the 90% confidence limits on the ratio of realized estimates for a particular pharmacokinetic parameter , say Cmax or AUC, for two products, falls between 0.8 and 1.25). Having said all this, however, it should be noted that the firm did show that fosphenytoin and phenytoin can deliver free phenytoin to the same rate and extent under one specific set conditions of dose and rate of administration. (see discussion of study 982-240).

[4]

1. IV loading in status epilepticus
2. IM or IV loading for treatment or prophylaxis
3. IM or IV use for maintenance therapy
4. IM or IV use for temporary substitution for oral Dilantin

identified in file documents (e.g., in both FDA review documents and sponsor's reports), is intended to represent the actual weight of fosphenytoin or the weight expressed in phenytoin equivalents (PE), that is, the weight of phenytoin that would yield an equimolar amount of phenytoin as the fosphenytoin dose actually administered. There is not much that can be done about these ambiguities in usage other than to be aware of them.

The table that follows provides a concrete example: it enumerates the actual mass doses for both fosphenytoin and phenytoin that would generate the same molar amount of phenytoin in status epilepticus. Note that the rate of phenytoin specified in the table is not actually deliverable with Dilantin® injection because the maximum rate of intravenous administration for that product is 50 mg/min.

Drug	dose	rate
fosphenytoin	22.5 to 30 mg/kg	150 to 225 mg/min
phenytoin	15 to 20 mg/kg	**100 to 150 mg/min

** theoretical: phenytoin cannot safely be delivered at this rate; 50 mg/min is the maximum recommended rate.

Study 98224 shows Cerebyx® and Dilantin® bioequivalent under the iv loading infusion regimen employed (i.e., see the table above). It bears repetition that this regimen is intended for use when phenytoin is being administered intravenously to a patient in status epilepticus; this is the only clinical setting, in our judgment, in which a decrease in the rate of systemic phenytoin delivery might have an adverse effect on clinical outcome. In all other settings, we assume that it is the extent, not the rate, of phenytoin delivery that is controlling.

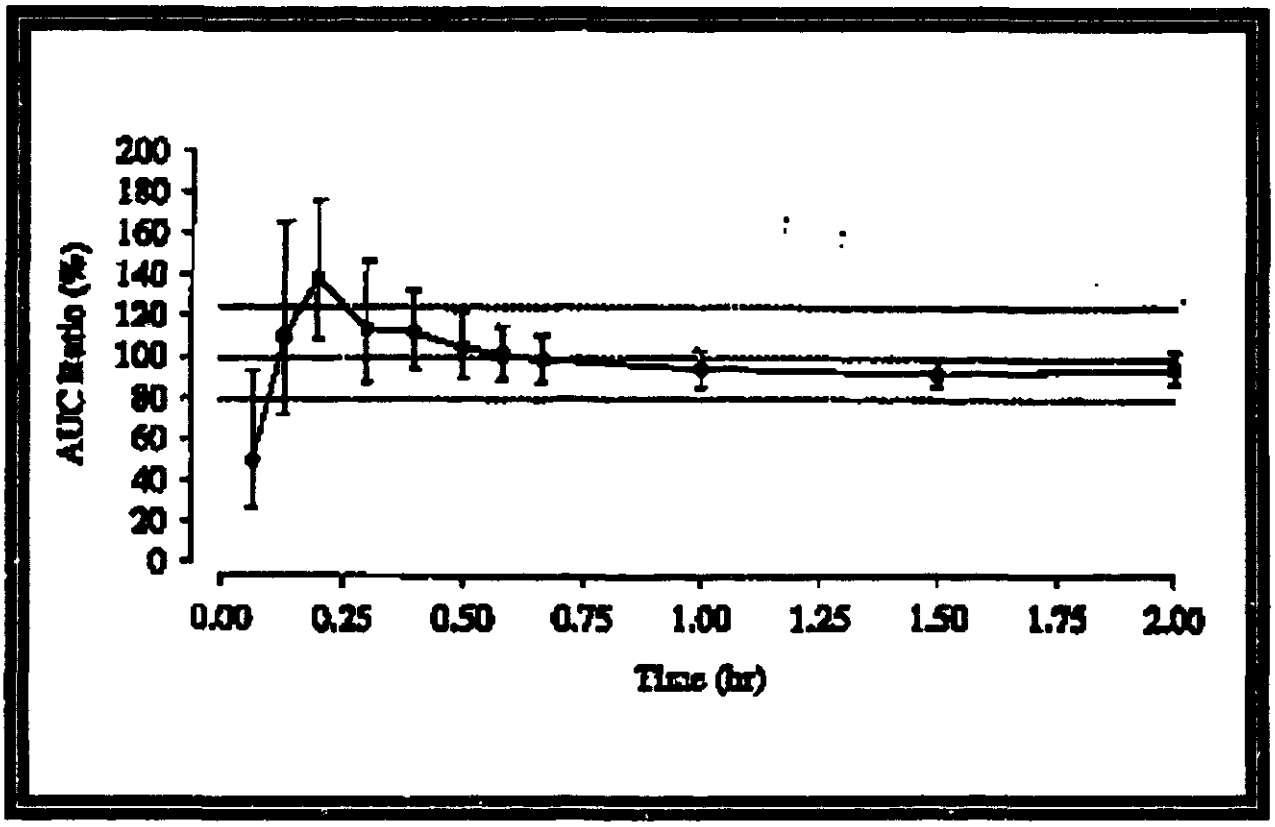
A digression about the method used to assess the relative rate at which Cerebyx® and Dilantin® infusions deliver free phenytoin is useful here. When drugs are administered by constant intravenous infusion, the Cmax and Tmax occur typically at the end of the infusion and the realized values of these parameter estimates are controlled, other variables held constant, by both the total dose and the rate of delivery of that dose.

In ordinary circumstances, therefore, the administration of two drug products that yield the same molar amounts of the same drug substance cannot possibly generate bioequivalent delivery profiles if they are administered at

different rates of infusion. The situation is different where Cerebyx® and Dilantin® are concerned, however.

A number of events and phenomena, including fosphenytoin protein binding, fosphenytoin hydrolysis, phenytoin protein binding, and phenytoin displacement from protein bound sites affect the rate at which Cerebyx® infusion delivers free phenytoin. As a consequence, Cerebyx® must be administered at a faster rate than Dilantin® injection to deliver free phenytoin at an equivalent rate and extent.

The parameter employed to compare the pace of free phenytoin delivery by the two products is the ratio of their cumulative AUCs for free phenytoin. The ratio is obtained by dividing the cumulative AUC for free phenytoin at some time, t, following the start of the infusion of Cerebyx®, by the cumulative AUC for free phenytoin at the same time, t, following the start of an infusion of Dilantin® injection. If the two products deliver free phenytoin at the same rate, the ratio will be unity at all times.



The Division's consultant biopharmaceutical review team has evaluated the firm's report of Study 98224 and concludes that it documents that a

dose of 1200 mg PE of fosphenytoin[5] delivered intravenously at a rate of 150 mg PE/min produces the same cumulative free phenytoin AUC over time as a dose of 1200 mg of phenytoin delivered at 50 mg/min.

Even in study 98224, however, the performance of the two products is not precisely identical throughout the entire post-dosing interval as the plot of the ratio of the cumulative free phenytoin AUC demonstrates (see the figure on the preceeding page which is reproduced from the top panel of Figure 13 on page 12 of the 12/21/95 biopharm review). In short, even in this study, the technical declaration of bioequivalence is somewhat arbitrary as it turns on the time after the start of infusion that is chosen for the evaluation of the cumulative AUC ratio.

In this regard, it is important to note that the regimen selected for Cerebyx® infusion ensures that in comparison to Dilantin® more, rather than less free phenytoin, is generated early on in the course of the infusion (e.g., from 10 to 30 minutes or so), the very period in which it is deemed critically important from a clinical perspective to ensure the rapid delivery of bioavailable phenytoin.

Safety in Use: specific issues.

Whether or not fosphenytoin is safe in use cannot rest on the knowledge that phenytoin is a safe drug, however. Because fosphenytoin is not only a prodrug for phenytoin but for phosphate[6] and formaldehyde/formate[6], the risks that might be associated with the parenteral administration of these products under the conditions of use recommended in Cerebyx labeling must be considered.

Both Dr. Edward Fisher, the primary reviewing pharmacologist, and Dr. John Feeney, the neurology group clinical reviewer responsible for the

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[5] 20 mg/kg given to a 60 kg patient results in 1200 mg total dose

[6] Each molar unit of fosphenytoin forms equimolar units of phosphate and formaldehyde. Formaldehyde is then converted to formate which is then converted to CO_2 and H_2O by a folate dependent step.

application, discuss risks that might derive from the generation of the byproducts of fosphenytoin hydrolysis.

It is important to acknowledge at the outset that concerns about the potential risks posed by these byproducts arise for theoretical reasons; there are no findings of serious injury or toxicity in either clinical or preclinical tests with fosphenytoin that indicate that either formate or phosphate derived from fosphenytoin administration has actually caused harm.

On the other side of coin, however, a systematic effort to detect toxicity that might have been caused by these byproducts (particularly formate) has not been carried out either in animals or humans. Perhaps more important as a reason for caution, the extent of clinical exposure to Cerebyx® at the highest doses and rates of delivery is limited[7] and, accordingly, the warrant provided by the absence of evidence of harm is less than robust.

Formate: the risk of ocular injury

Although no reports of blindness or diminished vision have been reported in association with the clinical testing of Cerebyx, formate, a known mammalian ocular toxin[8] is a by product of fosphenytoin hydrolysis. As much as 5 mmoles of formate may be delivered within 7 minutes under the regimen recommended for Cerebyx® in the management of status epilepticus [SE].

Although the firm had been repeatedly advised of our concern about the potential risk posed by formate exposure, it has yet to provide a systematic evaluation of the extent of, and variability in, formate

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[7] Only 128 patients have been exposed to doses of greater than 15 mg PE/kg at an infusion rates of ≥ 150 mg PE/min and only 66 patients at this rate and the higher dose of 20 mg PE/kg.

[8] Studies in monkeys document that formate levels as low as 7 MMOL/L can cause optic nerve damage; formate is presumably the agent immediately responsible for the blindness that is associated with methanol ingestion

generation following intravenous loading with fosphenytoin. In fact, only 4 patients have had formate levels measured, and then during infusions that delivered only one-half the load of fosphenytoin recommended for the treatment of status epilepticus.

Also, since the metabolism of formate is folate dependent, and a substantive proportion of patients with status epilepticus may be folate deficient (e.g., alcoholics), the issue is not only the extent of monitored experience, but the collateral conditions under which exposure has taken place.

The risk assessment process is further complicated by the sparseness of the information available from preclinical models. At present, we believe (know) that exposures as low 7 MMOL/L can cause ocular damage in monkeys, but do not know whether or not lower exposures can.

On the other hand, Dr. Fisher points out that sustained exposures to elevated levels of formate are probably required to cause injury in humans and that the firm did estimate, based on data available from other sources, the likely increment in serum formate that would follow an infusion of formate equivalent to that delivered by the maximum recommended dose of fosphenytoin, and that such an input would be unlikely to raise formate levels above background, let alone produce those known to cause injury.

Accordingly, in my view, concerns about formate are not of a concern vis a vis the approvability of Cerebyx, although they probably require mention in labeling, unless the firm can provide either argument or data, or both to convince us such mention is unnecessary.

Risks of a phosphate load.

Dr. Feeney draws attention to the risks that might follow rapid IV administration of a phosphate load. Both serum ionized calcium levels and pH may be affected, but neither have been systematically monitored by the sponsor. As with the concerns discussed in regard to formate, I believe we ought to require mention of the possibility of these effects in labeling unless the sponsor can provide evidence or argument to show that

such labeling statements are unnecessary.

Systemic sensations

In his review, Dr. Feeney discusses a set of sensations that are associated with infusion of Cerebyx (burning/pruritus affecting the extremities, the groin and in peri-rectal areas[9]); since these are not observed with phenytoin infusion, it is logical that they are the result of some unique property of fosphenytoin, its byproducts, or some secondary phenomena arising from their introduction into the systemic circulation.

Phosphate, for example, might act directly or indirectly through an effect on serum Calcium levels. The usual signs/symptoms of tetany (peri-oral dysthesias, tingling in the distal extremities, etc.), however, do seem distinguishable from those associated with fosphenytoin infusion; nonetheless, the possibility that changes in serum Calcium are involved cannot be dismissed out-of-hand.

The bottom line, however, is that our ability to assess any hypothesis regarding the cause of these phenomena is limited by the minimal monitoring of serum formate, Calcium, phosphate and pH done by the firm.

Fatalities

The population treated with fosphenytoin is likely to be at substantially greater risk of death than the typical cohort of patients with complex partial seizures who participate in the usual AED development program. In particular, the fosphenytoin cohort includes patients in status, those with head trauma, etc, and as a consequence is a cohort in which deaths, regardless of treatment, are expected.

Accordingly, I am not concerned about the number of deaths reported in

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[9] Dr. Feeney writes that "the character and location of the sensory disturbance described for Decadron and Hydrocortisone matches the dominant description in Cerebyx-treated subjects. With all 3 agents, patients describe a burning or itching which localizes primarily to the groin area."

association with the use of fosphenytoin. This judgment, however, is defended only by my personal intuition, no more, no less.

Safety and Common ADRs

This is largely a labeling display issue. The firm has studied Cerebyx® over a number of disparate conditions in different patient populations. It makes no sense in my view, to combine these experiences in an effort to provide a single, overall, table of untoward clinical event incidence. Instead, it makes far more sense to present the incidence within the various settings. We instruct the firm, within the text of labeling, how best to accomplish this goal.

Safety in Children

This important age group has not been evaluated; if approved, Cerebyx® is likely to be used in children, yet we do not have information on their handling of the product.

Safety in Use- overall considerations:

The extent of clinical experience with an investigational drug, the degree to which that experience is representative of the conditions under which the drug will be used if marketed, and the quality and kind of patient monitoring during the drug's clinical testing determine the strength and value of any warrant that may be offered about the safety of a drug at the time of its approval.

Obviously, the fewer the number of patients exposed, the less reliable any warrant about the drug; this applies both to risks that were and those that were not observed during the product's pre-marketing development.

This generic caveat applies to any regulatory conclusion that a drug is 'safe for use;' but it is especially applicable where Cerebyx® is concerned. First, because this product has been administered to relatively few individuals overall. The total numbers of subjects exposed are enumerated in the following table:

	NDA	SU 1	SU 2
Population			
Total Enrolled	849	861	994
Exposed to Fos	736	748	859
Cutoff Dates			
General Safety	Sept 1, 94	Feb 22, 95	Aug 1, 1995
Deaths/Serious AEs	Nov 18, 94	May 15, 95	Sept. 15, 1995

Of greater concern, Cerebyx® has been administered to even fewer under conditions of use where it is expected to cause the greatest number of problems: high rate intravenous infusion. Specifically, as of the last safety update, only 128 patients had been exposed to doses ≥15 mg PE/kg at an infusion rates of ≥ 150 mg PE/min and only 66 have been exposed to doses ≥ 20 PE/kg at infusion rates of ≥ 150 mg PE/min.

Whether or not this extent of clinical testing provides an adequate basis to allow the marketing of Cerebyx® under these conditions is a determination that turns on personal judgment, and, therefore, ultimately, the personal judgment of the agency official who has the delegated authority to act on the question, in this case, the Office Director.

Discussion of Options

Although the evidence provided by the sponsor is probably sufficient to allow some expert epileptologists to reach, responsibly, a conclusion that Cerebyx® has been shown to be safe for use under high dose, high rate conditions of use recommended in its proposed labeling, I cannot know whether most, or even a majority of experts, would reach the same conclusion.

Accordingly, the division has prepared an approval action letter because it believes such an action can be defended, although it is not necessarily the

action that any of us may individually prefer[10].

In any case, I could also defend an action approving the NDA under labeling that either 1) warns about the residual uncertainties concerning the safety of the high dose regimen, or 2) omits the high dose/high rate regimen on the grounds that there is insufficient evidence to ensure its safety.

Neither of these options is entirely appealing, however, because Cerebyx® is only able to deliver phenytoin as rapidly as Dilantin® injection under the high dose, high rate regimen, and, therefore, we could not be certain, under either of these options, that Cerebyx would be fully effective (or as effective as Dilantin® injection), when used in the management of status.

We could, of course, disapprove the NDA, arguing, as we did when it was first submitted, that more clinical experience (i.e., safe passage) with the product under the high intravenous loading dose regimen is required before we can conclude that it is safe in use regardless of the restrictions placed on its use in labeling. The argument being made here is that whatever the labeling limitations or restrictions applied, the product would, if marketed, be likely to be used under the high dose/high rate regimen, a regimen yet to be shown to be safe.

This would be a difficult regulatory position to defend, however, because we are only obliged, at least ordinarily, to determine whether or not a drug is safe for use under the conditions of use recommended in its labeling. In short, were it not for the status epilepticus indication, it would be easy to conclude that Cerebyx® has been shown to be safe for use. On the other hand, none of us is unaware of the extent of 'off label' use of marketed drug products and the potential for that use to cause harm.

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[10] Personally, I would clearly feel more comfortable with an approvable action if it were taken with the knowledge that 200, rather than 66 patients, had been exposed without serious incident to the highest dose and rate intravenous loading regimen. The problem, of course, is that I would take still greater comfort if there were 2000 such exposures.

Importantly, nothing in this discussion is intended to gainsay or undermine the potential advantages that may well be provided by Cerebyx®. An injectable form of phenytoin that is less locally irritating than Dilantin® (reasonably inferred from what we know but not proven) would be especially useful for intramuscular use. The point is that it is a matter of personal judgment whether the gains are sufficient to outweigh our residual doubts about its safety for use.

Finally, neither I, nor any member of the review team, to my knowledge, is so wedded to any single view of this matter that we are absolutely committed to one and only one course of action. To the contrary, this is a close decision and I can accept any of the 3 options enumerated. I am, as are members of the review team, available to discuss the matter further, as required.

2/9/96

Paul Leber, M.D.
2/9/96

NDA 20-450
HFD-100
Temple
HFD-120
Katz
Feeney
Fitzgerald
Fisher
Blum
Heimann
Nighswander
HFD-860
Harris
Miller
Baweja
Malinowski

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 20 1996

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Fosphenytoin, NDA 20-450 (Cerebyx)

TO: Dr. Paul Leber, HFD-120

I believe this application is approvable and that the available data and documented exposure are sufficient for a proding for a very familiar active moiety. The possibility remains, as you note, that some rare, "idiosyncratic" response to the short-liver parent molecule, or to a minor unsuspected metabolite of the parent, could occur, but a few 100 more patients will not resolve that question.

I have modified the letter slightly, I think still reflecting what was sought by the Division.

I have one regulatory, not scientific question: why is fosphenytoin considered an NME? Type 4 NDAs include new salts or esters of a previously approved active moiety. Although allowance is made for stable esters, especially where these are active (e.g., isorsorbide mono-odinitrate) that doesn't seem the case here, with the 15 minute half-life.

I have made a few labeling changes and note particularly the following changes and questions.

2 Pages
Purged

Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 22, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Reply to your memo of 2/20/96

TO: File, NDA 20-450 Cerebyx(fosphenytoin)
&
Robert Temple, M.D.
Director,
Office of Drug Evaluation 1

The Division's review team has reviewed the comments about the Cerebyx action presented in your memo to me of 2/20/96.

We take your point that the intravenous administration of Cerebyx under any dosing regimen cannot precisely reproduce the phenytoin input to the systemic circulation that is obtained with the direct infusion of phenytoin sodium at 50 mg/min. Accordingly, we have revised the dosing instructions so that the recommended regimen for the treatment of status is between 100 mg PE/min and 150 mg PE/min. This should result in an intermediate choice by many and that will be fine.

For the most part, we have otherwise made the changes in the labeling and letter as you requested, except for one or two places.

Dosing and Administration Section:

Here, we found your additional comments to be verbose and confusing. Accordingly, we simplified the instructions, providing the major points regarding iv use in a series of 4 brief bullets.

We did, however, incorporate the intent of your comments in this section in the Clinical Pharmacology Section.

Warning Section:

The instruction regarding the maximum rate of phosphenytoin infusion seems

unnecessarily confusing when it includes the phrase "at rates greater than 50 mg/min." We would prefer deleting the phrase. The call, however, is clearly yours and toward that end we provide two pages 6's, one with and one without the phrase.

Pharmacology:

I have allowed Ed Fisher and Glenna to repair and revise the pharm sections as they believe best. I find their changes reasonable and assume that you will as well.

Questions in the memorandum:

First, fosphenytoin is an ester, but not of phenytoin. It's an NME and we can take credit accordingly.

As to your other questions, I'm not sure that I can answer them in a meaningful manner; I'll try (John Feeney is my major source of inspiration and data on this).

4. How, if at all, renal and/or liver disease affects fosphenytoin to phenytoin conversion is unknown. The theory is that the free fraction of fosphenytoin is increased in the presence of hypoproteinemia.

5. Yes, because this is part of a regimen that will lead to the chronic use of phenytoin

#6. Dilantin is an ancient drug product--many things in its labeling got there the same way that they get into the labeling of all older drugs--in short. we don't know, and, don't have the resources available currently to find out.

I trust you can sign this approvable action as is; if not, let us know.

Paul Leber, M.D.
2/22/96

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	Third Safety Update
Correspondence Date:	April 12, 1996
Date Received:	April 15,1996

Background: This safety update consists of 2 volumes out of a 4 volume submission. The entire submission represents the sponsor's response to a recent Approvable Letter.

Exposure: The cutoff date for the last (second) safety update was September 15, 1995. This SU covers all deaths, serious AEs, and withdrawals for AEs that have occurred since then. Data are also provided from 2 studies of Fos which are being conducted under a separate IND Events from all studies are summarized through March 8, 1996.

It appears that there is only one ongoing study in status epilepticus. Only 5 additional pts have been enrolled since the last (second) SU. Of these 5, no deaths, serious AEs, or withdrawals because of serious AEs have been reported. Therefore, this SU reports almost entirely on the experience of Cerebyx in stroke.

Deaths: 10 deaths (on placebo or Fos) occurred out of 79 pts enrolled in stroke studies. We know that 1/10 deaths occurred on Fos and 1/10 deaths occurred on placebo. Because the blind has not been broken in the other stroke study, we do not know the treatment assignment of the 8 other deaths. All deaths appear related to the stroke itself or the sequelae of stroke. None of the deaths were attributed to Fos.

Serious, Nonfatal AEs: 5 pts had serious AEs that were nonfatal. One of these, severe hypotension related to Cerebyx was reported as an IND safety report on March 12, 1996 and is outlined in the next paragraph. The blind was not broken for the other AEs, but a review of them suggests that none would be considered attributed to study drug.

Pt 113 in Study 25, a 51-yr-old woman, developed an absolute decrease of 67 in her systolic pressure during a loading dose of Cerebyx for treatment of stroke. BP was 142/86 and dropped to 75/50. The investigator classified the event as life-threatening, although the BP returned to baseline with fluids.

Withdrawals Due to AEs: 5 pts withdrew due to AEs. 3/5 occurred in a completed stroke study so that we know all 3 received Cerebyx. The other 2 occurred in an ongoing stroke study where the blind has not been broken.

Patients 111 in Study 19 in stroke had the infusion stopped (note that the rate was 50 mgPE/min) because of perineal burning and itching. The event was called severe and occurred after only 27% of the injection was given. Symptoms resolved after13 minutes followed an hour later by recurrence of mild itching for 5 min.

Patients 118 in Study 19 in stroke had the infusion stopped (note that the rate was 50 mgPE/min) because of perineal itching. The event was called moderate and occurred after 16% of the injection was given. Symptoms resolved in 5 minutes.

Other events were mild hypotension, severe bradycardia (treatment assignment unknown), and atrial fibrillation in a pt with a history of AFib (treatment assignment unknown).

Summary:

Burning, itching, bradycardia, hypotension are all described in proposed labeling. Therefore, the safety profile of Cerebyx has not changed with the addition of this safety update.

John Feeney, M.D.
Medical Reviewer
April 23. 1996

cc:
HFD-120
IND 28,217
HFD-120/Leber/Katz/Feeney/Nighswander

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	Proposed labeling revisions
Correspondence Date:	April 12, 1996
Date Received:	April 15,1996

Background: The entire 4-volume submission represents the sponsor's response to a recent Approvable Letter. Two volumes represent the requested safety update and are reviewed in a separate document. The other two volumes represent the proposed labeling revisions along with supporting documentation.

Proposed Labeling Changes: Only major changes are addressed here.

Two pervasive changes made by the sponsor are the correct insertion of the word **sodium** whenever describing equivalent doses of Cerebyx and parenteral Dilantin. Phenytoin as the free acid (Dilantin-30 Pediatric and Dilantin-125 Suspensions and Dilantin Infatabs) would have a different dose equivalence. The sponsor would also like to delete the **PE** used throughout labeling to refer to doses of Cerebyx. The very fact that different phenytoin products already on the market provide different amounts of phenytoin for equivalent weight-based dosing regimens would support the use of the PE notation throughout labeling to point out the equivalence only to phenytoin sodium and not to the free acid.

Issues related to formate and phosphate have been addressed by the sponsor by presenting data from Study 27, a PK study of the high-dose, high-rate loading dose. Some of this data was presented in submissions (specifically requested by me) dated **May 2 and May 8, 1996**. This information is discussed in **Appendix I.**

5 Pages
Purged

John Feeney, M.D.
Medical Reviewer
June 17. 1996

cc:
HFD-120
IND 28,217
HFD-120/Leber/Katz/Feeney/Nighswander

CLINICAL REVIEW AND EVALUATION

NDA 20-450

Cerebyx (fosphenytoin)

Reviewer:	John Feeney, M.D.
Date:	February 1, 1996
Sponsor:	Parke-Davis
Indication:	Epilepsy
NDA Submission Date:	February 23, 1995

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Overview

Cerebyx (fosphenytoin) has been developed by Parke-Davis

The basis for an approval action on this NDA is the demonstrated bioequivalence of IV Cerebyx and IV Dilantin. When Cerebyx was administered at an IV rate that was three times greater on a molar basis than the rate of Dilantin, bioequivalence based on free phenytoin levels was demonstrated.

It became clear during the review of this NDA that confusion readily arises in discussing the dosage of Cerebyx. The molecular weight of Cerebyx is 50% greater than Dilantin, so that 150mg Cerebyx delivers the same molar amount of phenytoin as 100mg Dilantin. Therefore, an infusion rate of 75mg/min Cerebyx delivers the same molar amount of phenytoin as 50mg/min Dilantin (the maximal labeled rate for Dilantin). However, the bioequivalent rates (as defined above for free phenytoin levels) would be 225mg/min Cerebyx and 50mg/min Dilantin.

Since the use of Cerebyx will, by design, be temporary with conversion to oral phenytoin soon thereafter, I believe that Cerebyx dosing should be expressed in phenytoin equivalents in labeling. Thus, 150mg Cerebyx would be expressed as 100mg phenytoin equivalents (PE). This eliminates the one and only step in converting total oral phenytoin dosing to parenteral Cerebyx dosing, but still leaves one step in converting the Dilantin loading dose rate (50mg/min) to the bioequivalent Cerebyx loading dose rate (150mg/min phenytoin equivalents). By not expressing Cerebyx as PE in labeling, I believe there will be considerable confusion in dosing during the first few years of general use.

Cerebyx is a phosphate ester of phenytoin. The bioavailability of phenytoin after IM Cerebyx is 100% with good local tolerability in over 300 patients exposed. The sponsor contends that IV Cerebyx is better tolerated at the injection site than IV Dilantin. This latter point is supported by the normal volunteer studies when injection site irritation is examined in Cerebyx and Dilantin treated patients at bioequivalent rates. The active-control trials in patients did not adequately control for dose and rate betweeen Cerebyx and Dilantin patients, so that no additional comparative data on IV injection site irritation is yielded by those studies. Study 26 may provide comparative information along these lines, but we are not yet in possession of that final study report.

Cerebyx is rapidly converted to phenytoin with a half-life of 15 minutes. The two byproducts of this conversion are phosphate and formaldehyde. The theoretical safety concerns of formaldehyde formation have been addressed by the sponsor and are the subject of much discussion in the pharm/tox review of Dr. Fisher. On page 60 of his review, Dr. Fisher notes (page 60 of his review) that peak plasma formaldehyde levels would be predicted to be 5.4mg/L, with levels returning to background levels (2.6mg/L) within 20 minutes. In fact, formaldehyde levels are apparently difficult to measure in plasma, and beyond this, the toxicity of formaldehyde may in large part be due to its metabolism to formate as occurs in methanol poisoning.

Formate levels that produce optic nerve pathology are only 10-20 X background levels. Maximal formate levels were predicted by the sponsor to be no higher than background levels. This prediction has not been verified with empiric data to date. Formate levels were not measured in preclinical toxicity studies; in fact, models of formate toxicity in non-primates can only be produced in the presence of folate deficiency. Normal formate levels were measured in 4 normal volunteers, but at a Cerebyx-exposure much less than will occur with the standard loading dose. In the absence of formate levels in adequately loaded subjects, the safety margin cannot be stated.

Not addressed by the sponsor or the pharm/tox review is the phosphate load with Cerebyx. The loading dose of Cerebyx delivers 75mg elemental phosphorus. Assuming retention in the plasma, the theoretical increase in serum phosphorus would be 2mg/dL. If the calcium-phosphorus product

exceeded 60-70 in a given patient, the theoretical concern would be calcium deposition in soft tissues and a possible transient decrease in calcium. The sponsor has measured ionized free calcium at the end of a 7 minute loading dose in 5 volunteers and found these levels to be normal. Obviously, this is a small experience which should probably be expanded. Additionally, the sponsor should be asked to assess the distribution of the phosphorus load in varying states of decreased glomerular filtration. Labeling should certainly make note of this issue, especially in dialysis patients. (The sponsor performed a study in dialysis patients, but used a small loading dose administered over 30 minutes.)

The safety database accrued is complex and makes any exptrapolation of the results difficult. Several important points follow:

First, the two active-control trials with IV Dilantin (Studies 15 and 21) do not allow any direct comparisons between treatments. Both trials incorporated IV loading doses (one of the two also included maintenance IV dosing beyond the IV load) and I believe the loading dose presents the biggest safety concern in the use of Cerebyx. However, neither trial provided for Cerebyx and Dilantin to be administered at the bioequivalent rates. (Study 26 may allow for some direct comparisons, but we do not have the final study report yet.)

Second, as a general rule over the entire database, the high-dose, high-rate Cerebyx patients were also some of the sickest patients, usually patients with status epilepticus. While this may in fact mirror the intended usage of high-dose, high-rate Cerebyx, it makes the interpretation of the safety data more difficult.

Third, the patients exposed to Cerebyx tended to fall into one of two categories: 1) seriously ill patients with status epilepticus or pending neurosurgery and 2) relatively stable patients with epilepsy. The net effect of this is that the safety data from one group cannot really be merged with the other.

Normal volunteer studies were in general limited to escalating IV "loading" doses. Since the population of normal volunteers is relatively homogeneous, I believe it provides important information on rate-related adverse events, making some comparisons between Cerebyx and Dilantin treated subjects possible. For instance, one unique adverse event that

occurs with Cerebyx is a sensation of generalized itching or tingling which is variously coded as pruritus or paresthesia. In the normal volunteer studies, this phenomenon can be seen to be rate-related for both Cerebyx and Dilantin, but with a much higher incidence with Cerebyx at bioequivalent rates of administration.

Similarly, in the normal volunteer studies, injection site pain and injection site reaction are seen to be rate-related for IV Dilantin and occur only rarely for Cerebyx at any rate.

The sponsor has proposed use of Cerebyx for up to 14 days. However, only a few patients were exposed for longer than 5 days. I believe labeling should reflect the database with use allowed for 5 days or less.

For labeling purposes, the sponsor proposes to present adverse event data separately for the 3 controlled trials. Since the AE profiles in these trials only reflect the population studied (seriously ill neurosurgery patients vs stable epilepsy patients) and since the standard deviation around any point estimate from a given trial must be exceedingly large, I would argue to discard these tables from labeling and bring forward the descriptive list of AEs in the parenteral Dilantin labeling.

Finally, the sponsor has not fully addressed the unique adverse event of pruritus/paresthesia seen with Cerebyx. In particular, the ISS often uses descriptive language to the effect that this AE was "usually transient." In my review, I could not ascertain the outcome of all cases of this AE. I found no specific mention of a case of pruritus/paresthesia that persisted, but I would request the sponsor to directly address the question of reversibility of this AE. The second safety update (November 1995) added 100 individual exposures to the high-dose, high-rate experience with Cerebyx and confirmed the frequent occurrence of pruritus in that situation. The sponsor could provide more information on the experience of these individuals with the sensory disturbance.

Conclusions:

Cerebyx is approvable. The following additional information is needed before a final approval action can be taken:

1. The sponsor should provide a more complete description of the sensory

disturbance caused by Cerebyx, to include the reversibility over time.

2. Levels of phosphorus, magnesium, and free calcium should be measured at frequent timepoints during a 7 minute loading dose of Cerebyx and correlated with the character of the sensory disturbance.

3. Formate levels should be measured after a loading dose of Cerebyx. Since the breakdown of formate is folate dependent, and because folate deficiency may be common in the population treated with Cerebyx (alcoholics and/or patients on chronic phenytoin therapy), some attempt should be made to measure formate levels in a folate deficient population after a loading dose of Cerebyx.

The advantages of Cerebyx over parenteral Dilantin are:

1. Given IV, it produces fewer local reactions, can be given in one-third the time of Dilantin, and may be more compatible with other IV solutions.

2. It can be given IM with predictable absorption and fewer local reactions.

Peripheral Sensory Phenomena

Background: We refused to file the original NDA submission for Cerebyx because of the minimal safety database accrued at high dose, high rate (SE dosing) infusions. The sponsor only slightly improved upon this at the time of the resubmission. Again, the first safety update only minimally improved upon this. The second safety update in late 1995 more than doubled the exposure to SE dosing.

Looking only at the NDA submission, it became clear from normal volunteer studies that a dose- and rate-related sensory disturbance occurred with IV Cerebyx. In patient studies, the bulk of patients exposed to SE dosing were too obtunded to report sensory disturbances because they were in fact SE patients. Therefore, in patient studies, a dose- and rate-related sensory disturbance was less obvious.

The second safety update in late 1996 included the results of Study 26 performed from April 1995 to June 1995. Ninety patients were added to the SE dosing database. Half the patients were epilepsy patients (not SE patients and not neurosurgery patients) and would not be expected to be obtunded. Likewise half the patients reported pruritus. Because we are not in possession of all the information from Study 26, we cannot ascertain the exact proportion of patients who were alert enough to report sensory disturbances. It is possible, given the information provided, to assume that all awake patients in Study 26 experienced some degree of sensory disturbance; it is also possible that only half did.

These were not trivial disturbances. The infusion was interrupted or discontinued for 13/44 (30%) patients experiencing pruritus. The intensity was rated severe for 6/44 (14%) patients; moderate for 17/44 (39%) patients; and mild for the remainder.

The mean onset time was 2 minutes for these 44 patients. By the time of follow-up, outcome was unknown for 1/44 patients. Resolution of sensory symptoms is reported for all the rest. Because time-to-resolution is referenced to end of infusion, and because we are told that infusions were slowed or stopped because of pruritus in a third of patients, we cannot determine what happens in the absence of altered rate and time of

infusion. It sounds like most patients improve within 5-10 minutes of stopping the infusion (12-17 minutes from start of infusion, assuming the infusion is given over the prescribed 7 minutes). A fourth of patients have some degree of disturbance beyond this point (median, 1 hour).

The second safety update also mentioned the results of Study 27, a 16-subject PK and safety study. 75% of these normal volunteers experienced pruritus; 75% of these normal volunteers experienced p sthesia. Four of the 16 subjects (25%) reported "severe" pruritus.

Significance: Just based on what we know about this phenomenon, it is clear that the natural history of the disturbance must be elucidated more clearly in order to provide for the safe use of this drug. For instance, the intensity of symptoms for those patients who experience symptoms beyond one hour of dosing has not been provided to us. Do some patients have severe pruritus for days or do only mild symptoms persist beyond one hour ? Since many patients who receive IV loading with Cerebyx will not need rapid loading, labeling will need to reflect a rate for those patients which results in minimal discomfort.

Also, could the pathophysiology that underlies the sensory disturbances with SE dosing of Cerebyx herald some more serious pathology ?

In awake patients treated with SE dosing of Cerebyx, patient reporting of sensory disturbance could lead to lowering of rate. In obtunded patients, this margin of safety has been removed.

Example of Foscavir (foscarnet): Foscavir is an example of a drug where the onset of sensory disturbance does herald more serious problems, specifically with hypocalcemia. Foscavir was developed for IV administration for the treatment of CMV retinitis in the mid-1980s. Early on it became clear that many patients experienced distal and perioral paresthesias, tetany, and seizures. The constellation of symptoms and signs was identical to that seen with hypocalcemia and, in fact, total serum calcium levels were low in some patients. Cases of fatal hypocalcemia have been reported with this drug.

Experience with Foscavir has demonstrated that the labeled loading infusion may cause decreases in ionized free calcium even though total

serum calcium remains normal.[1,2] The mechanism of this ionized hypocalcemia is believed to be **chelation** of free calcium by foscarnet itself (structurally appearing as a phosphate moiety with a carboxyl group substituted for an oxygen). Foscarnet is excreted unchanged in the urine, presumably carrying calcium with it. There is no evidence that foscarnet is broken down to phosphate, and there is no evidence of phosphate precipitating out of solution with calcium. While foscarnet itself is toxic to renal tubule cells, there is no evidence of nephrocalcinosis (deposition of calcium-phosphate precipitates in the kidney) or other soft tissue calcium deposition.

The current labeling for Foscavir states (WARNINGS; Mineral and Electrolyte Imbalance) "Therefore, patients should be advised to report symptoms of low ionized calcium such as perioral tingling, numbness in the extremities and paresthesias. Physicians should be prepared to treat these as well as severe manifestations of electrolyte abnormalities such as tetany and seizures. The rate of Foscavir infusion may affect the transient decrease in ionized calcium. Slowing the rate may decrease or prevent symptoms."

Possible Mechanisms of Cerebyx-Induced Sensory Disturbance: There are many ways that Cerebyx could cause sensory symptoms. **Any explanation has to account for a lack of symptoms at bioequivalent dosing regimens of parenteral Dilantin.** Perhaps IV fosphenytoin (the parent compound) alone causes sensory disturbance. Or perhaps IV fosphenytoin results in a distribution of phenytoin in tissues that is different from the distribution that results from parenteral Dilantin. Formate and phosphate are the two byproducts of fosphenytoin metabolism. Either one of these could cause transient sensory disturbances either directly or via an intermediate step.

A. Formate: Note that several steps are necessary in the metabolism of Cerebyx before the formation of formate. Given the almost immediate

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[1]Jacobson, Gambertoglio, Aweeka, Causey, and Portale. Foscarnet-induced hypocalcemia and effects of foscarnet on calcium metabolism. J Clin Endocrinol Metab 72: 1130-1135, 1991.

[2]Lor and Liu. Neurologic sequelae associated with foscarnet therapy. Ann-Pharmacother 28(9): 1035-7, 1994.

onset of the sensory phenomenon, it seems unlikely that formate would be the causative agent.

B. Phosphate: When I investigated the degree of phosphate loading with Cerebyx, I was impressed. Approximately 1 gram of phosphorus is ingested each day in an average United States diet. Of this, 700mg is absorbed. In comparison, an IV loading dose of Cerebyx includes 75mg of phosphorus; the SE dosing regimen would introduce the fosphenytoin over 7 minutes. One outdated regimen for treating hypercalcemia[3] was to give phosphates IV at a dose of 20 to 30 mg of elemental phosphorus per kg over 12 to 16 hours. In a 70kg person, this would result in 100mg/hr. A stated hazard of this therapy was extraskeletal calcifications, including nephrocalcinosis with resulting renal failure.

C. Sponsor's Comments on Mechanisms: The sponsor first addresses underlying mechanisms of these sensory disturbances from Cerebyx on the third-to-the-last page of the second safety update. "Although the underlying mechanism of fosphenytoin-induced pruritus and paresthesia is unknown, similar symptoms have also been reported for other phosphate-ester prodrugs and for foscarnet." The "other phosphate-ester prodrugs" referenced by the sponsor are Decadron and Hydrocortone.

Curiously, the character and location of the sensory disturbance described for Decadron and Hydrocortone matches the dominant description in Cerebyx-treated subjects. With all 3 agents, patients describe a burning or itching which localizes primarily to the groin area.

By my calculation, IV loading doses of Decadron and Hydrocortone provide 1/20th-1/10th the elemental phosphorus provided by a loading dose of Cerebyx. Therefore, assuming phosphate is the common link, it would not be surprising that Cerebyx would produce more severe burning and itching.

Calcium Metabolism: Calcium is usually measured in the clinic as total serum calcium (normal 9-10.4mg/dL). About 50% of serum calcium is ionized and 10% is complexed with citrate, phosphate, bicarbonate, and lactate. The rest (40%) is protein-bound, mainly to albumin. The concentration of serum calcium is reflected in the proportion: [Ca] x

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[3]Renal and Electrolyte Disorders Schrier (editor). Little, Brown and Company, 1976; p 198.

[Phosphate]/[Calcium-Phosphate]. The normal range for phosphorus is 3-4.5mg/dL. The product of [Ca] (mg/dL) x [Ph] (mg/dL) therefore normally approaches 50. When the product approaches 60-70, most textbooks raise concern about precipitation with resultant soft tissue calcification, to include nephrocalcinosis.

By weight, phosphorus represents 15/406 or 3-4% of fosphenytoin so that a loading dose of Cerebyx delivers 75mg phosphorus. If this load remained in the vascular space, the serum phosphorus could theoretically rise by 2mg/dL, thereby raising the calcium-phosphorus product to 70. This would drive the equilibrium toward calcium-phosphate and tend to lower calcium. As with Foscavir, the ionized free calcium would probably reflect this drop better than total serum calcium values.

Note, however, that hypocalcemia typically causes a tingling sensation around the face and in the hands, not a burning in the groin as we have seen in many Cerebyx patients.

Although the sponsor has not acknowledged this theoretical concern, it must have crossed their minds. The second safety update briefly summarizes an open-label safety and PK study performed in June 1995 which incorporated 16 healthy subjects, each given a single SE dose of Cerebyx (Study 27). In reviewing individual lab listings for these subjects, I notice that 9/16 subjects had ionized free calcium levels performed at 18 minutes, while 5 of the same subjects had ionized free calcium levels performed at 8 minutes. None of the levels are remarkable, either when viewed as absolute values or as change from baseline. Certainly these measurements are not comparable to those reported for Foscavir. However, note that the SE dose of Cerebyx is delivered over 7 minutes. With only 5 ionized free calcium level checked at 8 minutes and the rest performed at 18 minutes, I do not believe we can rule out the occurrence of a transient hypocalcemia during the 7 minute infusion. Further, the clinical status of these 5 (or 9) subjects is not stated. Were they subjects with or without pruritus ?

In the absence of more data on ionized free calcium, I reviewed total calcium levels in Study 26. Note that, aside from the 8 and 18 minute clinical labs in Study 27, I am not aware of clinical labs in any other studies being performed early enough to be informative on this subject. Still, 25% of Cerebyx-treated patients in Study 26 are listed with low

calcium levels. Since this does not differ from the Dilantin-treated group, I would doubt it is important.

A review of all deaths and serious AEs in Study 26 raises no particular concerns regarding other manifestations of hypocalcemia. In particular, I do not see any description of seizures occurring in proximity to Cerebyx infusions, cardiac rhythm disturbance, or tetany. In fact, the profile of serious AEs appears roughly the same for Cerebyx and Dilantin treated patients in Study 26. Again, though, **patients in Study 26 "had near normal levels of consciousness to report adverse events and infusion tolerance" (2nd safety update,p35) which may not mirror the SE population most likely to receive the SE doses of Cerebyx. Patients in Study 26 could report sensory symptoms early and thereby cause their rate to be lowered.**

Summary:

1. The natural history of the sensory disturbance caused by Cerebyx at SE dosing has not been fully characterized. In particular, we do not know if the intensity (severe for many) correlated with duration (many hours for some), especially in the absence of dose and rate reductions.

Relevant to this last point is that the number of known obtunded patients given SE dosing regimens remains small. (We don't know the level of consciousness for all Study 26 patients.) For these patients, the longterm follow-up was short, 3-5 days by protocol. More obtunded patients, given SE dosing without rate reductions and followed for longer periods of time, would add a margin of safety to the Cerebyx experience. (Perhaps Study 26 contains some of this information.) Pertinent to this, the patients in Study 16 who were given the SE dosing regimen could have their status at the 3-5 day visit teased out and presented separately. Patient 2 at Center 8 has pruritus beginning on day 2, continuing, and not yet recovered, but the duration of follow-up is not clearly stated. The "mild itching feeling" reported for Patient 22, Center 9 in Study 16 on Day 4, just after experiencing post-ictal psychosis is intriguing along these lines.

2. One very plausible theory for the sensory disturbance (one which the sponsor has begun to investigate in Study 27) is a drug-induced transient drop in ionized free calcium. I believe this needs to be investigated more

comprehensively, prior to drug approval. This could be accomplished by checking free calcium levels more frequently, at earlier time points, and in more patients. There may be value in also checking magnesium levels at the same time, since magnesium is another example of a divalent cation. Sensory symptoms could be correlated with calcium and magnesium levels. (Indeed, presenting free calcium levels for 9/16 subjects in Study 27 raises the concern that values are not presented for the subjects with sensory disturbances.)

Relevant to the this, the sponsor could measure serum phosphate levels in closer proximity to the infusion since phosphate levels would predict potential for hypocalcemia.

Formate

For each mmole of Cerebyx administered, one mmole of formate is produced. Therefore, a loading dose of Cerebyx delivers about 5 mmoles of formate to the individual. Assuming all the formate stayed within the circulation (5 liters), a maximal theoretical increase of 1 MMOL/L in background formate levels could occur. This was recognized at the time the IND for fosphenytoin was first filed in 1986 (see the pharm/tox review of Dr. Fitzgerald from 1986).

In 1986, the sponsor at that time) measured formate levels in 4 subjects administered a small loading dose of fosphenytoin over 30 minutes (half as much fos as constitutes a current loading dose, given over a greater time interval). Background levels were 0.5 MMOL/L and did not increase. Since then, formate levels have not been measured in any human studies of Cerebyx.

Given the measured background levels in that study and the maximal theoretical increase, the maximal theoretical level that could be achieved after a Cerebyx loading dose is 1.5 MMOL/L.

In monkey studies referenced by Dr. Fisher in the current pharm/tox review, formate levels as low as 7 MMOL/L could cause the characteristic optic nerve lesions of formate toxicity (implied, but not clearly stated, is that levels below 7 MMOL/L did not cause the lesion in the monkey studies).

There are ongoing investigations into the mechanism of methanol toxicity, due in part to interest in methanol as an automotive fuel. Methanol is converted to formaldehyde and then to formate. Investigators have found that rats, normally resistant to methanol toxicity, can be made sensitive

to methanol toxicity by creating a state of folate deficiency.[1,2] This folate-reduced (FR) rat model has been the subject of some recent studies on methanol toxicity. In this model, 2.5-3.0 MMOL/L formate probably represents the NOEL (personal communication from Robert Louis-Ferdinand to Dr. Ed Fisher). Formate levels of 7-10 MMOL/L are associated with changes in the electroretinogram of the FR rat and with the histological abnormalities in the optic nerve.

In the NDA, preclinical studies were performed in non-primates which are not susceptible to formate toxicity unless they are made folate deficient. Formate levels were not measured in these studies.

The human clinical literature on methanol toxicity includes reported formate levels in patients who died, suffered visual loss, and who survived without deficits.[3,4] Formate levels as low as 2-4 MMOL/L are reported in some fatalities. Unfortunately, the timing of these levels in relation to the methanol exposure are not always clear. Some reported formate levels may be peak levels while others are trough levels. Levels of 10 MMOL/L and above do seem to consistently be associated with poor outcomes. Levels below 10 have outcomes that vary from complete recovery to death. Based on the information from monkey and FR rat studies, I believe the human levels below 10 in association with poor

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[1]Lee, Garner, and Terzo. A rat model manifesting methanol-induced visual dysfunction suitable for both acute and long-term exposure studies. Toxicol.Appl.Pharmacol. 128: 199-206, 1994.

[2]Garner, Lee, and Louis-Ferdinand. Muller cell involvement in methanol-induced retinal toxicity. Toxicol.Appl.Pharmacol. 130: 101-107, 1995.

[3]Brown-Woodman, Huq, Hayes, Herlihy, Picker, and Webster. In vitro assessment of the effect of methanol and the metabolite, formic acid, on embryonic development of the rat. Teratology 52: 233-243, 1995. (See their Table 9 for a range of reported formate levels in human methanol toxicity.)

[4]McMartin, Ambre, and Tephly. Methanol poisoning in human subjects: Role for formic acid accumulation in the metabolic acidosis. Am.J.Med. 68: 414-418, 1980.

outcomes may simply represent trough levels in patients who experience much higher levels at other times in their clinical course.

Folate-deficient populations are a topic of some discussion in the literature on methanol toxicity. Alcoholism, pregnancy, and chronic phenytoin therapy are all states known to be associated with folate deficiency. Treatments that alter folate metabolism, such as dietary manipulation, nitrous oxide, and methotrexate, have been shown to modify methanol toxicity in monkeys and rats. Methanol-derived levels of formate are higher in folate-deficient monkeys than in normal monkeys after similar exposures to methanol.[5] These authors found that elevations in formate levels after very high inhalation exposures, whether in normal or folate-deficient monkeys, were only a fraction of background formate levels.

Acidosis: Severe methanol toxicity is associated with a severe acidosis, as well as high formate levels. To quote one paper on methanol poisoning, "Formate accumulation occurs in a manner reciprocal to the depletion of bicarbonate."[4] When searching the line listings for Study 27 in the recent safety update, I found fairly complete data on bicarbonate levels from the 16 subjects given loading doses. These levels were collected at regular 30 minute intervals. For the 16 subjects entered, many of them showed some small decrement in bicarb with the nadir occurring at different times for different subjects. The biggest decrement occurred for subject 16, with a baseline bicarb of 25.4 and an end-of-infusion reading of 18.6. (19-26MMOL/L is given as the normal range.) It is unclear if these small decrements represent normal variability over time or some consistent effect of the infusions.

I wonder if the decrements seen in bicarbonate in Study 27 might be used as markers for elevations in formate levels. Again, the sponsor has not specifically called attention to the existence of the bicarbonate data or to its significance. (It is not clearly stated why the bicarb levels were checked in the first place.)

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[5]Dorman, Moss, Farris, Janszen, Bond, and Medinsky. Pharmacokinetics of inhaled [^{14}C] methanol and methanol-derived [^{14}C] formate in normal and folate-deficient cynomolgus monkeys. Toxicol.Appl.Pharmacol. 128: 229-238, 1994.

Labeling for Cerebyx will have to reflect the fact that patients with status epilepticus usually have an underlying metabolic acidosis, the degree of which varies with the severity of the status and the cause of the status (see Patient 11, Study 16; multiple drug overdose), and that Cerebyx may add to this derangement.

Anion Gap: If there is a transient decrease in bicarbonate in the absense of a change in sodium and chloride, we have defined an increase in the anion gap. Formation of formate and/or phosphate loading could increase the anion gap. For subject 16 in Study 27, the anion gap at the end of the infusion was 16 with a normal of 8-16.

Sensory Symptoms: In the animal toxicology studies, Dr. Fisher has not seen any evidence of severe sensory symptoms such as writhing. If the animals experience the same phosphate load as humans (or slightly greater), and if phosphate is the origin of sensory symptoms, some painful behavior would have been expected. Since we know that formate metabolism is one area where these non-primates differ from humans in Cerebyx-processing, the question arises whether formate accumulation in humans could be contributing to the sensory disturbance.

Summary:

1. Formate levels have not been measured in humans after a loading dose of Cerebyx.

2. Formate levels have not been measured in folate-deficient humans after a loading dose of Cerebyx.

Introduction

A. Administrative History

Following is a brief chronology of the IND and NDA:

1984	
1986	files IND for Fos
1990	transfers IND tc
1990	transfers IND to Warner Lambert/Parke-Davis
1991	Orphan drug designation for grand mal status
5/91	IM clinical studies begin
2/92	IV clinical studies begin
7/94	NDA filed
9/94	Refuse to file letter
2/95	Resubmission of NDA
6/95	First safety update
10/95	Second safety update

The basis for the refuse to file action in September 1994 was the small number of patients and volunteers treated with Fos at a rate of 150 mg/min PE. Only 4 pts with status epilepticus had been treated at that rate while about 20 normal volunteers had been treated at that rate.

The sponsor continued to enroll pts in an ongoing status epilepticus study after the NDA was filed. On the basis of the increased numbers of pts treated as well as a recalculation of infusion rates for some previously-treated pts, it was agreed that the sponsor would resubmit the NDA in 1995.

B. Material Utilized in Review

The NDA dated July 14, 1994 and received July 15, 1994 included 93 volumes. Volumes 1.1, 1.47-1.72, and 1.89-1.92 from that submission were used for purposes of this review.

After the refusal to file, a resubmission dated February 22, 1995 and received February 23, 1995 was submitted. The resubmission included 15 volumes. Volumes 3.1 and 3.9-3.12 from the resubmission were frequently used for purposes of this review. Those volumes included a rewritten Integrated Summary of Safety and rewritten study reports for Studies 982-15, 982-21, and 982-16.

The 4-month safety update dated June 22, 1995 and received June 23, 1995 was also used for this review. At my request, Tables 5 and 6 from the safety update were changed by the sponsor and submitted September 14, 1995.

The FDA Biopharm Review is also integral to the review of this NDA.

C. Background

Fosphenytoin Sodium (Fos) is the disodium phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin. It is a prodrug of phenytoin. It is rapidly and completely converted to phenytoin in vivo by ubiquitous phosphatases. Because of the phosphate ester, 150 mg Fos yields 100 mg phenytoin sodium. In this report, doses of Fos and dose rates of Fos will always be expressed as phenytoin equivalents (PE) as opposed to actual mg Fos.

According to the sponsor, the presumed advantages of Fos over parenteral phenytoin are:

- pH 8.8 as opposed to pH 12 of Dilantin
- freely soluble and stable in common IV fluids
- can be used IM
- shorter administration times; can be given at 150 mg/min while Dilantin is limited to 50 mg/min
- minimal tissue trauma at injection site (presumably due to lower pH
- no cardiovascular toxicity including hypotension

While shorter administration times could be a distinct advantage in emergent situations, it will be seen below that this is actually a necessity in order to meet bioequivalence standards based on free phenytoin levels after IV administration.

The relative local injection site toxicities and cardiovascular toxicities of Fos and parenteral Dilantin remain a topic for this review.

In fact, this NDA is unique in many ways. First, there are no controlled trials to support the efficacy of Fos. The "controlled trials" submitted were really not designed to show a difference between treatment groups on a protocol-specified efficacy outcome. The majority of patients studied were not having seizures, but were only at risk for seizures for one reason or another.

Secondly, the bioequivalence data submitted in support of this application really only applies to the isolated instance of IV loading. To my knowledge, no bioequivalence data for IV maintenance dosing, IM loading, or IM maintenance dosing has been submitted.

Thirdly, the limited safety database submitted in support of this application can be partitioned in two ways. The first way partitions the data by route of administration, IV versus IM. (In addition to the systemic toxicities that could be part and parcel of the route-determined bioavailability, there exists the route-specific local toxicities.) The second way partitions the data by loading versus maintenance dosing.

While the safety of a loading dose also speaks to the safety of a maintenance dose by the same route of administration, the converse is not true. Because of this last point, I have divided the patient safety database as seen in the table below. Subjects in normal volunteer studies are not included in this table. Since almost all normal volunteer studies (n=148 Fos-exposed subjects) were single loading dose studies, these studies would be expected to add information primarily to the IV loading group.

	Loading	Maintenance	Loading Plus Maintenance
IV Route	181	88	181
IM Route	178	297	357

Note that the definition of "Loading" for purposes of such a table can be complicated. We could look only at the "bioequivalent" IV loading dose,

with a very precise rate and total dose. Or we could include anyone with a total dose of 20mg/kg PE given over an hour or less (a subacute loading dose). Or we could include anyone with the "bioequivalent" rate even if the total dose was as low as 10mg/kg PE. Interestingly enough, for the IM route, a bioequivalent loading dose cannot be defined because parenteral Dilantin is rarely given IM. The systemic bioavailability of IM Fos is reported to be 100%

D. Proposed Directions for Use

The proposed labeling seeks an indication of Fos for short-term parenteral use for up to 14 days:

- o for status epilepticus
- o for the treatment or prophylaxis of seizures in patients with epilepsy or in neurosurgical patients
- o as a substitute for oral phenytoin when oral administration is not feasible

The Dosage and Administration Section of the proposed labeling describes 4 situations for use:

1. IV loading in status epilepticus
2. IM or IV loading for treatment or prophylaxis
3. IM or IV use for maintenance therapy
4. IM or IV use for temporary substitution for oral Dilantin

For status epilepticus, "the standard loading dose is 22.5 to 30 mg/kg (15-20 PE) infused at 150 to 225 mg/min (100-150 PE) in adults ... with vital signs ... and cardiac rhythm (ECG) monitored during and immediately after the infusion ... Cerebyx (19.5-25.5 mg/kg or 13-17 PE) administered at 225 mg/min (150 PE) is bioequivalent to an equimolar dose of Dilantin administered parenterally at 50 mg/min."

Further, "Guidelines for the treatment of status epilepticus suggest that patients still in status epilepticus after a phenytoin loading dose of 20 mg/kg may receive additional loading doses of 5 mg/kg up to a maximal dose of 30 mg/kg. **Based on these guidelines**, patients treated with Cerebyx still in status epilepticus after a Cerebyx loading dose of 30 mg/kg (20mg PE) may receive additional Cerebyx loading doses of 7.5 mg/kg (5mg PE) up to a maximal Cerebyx dose of 45 mg/kg (30mg PE)."

The sponsor has studied the loading doses above and, **based on free phenytoin concentrations,** has found that Cerebyx infusions at 225 mg/min (150mg PE) are bioequivalent to standard Dilantin loading doses. However, if the standard of care for **refractory** status includes additional boluses, the sponsor has not studied the PK of Cerebyx at these higher doses.

E. Foreign Marketing

Fosphenytoin is not marketed in any country.

F. Related INDs

Fosphenytoin is being developed under 2 separate INDs: IND epilepsy and IND

PK Studies

IM Fos Maintenance

The bioavailability of phenytoin, given as IM Fos, is 100%. In contrast, the bioavailability of phenytoin, given as Dilantin Kapseals is 90%.

Bioequivalence Studies for Emergent IV Loading

Study 18 was a 4-way crossover study of different doses and infusion rates. The concentration-time curves depicted in the publication of this study depict nearly superimposable curves for 1200 mg given at 100 mg/min and 150 mg/min. While not designed as a bioequivalence study, it appears that these 2 infusion rates would be bioequivalent and, additionally, both result in similar rise times for free phenytoin concentrations.

Data from a second published PK study shows Fos at 100 mg/min to have a slower rise time of free phenytoin concentration than Fos at 150 mg/min; the Cmax and AUCs appear similar otherwise. This study was designed as a bioequivalence study: Only Fos at 150 mg/min was bioequivalent to Dilantin at 50 mg/min. The rise time of free phenytoin levels was steeper for Fos, resulting in maximal levels about 5-7 minutes faster for Fos than Dilantin.

Safety Concerns for Emergent IV Loading in Light of PK Data

As described in later sections, there is minimal safety data for IV Fos given at a rate of 150 mg/min PE. The safety experience widens considerably if 100 mg/min is used as a cutoff.

The 2 PK studies present discrepant data. In one, 100 vs 150 appear equivalent with similar rise times for free phenytoin levels. In the other, only 150 is bioequivalent to Dilantin 50 mg/min.

The rise time for free phenytoin levels is significantly faster in one PK study compared to Dilantin. In the other study, the rise time is less steep and is similar for both 100 and 150 mg/min infusion rates. If the rise time is steeper with Fos 150 mg/min than for Dilantin at 50 mg/min, the potential exists for increased cardiovascular toxicity with Fos than with Dilantin. **The only way to resolve the safety issue would be to conduct a large enough safety study powered to detect a difference between parenteral Dilantin and Fos, given at 50mg/min and 150mg/min respectively.** A study with pts randomized to these 2 infusion rates has been designed by the sponsor to begin in April 1995, but it is unlikely that this study will have the power to detect a difference between the two drugs with respect to this AE.

Safety

Preclinical Safety Profile (see Dr. Fisher's review)

The toxicological profile of Fos was essentially the same as that of phenytoin. Acute IV toxicity studies were conducted in mice, rats, rabbits, and dogs. Multidose toxicity studies were conducted by both the IV and IM routes in rats and dogs. The IV studies were 4 weeks in duration while the IM studies were 13 weeks in duration.

Special studies of local tissue irritation were conducted. Fos produced significantly less venous and perivascular irritation than phenytoin at equimolar concentrations. Local irritation after IM injection of Fos to rabbits was significantly lower than after IM phenytoin.

The cardiovascular effects of equimolar doses of phenytoin and Fos were comparable following IV bolus injection to anesthetized female dogs. Any less pronounced effects seen after Fos administration are presumed to be due to the lower peak blood levels of phenytoin resulting from its administration (22 vs 49 mcg/ml).

The formation of formaldehyde after Fos administration raises a theoretical safety concern. The theoretical maximum dose of formaldehyde (assuming complete, instantaneous conversion) after an IV dose of 2100 mg Fos (proposed maximum human dose) based on a 1:1 molar ratio would be 5.17 mmol or about 0.1 mmol/kg (3 mg/kg) for a 50 kg person. Using modeling techniques, peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 minutes. Plasma formate levels measured in 4 healthy volunteers following administration of 1200 mg of Fos by IV infusion over 30 min were not significantly different from those observed in a placebo group or from baseline levels

(25 mg/L).

Dr. Fisher has reviewed the genetic toxicity and reproductive toxicity studies. Developmental toxicity seen in rats given Fos is consistent with that previously reported with phenytoin.

Fos was clastogenic in Chinese hamster lung cells. Phenytoin was reportedly not clastogenic in previous studies with CHO cells. One explanation for this discrepancy is that the clastogenicity of Fos is due to formaldehyde formation.

1.0 Exposure

849 volunteers and patients have participated in all Fos studies included in the NDA. These volunteers and patients account for 942 exposures to some study drug (Fos, phenytoin, or placebo) if patients in crossover studies are counted as 2 separate exposures.

736 volunteers or patients have been exposed to Fos, including 148 volunteers and 588 patients. 534 patients were part of the completed clinical studies while an additional 54 patients were part of ongoing Study 16 (status epilepticus).

The sponsor's list of all studies is attached.

Note that almost all 148 volunteers in the early dose-escalation and PK studies received single IV doses of Fos.

Two of the studies in patients were unusual in their dosing regimens. In study 005, patients received half of their maintenance oral dose of phenytoin as IV Fos and the other half as IM Fos. Study 10 was an isotope study.

TABLE 1. Description of Clinical Studies
(Page 1 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration: Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
STUDIES IN SUBJECTS									
Clinical Pharmacology Studies[a]									
982-001	*Total*	*Age Range*	*FOS, IV*	*150*	*100*	Single dose	3.3	5	Single dose
[9653-86-01]	25	19-35	FOS, IV	300	200	Single dose	6.7	5	Single dose
Single-blind, randomized, placebo-controlled, single-center *dose-ranging tolerance study in healthy subjects*	Treatment	Gender	FOS, IV	600	400	Single dose	13.3	5	Single dose
	5 PBO	*25 Males*	*FOS, IV*	*1200*	*800*	Single dose	26.7	5	Single dose
	20 FOS	0 Females	PBO, IV[b]	NA	NA	Single dose	NA	5	Single dose
		Race							
		20 White							
		3 Black							
		2 Other							
982-002	*Total*	*Age Range*	*FOS, IV*	*375*	*250*	Single dose	8.3	12	Single dose
[9653-86-02]	12	20-31	DIL, IV	250	250	Single dose	8.3	12	Single dose
Single-blind, randomized, 2-way crossover, single-center study of absolute bioavailability after IV administration in *healthy subjects*	Treatment	Gender							
	12 FOS	*12 Males*							
	12 DIL	0 Females							
		Race							
		9 White							
		2 Black							
		1 Other							
982-003	Total	Age Range	FOS, IV	375	250	Single dose	50	5	Single dose
[9653-86-03]	31	*18-44*	FOS, IV	750	500	Single dose	100	5	Single dose
Open-label, baseline controlled, escalating infusion rate, single center, safety and tolerance study in healthy subjects	*Treatment*	*Gender*				Single dose	150	1	Single dose
	3 PBO	*31 Males*	FOS, IV	1125	750	Single dose	50	5	Single dose
	28 FOS	*0 Females*				Single dose	75	5	Single dose
						Single dose	100	5	Single dose
		Race				Single dose	150	2	Single dose
		26 White	PBO, IV[b]	NA	NA	Single dose	NA	3	Single dose
		3 Black							
		2 Other							

PE = Phenytoin equivalents; FOS = Fosphenytoin; PBO = Placebo; NA = Not applicable; DIL = Difantin.

[a] Subjects in clinical pharmacology studies may have received more than 1 treatment.

[b] PBO was administered intravenously, in single doses, and at a rate similar to that of FOS.

TABLE 1. Description of Clinical Studies
(Page 2 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration						
			Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-006	Total	Age Range	FOS, IM	375	250	Single dose	NA	12	Single dose
[9653-86-06]	12	22-40	DIL, IV	250	250	Single dose	25	12	Single dose
Open-label, randomized, 2-way crossover, single-center study of bioavailability after IM administration in healthy subjects	Treatment 12 FOS 12 DIL	Gender 12 Males 0 Females Race 12 White							
982-007	Total	Age Range							
[9653-87-07]	15	24-68	FOS, IV	375	250	Single dose	8.3	15	Single dose
Open-label, single center, pharmacokinetic study in subjects with renal or hepatic disease and in healthy subjects	Treatment 15 FOS	Gender 15 Males 0 Females Race 10 White 4 Black 1 Other							
982-011	Total	Age Range							
[9653-87-11]	11	20-31	FOS, IV	1125	750	Single dose	50	10	Single dose
			DZ, IV	10	NA	Single dose	2[a]	9	Single dose
Open-label, randomized, 3-way crossover, single-center, drug-interaction study of fosphenytoin and diazepam in healthy subjects	Treatment 10 FOS 9 DZ 11 FOS/DZ	Gender 11 Males 0 Females Race 11 White	FOS/DZ, IV	1125/10	750	Single dose	50/2[a]	11	Single dose

PE = Phenytoin equivalents; FOS = Fosphenytoin; DIL = Dilantin; DZ = Diazepam; NA = Not applicable.

[a] Rate for diazepam represents mg DZ/min rather than phenytoin equivalents.

TABLE 1. Description of Clinical Studies
(Page 3 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration						
			Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
9R2-012	Total	Age Range	FOS, IV	900	600	Single dose	50	6	Single dose
	6	19-35	DIL, IV	600	600	Single dose	50	6	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, escalating single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects. Study ended prematurely			PBO, IV[b]	NA	NA	Single dose	NA	6	Single dose
	Treatment	Gender							
	6 PBO	6 Males							
	6 FOS	0 Females							
	6 DIL								
		Race							
		5 White							
		1 Black							
9R2-017	Total	Age Range							
	2	18-23	DIL, IV	600	600	Single dose	25	2	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, escalating single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects. Study ended prematurely.									
	Treatment	Gender							
	2 DIL	2 Males							
		Race							
		1 White							
		1 Black							
9R2-018	Total	Age Range	FOS, IV	600	400	Single dose	12.5	4	Single dose
	21	19-43				Single dose	25	4	Single dose
						Single dose	50	4	Single dose
Double-blind, randomized, placebo-controlled, 4-way crossover, escalating single-dose and infusion rate, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin in healthy subjects	Treatment	Gender				Single dose	100	4	Single dose
	21 PBO	21 Males				Single dose	150	4	Single dose
	20 FOS	0 Females	FOS, IV	1200	800	Single dose	12.5	4	Single dose
						Single dose	25	4	Single dose
		Race				Single dose	50	4	Single dose
		19 White				Single dose	100	4	Single dose
		2 Other				Single dose	150	4	Single dose
			FOS, IV	1800	1200	Single dose	12.5	4	Single dose
						Single dose	25	4	Single dose
						Single dose	50	4	Single dose
						Single dose	100	4	Single dose
						Single dose	150	4	Single dose
			PBO, IV[b]	NA	NA	Single dose	NA	21	Single dose

PE = Phenytoin equivalents; FOS = Fosphenytoin; PBO = Placebo; DIL = Dilantin; NA = Not applicable.

[b] PBO was administered intravenously, in single doses, at a rate similar to IV fosphenytoin.

TABLE 1. Description of Clinical Studies
(Page 4 of 7)

Study No. and Description	No. Entered	Demographic	Drug Administration						
			Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
9R2-020	Total	Age Range	FOS, IV	1800	1200	Single dose	50	12	Single dose
	12	18-49	DIL, IV	1200	1200	Single dose	50	12	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects			PBO, IV[b]	NA	NA	Single dose	NA	12	Single dose
	Treatment	Gender							
	12 PBO	12 Males							
	12 FOS	0 Females							
	12 DIL								
		Race							
		10 White							
		1 Black							
		1 Other							
9R2-024	Total	Age Range							
	12	20-42	FOS, IV	1800	1200	Single dose	100	12	Single dose
			FOS, IV	1800	1200	Single dose	150	12	Single dose
Nonblind, randomized, 3-way crossover, single dose, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects	Treatment	Gender	DIL, IV	1200	1200	Single dose	50	12	Single dose
	12 FOS	12 Males							
	12 DIL	0 Females							
		Race							
		10 White							
		2 Other							
COMPLETED STUDIES IN PATIENTS									
Clinical Pharmacology Studies									
9R2-005	Total	Age Range	FOS, IV	NS[c]	NS	Single dose	50	43	Single dose
[9653-86-05]	43	20-73	FOS, IM	NS[c]	NS	Single dose	NA	42	Single dose
Open-label, baseline-controlled, single-dose, multicenter, safety, tolerance, and pharmacokinetic study of IV and IM fosphenytoin in patients with epilepsy maintained on oral Dilantin	Treatment	Gender							
	43 FOS	32 Males							
		11 Females							
		Race							
		38 White							
		5 Black							

Subjects in clinical pharmacology studies may have received more than 1 treatment.
FOS = Fosphenytoin; DIL = Dilantin; PBO = Placebo; NA = Not applicable; NS = Not specified.
[b] PBO was administered intravenously, in single doses, at a rate similar to IV fosphenytoin.
[c] Doses administered were equivalent to half the patients daily dose of PO Dilantin prior to study entry.

TABLE 1. Description of Clinical Studies
(Page 5 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration: Drug, Route	Planned Dose (mg)	Planned Dose (mg PE)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-010	Total	Age Range	FOS, IV	208	139	Single dose	12[d]	7	Single dose
[9653-87-10]	7	20-61	DIL, IV	144	144	Single dose	12[d]	7	Single dose
Open-label, baseline-controlled, single-center study of absolute bioavailability in patients using stable isotope techniques	Treatment 7 FOS 7 DIL	Gender 7 Males 0 Females Race 7 White							
Controlled Clinical Studies									
982-013	Total	Age Range	FOS, IM	NS[e]	NS	QD/BID	NA	179	5 days
	240	18-83	DIL, PO	NS[e]	NS	QD/BID	NA	61	5 days
Double-blind, placebo controlled, multiple-dose, parallel-group, multicenter, safety, tolerance, and pharmacokinetic study of IM fosphenytoin substituted for oral Dilantin in epilepsy and neurosurgical patients	Treatment 179 FOS 61 DIL	Gender 141 Males 99 Females Race 196 White 36 Black 8 Other							

Subjects in clinical pharmacology studies may have received more than 1 treatment.
PE = Phenytoin equivalents; FOS = Fosphenytoin; DIL = Dilantin; NA = Not applicable; NS = Not specified.
[d] Both drugs were infused simultaneously over a 12-minute period.
[e] Eligible patients were receiving 200 to 500 mg/day PO Dilantin. Doses administered were equivalent to the dose of PO Dilantin taken prior to study entry.

TABLE 1. Description of Clinical Studies
(Page 6 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration						
			Drug, Route	Planned Dose (mg/kg)	Planned Dose (mg PE/kg)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-015	Total	Age Range	FOS, IV[f]						
	116	15-89	Loading	18-21	12-14	Single dose	≤50	88	Single dose
Double-blind, active-controlled, parallel group, multiple dose, multicenter, safety, tolerance, and pharmacokinetic study of IV fosphenytoin versus Dilantin in neurosurgical patients			Maintenance	NS	NS	QD/BID	≤50	88	3-14 days
	Treatment	Gender							
	88 FOS	72 Males	DIL IV[f]						
	28 DIL	44 Females	Loading	12-14	12-14	Single dose	≤50	28	Single dose
			Maintenance	NS	NS	QD/BID	≤50	27	3-14 days
		Race							
		88 White							
		26 Black							
		2 Other							
982-021	Total	Age Range							
	52	16-73	FOS, IV	≥15	≥10[g]	Single dose	≤100	39	Single dose
Double-blind, active-controlled, parallel group, single dose, multicenter safety and tolerance study of IV fosphenytoin versus Dilantin in patients requiring a loading dose of phenytoin			DIL, IV	≥10	≥10[g]	Single dose	≤50	13	Single dose
	Treatment	Gender							
	39 FOS	33 Males							
	13 DIL	19 Females							
		Race							
		28 White							
		16 Black							
		8 Other							

PE = Phenytoin equivalents; FOS = Fosphenytoin; DIL = Dilantin; NA = Not applicable; NS = Not specified.

[f] Suggested loading dose range. Protocol specified that loading and maintenance doses should achieve and maintain plasma phenytoin concentrations ≥10 mg/mL.

[g] Maximum single dose of 2000 mg.

TABLE 1. Description of Clinical Studies
(Page 7 of 7)

Study No. and Description	No. Entered	Demography	Drug Administration: Drug, Route	Planned Dose (mg/kg)	Planned Dose (mg PE/kg)	Regimen	Planned Rate (mg PE/min)	No. of Participants	Duration of Dosing
Uncontrolled Clinical Studies									
9N2-014	Total 118	Age Range 16-98	FOS, IM[f]						
Open-label, multiple-dose, multicenter, safety, tolerance, and pharmacokinetic study of IM fosphenytoin in neurosurgery patients	Treatment 118 FOS	Gender 78 Males 40 Females	Loading	12-18	8-12	QD/BID	NA	118	Single dose
			Maintenance	NS	NS	QD/BID	NA	117	3-14 days
		Race 93 White 25 Black							
9N2-022	Total 60	Age Range 16-80	FOS, IM	≥15	≥10[g]	Single dose	NA	60	Single dose
Open-label, single dose, multicenter, safety, and tolerance study of IM fosphenytoin in patients requiring a loading dose of phenytoin	Treatment 60 FOS	Gender 34 Males 26 Females							
		Race 32 White 24 Black 4 Other							
Ongoing Studies in Patients									
9N2-016	Total 54	Age Range 5-75	FOS, IV	15-30	10-20[h]	Single dose	≤150[i]	54	Single dose
(Interim) Open-label, single dose, rate escalation, multicenter safety, tolerance, and pharmacokinetic study of IV fosphenytoin in patients with status epilepticus	Treatment 54 FOS	Gender 32 Males 22 Females							
		Race 23 White 23 Black 8 Other							

PE = Phenytoin equivalents; FOS = Fosphenytoin; NA = Not applicable; NS = Not specified.

f Suggested loading dose range. Protocol specified that loading and maintenance doses should achieve and maintain plasma phenytoin concentrations ≥10 mg/mL.

g Maximum single dose of 2000 mg.

h Target dose of 18 mg/kg to a maximum single dose of 2000 mg.

i Protocol specified an initial rate of 2 mg/kg/min to a maximum of 100 mg/min, with subsequent escalation to 3 mg/kg/min to a maximum of 150 mg/min based on safety at the lower rate.

Excluding those 2 studies, the remaining patients in clinical studies can be divided as follows:

IV "Load"

Study 21: 39 Fos patients*
Study 15: 88 Fos patients**
Study 16: 54 Fos patients***

IV Maintenance

Study 15: 88 Fos patients (1 week)**

IM Load

Study 22: 60 Fos patients*
Study 14: 118 Fos patients**

IM Maintenance

Study 13: 179 Fos patients*
Study 14: 118 Fos patients**

* epilepsy patients
** neurosurgery patients
*** status epilepticus

With the exception of 6 patients in Study 16 (status epilepticus), all patients were 16 years of age or older. Study 16 included 6 patients between the ages of 5 and 10 years.

Duration of exposure by route of administration (see sponsor's Figure 4):

Approximately 200 patients received IM Fos for 5 days, but only about 20 patients received IM Fos for 6 days or greater. IM exposure to Fos was heavily influenced by Study 13 which was designed as a 5-day study.

Approximately 60 patients received IV Fos for 4 days, but only about 18 patients received IV Fos for 5 days or greater. IV exposure to Fos was dependent on Study 15 where there was a protocol-specified option to switch to PO Dilantin after 3 days at the investigators' discretion.

Dose and Rate (see sponsor's Figure 7 which incorporates both volunteers and patients):

The total dose given obviously depended on whether the dose was designed as a loading dose or a maintenance dose.

The rate of administration for IV dosing was generally about 50 mg/min ± 20 except where specifically pushed higher to the bioequivalent rates necessary in status (150 mg/min).

2.0 Volunteer Studies

148 unique volunteers were exposed to Fos. Some of these individuals may have received more than one exposure to Fos. As mentioned above, most of these volunteers received single IV doses as part of dose-escalation or PK studies. Sponsor's Table 3 represents the number of unique volunteers exposed to Fos, Dilantin, and placebo in these studies.

2.1 Deaths

There were no deaths in volunteer studies.

2.2 Serious AEs and Discontinuations

There were 3 serious AEs reported in volunteer studies, 2 were on Fos and

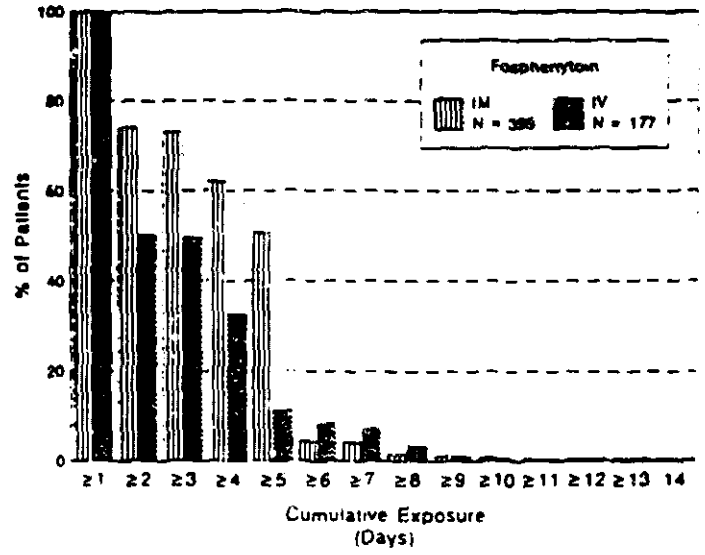

FIGURE 4. Exposure to Fosphenytoin by Route: Patients

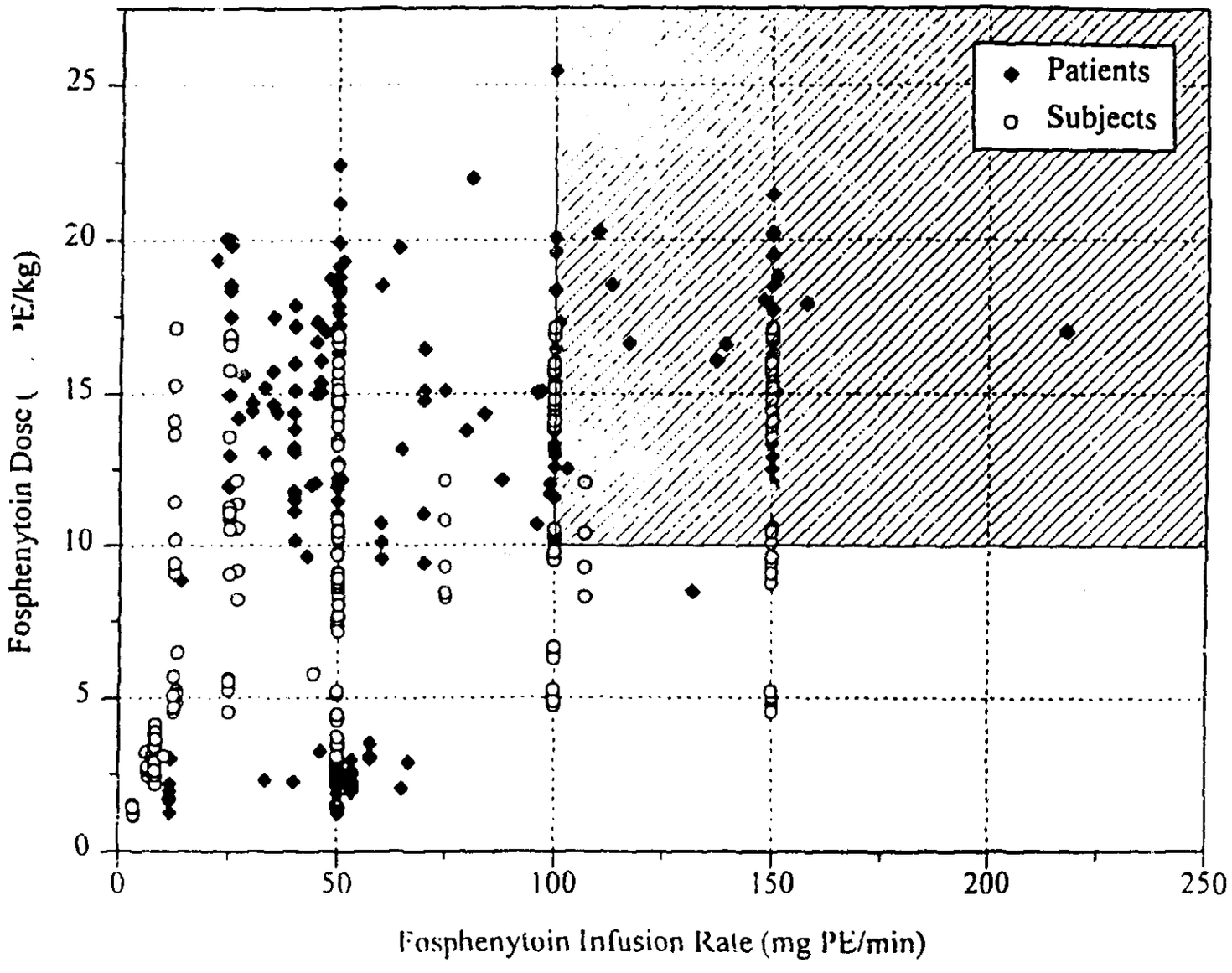

FIGURE 7. Subject and Patient Exposure to Fosphenytoin by Dose and Rate

TABLE 3. Source and Number of Subjects

Study	Placebo	Fosphenytoin		Dilantin	Total in Study[a]	Total Exposed to Fosphenytoin[a]
	IV	IM	IV	IV		
982-001	5	0	20	0	25	20
982-002	0	0	12	12	12	12
982-003	3	0	28	0	31	28
982-006	0	12	0	12	12	12
982-007	0	0	15	0	15	15
982-011	0	0	11	0	11	11
982-012	6	0	6	6	6	6
982-017	0	0	0	2	2	0
982-018	21	0	20	0	21	20
982-020	12	0	12	12	12	12
982-024	0	0	12	12	12	12
Total	47	12	136	56	159	148

[a] Each subject counted once

1 was on Dilantin. The patient narratives for all 3 patients are included below. The first Fos volunteer experienced progressive bradycardia leading to asystole for 23 seconds. During the asystole, the volunteer experienced 15 seconds of tonic-clonic movement. Because of subsequent abnormal electrophysiologic testing, the case was deemed unrelated to study drug. The subject had received 500mg of a planned 750mg bolus at 150mg/min.

The second Fos patient had hypotension and syncope after receiving 650mg of a planned 750mg bolus at 50mg/min. Bradycardia accompanied the event.

The Dilantin subject experienced hypotension after receiving 600mg of Dilantin at 50mg/min.

All 3 events seem most consistent with vasovagal reactions.

The classification of "discontinuations" or "withdrawals" would be somewhat uninformative for these volunteer studies since most of the studies were single dose IV studies. Nevertheless, there were 3 discontinuations. The 2 previously mentioned Fos serious AEs account for 2 of the 3 discontinuations. The third discontinuation was a Dilantin treated subject who developed a wandering cardiac pacemaker during infusion.

2.3 Severe AEs

Severe AEs were reported in 5 Fos subjects and 3 Dilantin subjects. 1/5 severe Fos reactions was described as a serious AE; the other 4 severe AEs were: ataxia, stupor, tinnitus, and pruritus. The 3 severe Dilantin AEs were: injection site pain in 2 subjects and hypotension in 1 subject.

2.4 All AEs

The sponsor has chosen to present the AE data relative to the number of exposures vs the number of subjects. For this reason, the denominators differ from Table 3 above in that there were 211 Fos exposures in 148 subjects. The number of exposures = number of subjects for placebo and Dilantin subjects. Sponsor's Table 6 shows all AEs, as well as those characterized as associated with test drug.

TABLE 6. All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 1 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47		Fosphenytoin* N = 211		Dilantin N = 56	
	All	Associated	All	Associated	All	Associated
ANY BODY SYSTEM	14 (29.8)	12 (25.5)	141 (66.8)	136 (64.5)	38 (67.9)	36 (64.3)
NERVOUS	6 (12.8)	6 (12.8)	123 (58.3)	121 (57.3)	32 (57.1)	32 (57.1)
Nystagmus	3 (6.4)	3 (6.4)	53 (25.1)	53 (25.1)	29 (51.8)	29 (51.8)
Dizziness	2 (4.3)	2 (4.3)	80 (37.9)	80 (37.9)	20 (35.7)	20 (35.7)
Paresthesia	1 (2.1)	1 (2.1)	68 (32.2)	66 (31.3)	11 (19.6)	11 (19.6)
Somnolence	0 (0.0)	0 (0.0)	7 (3.3)	7 (3.3)	0 (0.0)	0 (0.0)
Ataxia	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	2 (3.6)	2 (3.6)
Tremor	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)
Incoordination	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)
Hypertonia	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Stupor	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Euphoria	0 (0.0)	0 (0.0)	5 (2.4)	5 (2.4)	3 (5.4)	3 (5.4)
Anxiety	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (1.8)	1 (1.8)
Hypesthesia	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	0 (0.0)	0 (0.0)
Thinking Abnormal	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	2 (3.6)	2 (3.6)
Nervousness	1 (2.1)	1 (2.1)	2 (0.9)	2 (0.9)	2 (3.6)	2 (3.6)
Abnormal Gait	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Dysarthria	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	3 (5.4)	3 (5.4)
Twitching	0 (0.0)	0 (0.0)	4 (1.9)	4 (1.9)	2 (3.6)	2 (3.6)
Convulsion	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Circumoral Paresthesia	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	3 (5.4)	3 (5.4)
CNS Depression	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

* Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

TABLE 6. All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 2 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47				Fosphenytoin[a] N = 211				Dilantin N = 56			
	All		Associated		All		Associated		All		Associated	
BODY AS A WHOLE	6	(12.8)	5	(10.6)	45	(21.3)	39	(18.5)	25	(44.6)	24	(42.9)
Headache	1	(2.1)	1	(2.1)	26	(12.3)	24	(11.4)	8	(14.3)	5	(8.9)
Pain	0	(0.0)	0	(0.0)	2	(0.9)	1	(0.5)	1	(1.8)	1	(1.8)
Accidental Injury	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Injection-Site Reaction	2	(4.3)	1	(2.1)	4	(1.9)	3	(1.4)	7	(12.5)	7	(12.5)
Infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Injection-Site Pain	3	(6.4)	3	(6.4)	4	(1.9)	4	(1.9)	17	(30.4)	17	(30.4)
Asthenia	0	(0.0)	0	(0.0)	3	(1.4)	2	(0.9)	0	(0.0)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	7	(3.3)	7	(3.3)	2	(3.6)	2	(3.6)
Chest Pain	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Injection-Site Inflammation	0	(0.0)	0	(0.0)	2	(0.9)	1	(0.5)	2	(3.6)	2	(3.6)
Flu Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Photosensitivity Reaction	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
DIGESTIVE	1	(2.1)	1	(2.1)	24	(11.4)	21	(10.0)	10	(17.9)	10	(17.9)
Nausea	1	(2.1)	1	(2.1)	15	(7.1)	14	(6.6)	4	(7.1)	4	(7.1)
Constipation	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Dry Mouth	0	(0.0)	0	(0.0)	6	(2.8)	6	(2.8)	4	(7.1)	4	(7.1)
Dyspepsia	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Diarrhea	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Gastrointestinal Disorder	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

[a] Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

TABLE 6 All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 3 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47				Fosphenytoin[a] N = 211				Dilantin N = 56			
	All		Associated		All		Associated		All		Associated	
DIGESTIVE (continued)												
Increased Salivation	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Dysphagia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Cheilitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
CARDIOVASCULAR	1	(2.1)	1	(2.1)	6	(2.8)	6	(2.8)	5	(8.9)	5	(8.9)
Hypotension	0	(0.0)	0	(0.0)	3	(1.4)	3	(1.4)	3	(5.4)	3	(5.4)
Bradycardia	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
Arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.6)	1	(1.8)
Vasodilatation	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	2	(3.6)	2	(3.6)
Vascular Disorder	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Syncope	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Heart Arrest	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
AV Block Second Degree	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Pallor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Phlebitis	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SPECIAL SENSES	1	(2.1)	1	(2.1)	58	(27.5)	57	(27.0)	17	(30.4)	16	(28.6)
Tinnitus	1	(2.1)	1	(2.1)	29	(13.7)	29	(13.7)	9	(16.1)	9	(16.1)
Ear Disorder	0	(0.0)	0	(0.0)	22	(10.4)	20	(9.5)	8	(14.3)	8	(14.3)
Taste Perversion	0	(0.0)	0	(0.0)	10	(4.7)	10	(4.7)	0	(0.0)	0	(0.0)
Amblyopia	0	(0.0)	0	(0.0)	3	(1.4)	2	(0.9)	1	(1.8)	1	(1.8)
Abnormal Vision	0	(0.0)	0	(0.0)	7	(3.3)	7	(3.3)	4	(7.1)	4	(7.1)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

[a] Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

TABLE 6. All and Associated Adverse Events by Body System and Treatment
[Number (%) of Exposures in Subjects]
(Page 4 of 4)

BODY SYSTEM/ Preferred Term	Placebo N = 47				Fosphenytoin[a] N = 211				Dilantin N = 56			
	All		Associated		All		Associated		All		Associated	
SPECIAL SENSES (continued)												
Diplopia	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	1	(1.8)	1	(1.8)
Hyperacusis	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(1.8)	1	(1.8)
Mydriasis	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Conjunctivitis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(1.8)	0	(0.0)
Ear Pain	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES	1	(2.1)	1	(2.1)	31	(14.7)	30	(14.2)	6	(10.7)	6	(10.7)
Pruritus	0	(0.0)	0	(0.0)	30	(14.2)	30	(14.2)	1	(1.8)	1	(1.8)
Rash	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(1.8)	1	(1.8)
Urticaria	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Sweating	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(5.4)	3	(5.4)
Contact Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)
Skin Disorder	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
RESPIRATORY	1	(2.1)	0	(0.0)	9	(4.3)	4	(1.9)	1	(1.8)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	5	(2.4)	1	(0.5)	0	(0.0)	0	(0.0)
Hyperventilation	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
Rhinitis	1	(2.1)	0	(0.0)	2	(0.9)	1	(0.5)	1	(1.8)	0	(0.0)
UROGENITAL	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	1	(1.8)	1	(1.8)
Urination Impaired	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	1	(1.8)	1	(1.8)

Associated = Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment.

[a] Data for subjects in Study 982-011 who received both fosphenytoin and fosphenytoin plus diazepam are included as 2 separate exposures in the fosphenytoin column. Data for subjects in Study 982-011 for the periods during which they received diazepam alone are not included in this table.

The most common AEs for Fos were:

Dizziness	38%
Paresthesia	32%
Nystagmus	25%
Tinnitus	14%
Pruritus	14%
Headache	12%
Ear disorder	10%

Except for paresthesia and pruritus, the incidence for all the above AEs was equal to or less than that for Dilantin.

Injection site pain was 2% for Fos vs 30% for Dilantin. Injection site reaction was 2% for Fos vs 13% for Dilantin.

2.5 Rate-related AEs After IV Administration

Some AEs were rate-related after IV administration in both Fos and Dilantin treated subjects. More informative, however, are the discrepancies between Fos and Dilantin treated subjects, situations where an AE was clearly rate-related for one treatment but not the other.

Taste perversion was rate-related for Fos, reaching 19% of Fos subjects when Fos was administered at 100-150 mg/min, but did not occur at any rate for Dilantin administration.

Likewise, pruritus was rate-related for Fos, reaching 38% of Fos subjects when Fos was administered at 100-150 mg/min, but only occurred in a single Dilantin-treated subject.

Paresthesia were rate-related for Dilantin as follows:

0/12 cases at 15 mg/min or less
0/14 cases at 15-30 mg/min
11/30 (37%) cases at 30-50 mg/min

Paresthesia were also rate-related for Fos as follows:

3/54 (6%) at 15 mg/min or less
3/17 (18%) at 15-30 mg/min
18/62 (29%) at 30-50 mg/min

23/35 (66%) at 50-100 mg/min
21/31 (68%) at 100-150 mg/min

Note that at bioequivalent rates, 37% Dilantin subjects vs 68% Fos subjects reported paresthesia. Of course, the total dose was not controlled for in these comparisons.

2.6 Dose-related AEs After IV Administration

No new trends over those reported in the rate-related AE section are obvious here. Taste perversion and pruritus increase with dose (as opposed to rate) in the absence of any significant number of events in Dilantin subjects at any dose.

2.7 Clinical Labs

The sponsor reports no clinically significant changes after Fos administration. Recall that most exposures in volunteers were single dose exposures.

2.8 Injection Site Reactions

Sponsor's Table 10 summarizes injection site reactions for the volunteer studies. Based on 102 Fos exposures and 39 placebo exposures, the profile of reactions for Fos and placebo are not significantly different. 97% of exposures in both groups resulted in none-mild reactions. For the Dilantin-exposures (n=32), 15% resulted in moderate reactions and 6% resulted in severe reactions.

When rate-relatedness was examined, up to 23% of high-rate Dilantin exposures resulted in reactions. Reactions were not rate-related with Fos. Up to 43% of high-rate Dilantin exposures resulted in injection site pain. Pain was not rate-related with Fos.

2.9 Vital Signs

The ISS does not address vital signs in volunteer studies.

TABLE 10. Evaluation of Infusion-Site Reactions: Subjects (Parke-Davis Studies)
[Number (%) of Exposures in Subjects]

Study	Treatment	No. of Exposures in Subjects Evaluated	Maximum Intensity of Infusion-Site Adverse Reaction									
			None		Mild		Moderate		Severe		Missing/Not Done	
982-012	Placebo	6	6	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Fosphenytoin	6	6	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Dilantin	6	1	(16.7)	5	(83.3)	0	(0.0)	0	(0.0)	0	(0.0)
982-017	Dilantin	2	0	(0.0)	2	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
982-018	Placebo	21	20	(95.2)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
	Fosphenytoin	60	56	(93.3)	3	(5.0)	1	(1.7)	0	(0.0)	0	(0.0)
982-020	Placebo	12	10	(83.3)	1	(8.3)	1	(8.3)	0	(0.0)	0	(0.0)
	Fosphenytoin	12	8	(66.7)	3	(25.0)	1	(8.3)	0	(0.0)	0	(0.0)
	Dilantin	12	2	(16.7)	4	(33.3)	4	(33.3)	2	(16.7)	0	(0.0)
982-024	Fosphenytoin	24	18	(75.0)	6	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Dilantin	12	0	(0.0)	11	(91.7)	1	(8.3)	0	(0.0)	0	(0.0)
Total	Placebo	39	36	(92.3)	2	(5.1)	1	(2.6)	0	(0.0)	0	(0.0)
	Fosphenytoin	102	88	(86.3)	12	(11.8)	2	(2.0)	0	(0.0)	0	(0.0)
	Dilantin	32	3	(9.4)	22	(68.8)	5	(15.6)	2	(6.3)	0	(0.0)

2.10 Conclusions From Normal Volunteer Studies

The great majority of data collected in normal volunteers is applicable to the IV bolus situation (at varying rates). In the categories severe AEs, all AEs, rate-related AEs, and dose-related AEs, there is a consistent trade-off between the occurrence of local injection site reactions and pain with IV Dilantin and the occurrence of generalized paresthesia and pruritus with IV Fos.

Paresthesia are reported with IV Dilantin, but only at high rate or high dose. Even at high rate or high dose though, the incidence of paresthesia is less than expected for Dilantin given the incidence for Fos. Taste perversion is an additional AE that appeared for Fos subjects but not Dilantin subjects.

The sponsor does not address the reversibility of Fos-associated paresthesia, pruritus, and taste perversion directly in the ISS. Statements are made to the effect that these 3 AEs tend to be limited to the post-infusion times. Whether some subjects continued with these AEs is not directly obvious from reading the ISS.

3.0 Completed Studies in Patients

534 patients participated in completed clinical studies. The breakdown of these 534 patients has been presented above in "Section 1.0 Exposure." In the ISS, the sponsor presents different cross-sectional views of AE data, but each is inadequate for not accounting for other relevant variables. For instance, a breakdown by route of administration does not account for whether the individual patients were given loading doses or maintenance doses. For this reason, I believe that only individual study reports are interpretable. Even these present problems by not controlling for rate and dose in may circumstances (see individual study reviews).

The appropriateness of combining results from different studies in patients even when ostensibly the same medications were given by the same route and same dosing regimen (loading vs maintenance) can be questioned. For instance, patients in Studies 15 and 21 received IV loading doses of Fos or Dilantin. But the AE profile for the Dilantin arms of the two trials differ significantly (see tables of common AEs from these 2 trials on following pages). One possible explanation is that one study was in neurosurgical patients and the other in epilepsy patients.

In Study 21 in epilepsy patients, nystagmus, dizziness, vertigo, and ataxia are reported in 38%, 38%, 23%, and 15% of patients respectively. In Study 15 in neurosurgery patients, the same AEs are reported in 14%, 11%, 0%, and 7% of patients respectively. All these AEs would be more likely to be ascertained in an ambulatory, alert population like the epilepsy population.

3.1 All AEs

Sponsor's Table 12 presents all AEs occurring in patients in completed studies. Suffice it to say that no alarming safety concerns arise in reviewing data presented this way. At the same time, no convincing advantages of Fos over Dilantin emerge.

While injection site pain is reported in 1.5% of Fos patients and 6.9% of Dilantin patients, the comparability of rate and dose of administration between groups is not obvious. Likewise, while injection site reaction is reported in 2.8% of Fos patients and 4.9% of Dilantin patients, the rates and doses may not be comparable. Note that when data is grouped as it is

TABLE 12. All and Associated Adverse Events Occurring in ≥1% of Patients by Body System and Treatment[a,b]
[Number (%) of Patients]
(Page 1 of 2)

BODY SYSTEM/ Preferred Term	Fosphenytoin N = 534				Dilantin N = 102			
	All		Associated		All		Associated	
NERVOUS								
Nystagmus	99	(18.5)	71	(13.3)	14	(13.7)	7	(6.9)
Dizziness	48	(9.0)	43	(8.1)	10	(9.8)	9	(8.8)
Ataxia	48	(9.0)	20	(3.7)	9	(8.8)	2	(2.0)
Somnolence	45	(8.4)	25	(4.7)	10	(9.8)	8	(7.8)
Tremor	31	(5.8)	19	(3.6)	9	(8.8)	5	(4.9)
Incoordination	28	(5.2)	15	(2.8)	4	(3.9)	2	(2.0)
Paresthesia	26	(4.9)	19	(3.6)	3	(2.9)	2	(2.0)
Neuropathy	25	(4.7)	2	(0.4)	4	(3.9)	0	(0.0)
Reflexes Increased	16	(3.0)	1	(0.2)	3	(2.9)	0	(0.0)
Speech Disorder	15	(2.8)	4	(0.7)	3	(2.9)	2	(2.0)
Hypertonia	12	(2.2)	2	(0.4)	0	(0.0)	0	(0.0)
Reflexes Decreased	10	(1.9)	2	(0.4)	4	(3.9)	2	(2.0)
Intracranial Hypertension	9	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Stupor	8	(1.5)	3	(0.6)	1	(1.0)	0	(0.0)
Anxiety	7	(1.3)	2	(0.4)	0	(0.0)	0	(0.0)
Confusion	6	(1.1)	2	(0.4)	0	(0.0)	0	(0.0)
Agitation	6	(1.1)	0	(0.0)	1	(1.0)	0	(0.0)
BODY AS A WHOLE								
Headache	41	(7.7)	13	(2.4)	6	(5.9)	2	(2.0)
Fever	35	(6.6)	0	(0.0)	6	(5.9)	0	(0.0)
Pain	29	(5.4)	10	(1.9)	2	(2.0)	2	(2.0)
Accidental Injury	22	(4.1)	2	(0.4)	7	(6.9)	2	(2.0)
Infection	17	(3.2)	0	(0.0)	5	(4.9)	0	(0.0)
Injection-Site Reaction	15	(2.8)	10	(1.9)	5	(4.9)	2	(2.0)
Asthenia	9	(1.7)	7	(1.3)	2	(2.0)	1	(1.0)
Back Pain	9	(1.7)	1	(0.2)	0	(0.0)	0	(0.0)
Face Edema	9	(1.7)	0	(0.0)	4	(3.9)	0	(0.0)
Injection-Site Pain	8	(1.5)	7	(1.3)	7	(6.9)	7	(6.9)
Reaction Unevaluable	7	(1.3)	2	(0.4)	1	(1.0)	1	(1.0)
Sepsis	7	(1.3)	0	(0.0)	1	(1.0)	0	(0.0)
DIGESTIVE								
Nausea	30	(5.6)	12	(2.2)	6	(5.9)	1	(1.0)
Constipation	26	(4.9)	2	(0.4)	3	(2.9)	0	(0.0)
Vomiting	17	(3.2)	2	(0.4)	5	(4.9)	0	(0.0)

[a] Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment. Events occurring in ≥1% of patients were based upon all adverse events occurring in fosphenytoin-treated patients.

[b] See Appendix B.2 for a complete listing of all and associated adverse events.

TABLE 12. All and Associated Adverse Events Occurring in ≥1% of Patients by Body System and Treatment[a,b]
[Number (%) of Patients]
(Page 2 of 2)

BODY SYSTEM/ Preferred Term	Fosphenytoin N = 534				Dilantin N = 102			
	All		Associated		All		Associated	
CARDIOVASCULAR								
Hypotension	13	(2.4)	4	(0.7)	3	(2.9)	2	(2.0)
Hypertension	10	(1.9)	1	(0.2)	2	(2.0)	0	(0.0)
Tachycardia	9	(1.7)	0	(0.0)	2	(2.0)	0	(0.0)
Bradycardia	7	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES								
Pruritus	27	(5.1)	24	(4.5)	0	(0.0)	0	(0.0)
Rash	7	(1.3)	1	(0.2)	2	(2.0)	1	(1.0)
HEMIC AND LYMPHATIC								
Ecchymosis	30	(5.6)	13	(2.4)	4	(3.9)	2	(2.0)
SURGERIES/PROCEDURES								
Surgeries/Procedures	26	(4.9)	0	(0.0)	5	(4.9)	0	(0.0)
RESPIRATORY								
Pneumonia	10	(1.9)	0	(0.0)	6	(5.9)	0	(0.0)
Lung Disorder	7	(1.3)	0	(0.0)	1	(1.0)	0	(0.0)
UROGENITAL								
Urinary Retention	8	(1.5)	0	(0.0)	3	(2.9)	0	(0.0)
Urinary Tract Infection	6	(1.1)	0	(0.0)	2	(2.0)	0	(0.0)
MUSCULOSKELETAL								
Myasthenia	11	(2.1)	1	(0.2)	2	(2.0)	0	(0.0)
SPECIAL SENSES								
Amblyopia	9	(1.7)	4	(0.7)	3	(2.9)	3	(2.9)
METABOLIC AND NUTRITIONAL								
Hypokalemia	8	(1.5)	0	(0.0)	2	(2.0)	0	(0.0)

[a] Associated adverse events are the events considered by the investigator to be related, probably related, possibly related, or of unknown relationship to treatment. Events occurring in ≥1% of patients were based upon all adverse events occurring in fosphenytoin-treated patients.

[b] See Appendix B.2 for a complete listing of all and associated adverse events.

here for all patients, the term "injection site" could apply to either IM or IV injection site !

On page 48 of the ISS, the sponsor describes the experience with paresthesia and pruritus in more detail. For 13 patients treated with IV Fos, the investigator chose to manage the events by changing the infusion rate or administering medication (steroids or antihistamines). The number of events after IM Fos is not stated here, but no interventions were utilized. One patient withdrew because of severe pruritus that occurred with severe allergic reaction (Pt 13, Study 13, Center 1).

Also on page 48, the sponsor reports that in completed patient studies, discrepancies between Fos and Dilantin treated patients with regard to pruritus and paresthesia were not as great as in the normal volunteer studies. This fact is misleading because the 2 different comparative studies in patients reported different experiences. With regard to paresthesia, Study 21 reported a 10% vs 0% incidence in paresthesia in favor of Dilantin. With regard to pruritus, Study 21 reported a 31% vs 0% incidence in pruritus in favor of Dilantin. In short, in some patient studies, discrepancies in Fos and Dilantin treated subjects with regard to paresthesia and pruritus were as great as or greater than those seen in the normal volunteer studies.

3.2 Common AEs Within the Two Active-Control Trials

The 2 active-control trials in the NDA differ in two respects: first, one had only an IV loading dose while the other had an IV load followed by IV maintenance dosing; second, one was in neurosurgery patients and one was in epilepsy patients.

When the 2 Dilantin-control trials (Studies 15 and 21) are looked at separately, the magnitude of the discrepancies between Fos and Dilantin for certain AEs varies.

For all studies combined, pruritus was reported in 5% Fos patients and 0% Dilantin patients. In Study 15 (neurosurgery patients), pruritus was reported in 6% Fos patients and 0% Dilantin patients. But in Study 21 (epilepsy patients), pruritus was reported in 31% Fos patients vs 0% Dilantin patients.

TABLE 16. Most Frequent Adverse Events With IV Administration to Neurosurgical Patients (Study 982-015)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 88		Dilantin N = 28	
NERVOUS				
Nystagmus	12	(13.6)	4	(14.3)
Neuropathy	9	(10.2)	4	(14.3)
Reflexes Increased	7	(8.0)	0	(0.0)
Dizziness	6	(6.8)	3	(10.7)
Somnolence	6	(6.8)	3	(10.7)
Speech Disorder	5	(5.7)	1	(3.6)
BODY AS A WHOLE				
Fever	11	(12.5)	6	(21.4)
Face Edema	7	(8.0)	4	(14.3)
Injection-Site Reaction	6	(6.8)	5	(17.9)
Infection	6	(6.8)	2	(7.1)
DIGESTIVE				
Constipation	11	(12.5)	3	(10.7)
Nausea	9	(10.2)	4	(14.3)
Vomiting	6	(6.8)	5	(17.9)
CARDIOVASCULAR				
Tachycardia	7	(8.0)	2	(7.1)
Hypotension	6	(6.8)	2	(7.1)
SKIN AND APPENDAGES				
Pruritus	5	(5.7)	0	(0.0)
SURGERIES/PROCEDURES				
Surgeries/Procedures	9	(10.2)	3	(10.7)
RESPIRATORY				
Pneumonia	6	(6.8)	6	(21.4)
UROGENITAL				
Urinary Retention	7	(8.0)	3	(10.7)
MUSCULOSKELETAL				
Myasthenia	7	(8.0)	2	(7.1)
METABOLIC AND NUTRITIONAL				
Hypokalemia	8	(9.1)	2	(7.1)

TABLE 15. Most Frequent Adverse Events With IV Administration to Patients With Epilepsy (Study 982-021)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 39		Dilantin N = 13	
NERVOUS				
Nystagmus	18	(46.2)	5	(38.5)
Dizziness	10	(25.6)	5	(38.5)
Ataxia	7	(17.9)	2	(15.4)
Vertigo	4	(10.3)	3	(23.1)
Paresthesia	4	(10.3)	0	(0.0)
Tremor	3	(7.7)	0	(0.0)
Neuropathy	3	(7.7)	0	(0.0)
Somnolence	2	(5.1)	1	(7.7)
Speech Disorder	2	(5.1)	2	(15.4)
BODY AS A WHOLE				
Headache	7	(17.9)	1	(7.7)
Pain	5	(12.8)	1	(7.7)
Reaction Unevaluable	4	(10.3)	1	(7.7)
Chills	2	(5.1)	0	(0.0)
Chest Pain	2	(5.1)	0	(0.0)
CARDIOVASCULAR				
Hypotension	3	(7.7)	1	(7.7)
SKIN AND APPENDAGES				
Pruritus	12	(30.8)	0	(0.0)
SPECIAL SENSES				
Amblyopia	4	(10.3)	3	(23.1)
Ear Disorder	2	(5.1)	0	(0.0)

Overall, in Study 21, the big differences in AEs between Fos and Dilantin occurred for pruritus (31 vs 0 %), paresthesia (10 vs 0 %), neuropathy (8 vs 0 %), and tremor (8 vs 0 %).

Overall, in Study 15, the big differences in AEs between Fos and Dilantin occurred for pruritus (6 vs 0 %), increased reflexes (8 vs 0 %), and injection site reaction (7 vs 18 %).

Note that injection site reactions were not unusual in Study 15 and demonstrated a difference between Fos and Dilantin. In Study 21, only a single injection site reaction was reported (it happened to be in a Fos patient) so that no difference between Fos and Dilantin was really demonstrated. In all likelihood, this difference between studies was because Study 21 was only a single dose study while Study 15 incorporated a loading dose followed by several days of maintenance dosing. (Another alternative explanation is that the Dilantin rates in Study 21 were lowered in 5 patients because of local pain, thereby decreasing the later emergence of injection site reactions in those patients.)

One might infer from the last paragraph that, for IV dosing, the advantage of Fos over Dilantin with regard to local tissue reactions is confered only upon patients who receive maintenance dosing. However, in both Study 15 and Study 21, the rates of infusion of the loading doses were so low as to contribute almost nothing to our understanding of IV loading in an emergent setting i.e. status epilepticus where the bioequivalent rate of 100-150 mg/min should be approached. In those situations of rapid infusion, local injection site reactions might occur with both Dilantin and Fos, perhaps even with an advantage for Fos. Unfortunately, a head-to-head comparison of Dilantin and Fos in comparable rapid infusions has only recently begun. Until that study is completed, no definitive statements about a Fos advantage over Dilantin for injection site reactions in emergent settings can be made.

3.3 Common AEs in IV Maintenance Study

The only study that really speaks to the safety of IV maintenance therapy is Study 15. As alluded to previously, this study in neurosurgical patients appears to underrepresent (in the face of comparable dose and rate) certain AEs which were shown in another study (Study 21) to occur with

high frequency in another population (epilepsy).

If exposure is assumed to be the same after IM maintenance therapy in neurosurgery patients, Study 14 (uncontrolled) can also be used to support IV maintenance therapy and, alternatively, Study 15 can be used to support IM maintenance therapy (albeit without the local IM safety data).

3.4 "Slow" Loading Doses

For all their differences, there are 4 studies (2 active-control and 2 uncontrolled) which support subacute loading doses. Studies 14 and 15 were performed in neurosurgery patients and studies 21 and 22 were performed in epilepsy patients. Studies 15 and 21 had IV loading doses while studies 14 and 22 had IM loading doses.

3.5 "Rapid" IV Loading Doses

Only one study, Study 16, really addresses the safety of IV loading doses in status epilepticus. This was an uncontrolled study.

Some comparative safety data on IV loading is accrued in Studies 15 and 21 and, although bioequivalent rates were only rarely achieved in those studies, do provide some picture of comparative safety.

In particular, one concern might be that significant AEs might be missed in Study 16 if the patients with status epilepticus were too obtunded to report them. In Study 21 in epilepsy patients, obtundation is not a problem so that reporting rates for some AEs would be expected to be higher, albeit with the less-than-bioequivalent rates.

This indication is also the subject of a new active-control trial with Dilantin in which bioequivalent rates will be maintained.

3.6 Rate-related AEs After IV Administration

As in the normal volunteer studies, paresthesia and pruritus were rate-related AEs in Fos patients. At rates that might be bioequivalent, Dilantin patients had a 3-fold less incidence of paresthesia and no cases of pruritus (compared to a 28% incidence of pruritus in Fos patients).

3.7 Severe AEs

Across all patient studies, there were 39 severe AEs among 534 Fos treated patients (7%). These AEs included ataxia, dizziness, somnolence, pain, nausea, ecchymosis, paresthesia, and pruritus.

3.8 Frequent AEs by Gender

Paresthesia and nystagmus were more common in men. Headache, pruritus, somnolence, and ecchymosis were more common in women. However, the sponsor has not adjusted the gender analysis for dose, rate, route, or clinical setting.

3.9 Frequent AEs by Age

Except for somnolence, the incidence of AEs in Fos patients was no different for the 40-65 year old group compared to the > 65 year old group (n=67). Somnolence was more common in the > 65 age group. However, the sponsor has not adjusted the gender analysis for dose, rate, route, or clinical setting.

3.10 Frequent AEs by Race

404 patients were white and 110 patients were black. 20 remaining patients represented other races. Headache, nausea, and paresthesia showed discrepant rates between white and black patients. Paresthesia occurred in 6% of white patients and only 1% of black patients. However, the sponsor has not adjusted the gender analysis for dose, rate, route, or clinical setting.

3.11 Clinical Labs

No overall pattern of change in laboratory values emerges for any of the parameters reported by the sponsor in the ISS. More detailed reviews of patients with extremely high or low values of lab parameters did not raise any additional concern. Recall that many patients were only treated with a single loading dose of Fos and many patients had concomitant conditions that would be expected to cause some lab abnormalities. No pattern of change in serum phosphorus was noted.

3.12 IM Local Tolerability

Of the 357 patients who received at least one IM injection, there were no severe injection site reactions. Two moderate injection reactions occurred and thirty-one mild reactions occurred.

3.13 IV Local Tolerability

Of the 127 patients who received at least one IV injection, there were no severe infusion-site reactions. There was one moderate reaction and nine mild reactions.

3.14 Deaths, Serious AEs, and Withdrawals

Eleven Cerebyx treated patients died. Ten of these deaths occurred in neurosurgery studies or status epilepticus studies. A review of these deaths raises no new concerns about Cerebyx. None of the deaths can be reasonably attributed to Cerebyx.

A review of the serious AEs and the withdrawals raised no new concerns with regard to Cerebyx. The serious AEs that occur with Dilantin may also occur with Cerebyx.

4.0 Study 16: Ongoing Study in Status Epilepticus

No new safety issues were defined in this uncontrolled study. See the review of the study for additional information. The two safety updates add additional information about this study.

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	4-Month Safety Update
Correspondence Date:	June 22, 1995
Date Received:	June 23, 1995

As per the adopted convention, all Fos doses and rates are expressed as mg phenytoin equivalents in this review.

The cut-off for the safety database for this submission was Feb 22, 1995. Additionally, all deaths and serious adverse events through May 15, 1995 are reported.

In fact this SU only adds data on 12 additional patients, patients who were enrolled in the ongoing study of status epilepticus (SE). Thus a total of 66 pts with SE are included in the SU as opposed to 54 in the NDA. The SU presents cumulative data on exposure to Fos, demographics, safety, deaths, withdrawals due to AEs, and serious AEs for the 861 participants in trials. Also, AE data for the 90 participants exposed to Fos at doses of at least 10mg/kg and rates of at least 100mg/min were examined.

The table below summarizes cutoff dates and patient numbers for the NDA and this SU:

	NDA	SU 1
Population		
Total Enrolled	849	861
Exposed to Fos	736	748
Cutoff Dates		
General Safety	Sept 1, 94	Feb 22, 95
Deaths/Serious AEs	Nov 18, 94	May 15, 95

Deaths and Serious AEs from NDA Cutoff Until Feb 22, 1995:

Deaths: One additional death occurred since the filing of the NDA. Patient 16 from Study 16, died from an intracranial bleed that was present prior to Fos administration.

Serious AEs: Four additional pts had serious AEs between NDA cutoff and Feb 22, 1995. Pt 16 from Study 16 is mentioned above under the category "deaths." Pt 20 from Study 16 developed apnea, CHF, and pulmonary edema. The pt had been treated for SE in the setting of a subdural hematoma; a history of IDDM was obtained. Apnea occurred on day 2 and CHF on day 3. Pts 21 and 22 from Study 16 both developed postictal psychosis. All 3 pts with nonfatal serious AEs recovered.

Withdrawals: No pts were withdrawn from Study 16 since the NDA was compiled.

Deaths and Serious AEs from Feb 22, 1995 Until May 15, 1995:

Deaths: One additional death occurred. Pt 1 from Study 26 (an ongoing active control study of IV loading with Fos vs IV loading with Dilantin) developed cryptococcal meningitis in the setting of AIDS and died.

Serious AEs: Pt 2 from Study 26 was hospitalized for AED toxicity, which the investigator considered severe and possibly related to study medication. 5 days after treatment in the ER for seizures, the pt was admitted with phenytoin toxicity manifested by ataxia with a level of 30; he had been taking maintenance phenytoin, 400 mg/day.

Note: Sponsor's Appendix C.2 (not included) tabulates all deaths, serious AEs, and withdrawals because of AEs for the NDA and through May 15, 95.

Demographics: The demographics of the pts with SE do not change with the addition of the 12 pts.

Adverse Events: The AE tables on page 6-7 of the SU (not included) encompass all 748 subjects/pts exposed to Fos. Such a table is fairly uninformative, given the different routes of administration included. The addition of 12 pts to the 736 reported in the NDA did not change the AE profile.

More relevant is the updated list of all AEs (as well as those deemed associated with use of drug) from **Study 982-16** which occurs as Appendix B.1 (not included) of the SU. The 12 additional pts with SE were treated under this protocol, with pts receiving IV loading doses of Fos. The predominant (>5%) AEs in Study 16 are nystagmus (29%), headache (15%), ataxia (14%), somnolence (12%), agitation (12%), vomiting (11%), pruritus (9%), dizziness (8%), dysarthria (6%), and fever (6%).

Vital signs: Sponsor's Appendix B.2 from the SU (not included) provides the incidence of changes in systolic BP >20 mmHg from Study 16. 37/65 (57%) pts had such a decrease. The sponsor further divides this group by those with a "symptomatic decrease," associated with the AE dizziness, vertigo, lightheadedness, or hypotension.

Infusion site evaluations: Appendix B.3 (not included) from the SU provides the incidence of local skin reactions from Study 16. Data are grouped for 24-hour posttreatment or discharge. If both 24 hour data and discharge data are available, it is not clear how the sponsor chose one over the other. The way the data are collected, mild tenderness, swelling, bruising, and erythema are reported for 3-8% of pts. One pt had moderate bruising.

Clinical lab data: The sponsor states that no clinically significant changes were noted for the 12 additional pts in the SU.

Cohort of Patients Adequately Loaded IV: Sponsor's Appendix D.1 (not included) tabulates patients/subjects treated with Fos at doses >10mg/kg and rates > 100mg/min. 105 **individual exposures** are listed. 15 normal volunteers had 2 exposures at either different doses or different rates; therefore a total of 90 **individual subjects** are included.

37 of the exposures were in normal volunteers, so that 68 patients were treated in this cohort. 51 of these pts came from Study 16, a study of SE. 17 came from Study 21, a study in pts who simply "required a loading dose of phenytoin." The 12 new treated pts in this SU all came from Study 16, but only 11/12 are included in this cohort of high dose/high rate pts.

At this point in time, only 35 individuals have been dosed at 15mg/kg or greater, as well as 150mg/min.

Sponsor's Tables 5 and 6 summarize the breakdown of AEs by dose and rate for the 90 individual subjects exposed. (Note that these Tables were reformatted by the sponsor at my request so that pts treated at the higher doses and rates are not included in the columns for the lower doses and rates as they were in the original tables.) The sponsor concludes that "an increased incidence of AEs was not shown for successive increments of participants in this subgroup treated with increasing doses and rates. In particular, cardiovascular events occurred at a similar incidence across groups and did not appear to be related to the dose or rate of fosphenytoin administration."

However, there are several problems with inferences drawn from Tables 5 and 6. First, the denominators at any dose or rate window will be low, so that we cannot be sure we have captured the true AE profile with any certainty. Second, there is no control group. In particular, it would be interesting to compare the AE profile between pts randomized to phenytoin at 50mg/min vs Fos at 150mg/min. This latter information is being collected in the sponsor's ongoing study, Study 26. Finally, recall that these pts are often obtunded and cannot report some AEs that an awake, alert pt could report.

Literature Review: The sponsor's literature review covers the time period through March 10, 1995. One report of phlebitis in a Fos treated pt

is included. The sponsor maintains that, because of the mild tenderness alone, a clinical diagnosis of phlebitis was not applicable. This is an important issue in that the sponsor has proposed a lower incidence of phlebitis with Fos than with parenteral Dilantin.

Sponsor's Conclusions: The sponsor maintains that the safety profile has not changed with the additional information provided in the SU. The sponsor maintains that:

1. Overall, the AE profile of Fos is similar to that of parenteral Dilantin.

2. IV Fos is associated with fewer infusion site reactions than IV Dilantin (i.e. less pain and burning).

3. IM Fos produced no more injection site reactions than placebo.

4. High-dose, high-rate Fos IV (i.e. the bioequivalent dose and rate) has no more AEs associated with it than lower-dose, lower-rate Fos.

Reviewer's Conclusions: No significant change in the safety profile of Fos has arisen with the addition of the 12 new patients. The sponsor's 4 points above can be addressed as follows:

1. The AE profiles of Fos and parenteral Dilantin must be compared by route of administration. Further, only randomized trials that are adequately powered to detect a difference between treatments can truly assess the comparability of treatments.

2. IV Fos at high-dose, high-rate administration (the bioequivalent dose and rate) has only been given to 35 individuals. The sponsor's literature review demonstrates that IV Fos is not without some risk of local irritation; any estimate of the incidence of infusion site reactions must be so imprecise as to preclude any statements in favor of Fos.

3. The statement about IM Fos may be correct based on a study where IM **maintenance** therapy was studied. Whether this holds true for IM loading with Fos is unknown.

4. The populations of pts that received high-dose, high-rate Fos and lower-dose, lower-rate Fos may be so different as to preclude any statements about the safety of one regimen vs the other. (I suspect that pts with SE were more likely to receive the more aggressive regimens. These pts might be sicker on average and thus less likely to report events such as dizziness or tinnitus.) Only a randomized study can answer this question.

Looking at **IV loading doses** alone, Fos, at the bioequivalent dose and rate, has the potential to cause local reactions and has been shown to cause hypotension (as defined by > 20mmHg drop in SBP) in 57% of pts. The advantages of IV Fos are: 1) It can be given in 1/3 the time required to give an equimolar dose of Dilantin; and 2) It is more compatible with other IV fluids and drugs than Dilantin.

IV maintenance Fos has the same two advantages over Dilantin.

IM loading with Fos is tolerated, while Dilantin is reported to cause local irritation and unpredictable systemic absorption. The SU has not changed the database to either support or refute the use of IM loading with Fos.

IM maintenance with Fos presents the same situation as IM loading. Again the SU has not changed the position of Fos in this regard.

John Feeney, M.D.
Medical Reviewer

cc:
HFD-120
NDA 20-450
HFD-120/Leber/Katz/Feeney/Nighswander

REFORMATTED TABLE 5. Number of Subjects and Patients Exposed to Fosphenytoin at High Doses and Rates

	SU1 Infusion Rate (mg/min)	
Dose (mg/kg)	≥100 to < 150	≥150
≥10 to <15	19	15
≥15	21	35

REFORMATTED TABLE 6 (a). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Rate and Increments of Dose
[Number (%) of Participants]
(Page 1 of 4)

BODY SYSTEM/ Preferred Term	SU1 FOS at ≥100 to 150 mg/min ≥10 to <15 mg/kg N = 19		SU1 FOS at ≥100 to 150 mg/min ≥15 mg/kg N = 21	
ANY ADVERSE EVENT	18	(94.7)	21	(100)
NERVOUS				
Nystagmus	7	(36.8)	11	(52.4)
Dizziness	7	(36.8)	5	(23.8)
Paresthesia	4	(21)	6	(28.6)
Somnolence	0	(0)	3	(14.3)
Ataxia	0	(0)	6	(28.6)
BODY AS A WHOLE				
Headache	6	(31.6)	6	(28.6)
DIGESTIVE				
Nausea	1	(5.3)	1	(4.8)
SPECIAL SENSES				
Tinnitus	1	(5.3)	1	(4.8)
SKIN AND APPENDAGES				
Pruritus	7	(36.8)	5	(23.8)

REFORMATTED TABLE 6 (b). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Rate and Increments of Dose
[Number (%) of Participants]
(Page 2 of 4)

	SU1			
BODY SYSTEM/ Preferred Term	FOS at ≥ 150 mg/min			
	≥10 to <15 mg/kg N = 15		≥15 mg/kg N = 35	
ANY ADVERSE EVENT	14	(93.3)	32	(91.4)
NERVOUS				
Nystagmus	9	(60)	14	(40)
Dizziness	6	(40)	6	(17.1)
Paresthesia	4	(26.7)	6	(17.1)
Somnolence	2	(13.3)	2	(5.7)
Ataxia	2	(13.3)	1	(2.9)
BODY AS A WHOLE				
Headache	5	(33.3)	1	(2.9)
DIGESTIVE				
Nausea	1	(6.7)	1	(2.9)
SPECIAL SENSES				
Tinnitus	2	(13.3)	1	(2.9)
SKIN AND APPENDAGES				
Pruritus	7	(46.7)	5	(14.3)

REFORMATTED TABLE 6 (c). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Dose and Increments of Rate

[Number (%) of Participants]

	SU1			
BODY SYSTEM/ Preferred Term	FOS at ≥10 to <15 mg/kg			
	≥100 to <150 mg/min N = 19		≥150 mg/min N = 15	
ANY ADVERSE EVENT	18	(94.7)	14	(93.3)
NERVOUS				
Nystagmus	7	(36.8)	9	(60)
Dizziness	7	(36.8)	6	(40)
Paresthesia	4	(21)	4	(26.7)
Somnolence	0	(0)	2	(13.3)
Ataxia	0	(0)	2	(13.3,
BODY AS A WHOLE				
Headache	6	(31.6)	5	(33.3)
DIGESTIVE				
Nausea	1	(5.3)	1	(6.7)
SPECIAL SENSES				
Tinnitus	1	(5.3)	2	(13.3)
SKIN AND APPENDAGES				
Pruritus	7	(36.8)	7	(46.7)

REFORMATTED TABLE 6 (d). All Adverse Events Occurring in ≥5% of Subjects or Patients Who Received IV Fosphenytoin, by Dose and Increments of Rate

[Number (%) of Participants]

	SU1	
	FOS at ≥15 mg/kg	
BODY SYSTEM/ Preferred Term	≥100 to <150 mg/min N = 21	≥150 mg/min N = 35
ANY ADVERSE EVENT	21 (100)	32 (91.4)
NERVOUS		
Nystagmus	11 (52.4)	14 (40)
Dizziness	5 (23.8)	6 (17.1)
Paresthesia	6 (28.6)	6 (17.1)
Somnolence	3 (14.3)	2 (5.7)
Ataxia	6 (28.6)	1 (2.9)
BODY AS A WHOLE		
Headache	6 (28.6)	1 (2.9)
DIGESTIVE		
Nausea	1 (4.8)	1 (2.9)
SPECIAL SENSES		
Tinnitus	1 (4.8)	1 (2.9)
SKIN AND APPENDAGES		
Pruritus	5 (23.8)	5 (14.3)

Review and Evaluation of Clinical Data
NDA 20-450

Sponsor:	Parke-Davis
Drug:	Fosphenytoin IV
Proposed Indication:	Epilepsy
Material Submitted:	Second Safety Update
Correspondence Date:	October 31, 1995
Date Received:	November 4, 1995

As per the adopted convention, all Fos doses and rates are expressed as mg phenytoin equivalents (PE) in this review.

The cut-off for the safety database for this submission was Aug 1, 1995. Additionally, all deaths and serious adverse events through Sept 15, 1995 are reported.

In fact this SU adds data on 111 additional patients since the first safety update. The sponsor reports that the safety profile of Cerebyx in the safety update is consistent with that reported in the NDA and first safety update.

Since the first safety update, 3 deaths, 4 serious AEs, and 8 withdrawals due to AEs have occurred in 8 Cerebyx treated patients. The 3 deaths were due to cerebral edema, accidental drowning, and GI bleeding. Reasons for withdrawal included generalized itching, burning and itching, nausea and itching, hypotension, and agitation.

All 111 new exposures to Cerebyx were to the IV formulation. No new IM data is provided.

Data from 2 studies initiated and completed since the submission of the NDA and first safety update are included, Study 27 and Study 26.

TABLE 1. Number of Participants and Time Periods Covered in Safety Documents

	NDA	SU1	SU2
Population			
Total Enrolled	849	861[b]	994
Heathy Subjects[a]	159	159	175
Patients (epilepsy or neurosurgical) From Completed Studies	636	636	748
Status Epilepticus Patients From Ongoing Study	54	66[b]	71
Exposed to Fosphenytoin	736	748	859
Healthy Subjects[a]	148	148	164
Patients (epilepsy or neurosurgical) From Completed Studies	534	534	624
Status Epilepticus Patients From Ongoing Study	54	66[b]	71
Exposed to Fosphenytoin at High Dose (≥10 mg/kg) and High Rate (≥100 mg/min)	79	90[b]	194
Healthy Subjects[a]	22	22	38
Patients (epilepsy or neurosurgical) From Completed Studies	17	17	101
Status Epilepticus Patients From Ongoing Study	40	51[b]	55
Cut-Off Dates			
General Safety Information	09/01/94	02/22/95	08/01/95
Deaths and Serious Adverse Events	11/18/94	05/15/95	09/15/95

[a] Some subjects received multiple exposures to fosphenytoin but are only counted once in this table.
[b] All additional exposures were from an ongoing study of patients with status epilepticus (982-16).

Study 27

The final study report for Study 27 is not provided.

This was an open-label single dose study in which 16 normal volunteers received 1200mg Fos at 150mg/min. There were no deaths, no serious AEs, or withdrawals due to AEs. No slowing or discontinuation of infusions because of AEs is specifically reported.

226 AEs were reported. 108 were mild. 106 were moderate. 12 were severe in intensity. The severe AEs included:

pruritus	4 events
paresthesia	2 events
dizziness	2 events
aching knees	1 event
pelvic pain (burning)	1 event
asthenia	1 event
tinnitus	1 event

"The duration of the event ... was <30 minutes for 7 subjects, <2 hours for 2 subjects, <5 hours for 1 subject, and <21 hours for 2 subjects."

Injection-site symptoms including inflammation and reaction were experienced by 3 subjects and were all rated mild in intensity.

75% of subjects experienced paresthesia. 75% of subjects experienced pruritus.

The sponsor reports no changes in ECGs or clinical labs of clinical significance. One subject experienced a drop in BP to 67/43 10 minutes after infusion.

In reviewing the clinical lab data listings, I note that 9 subjects had ionized free calcium levels checked at variable times after infusion. All of the values reported are unremarkable. 5 of the 9 had free calcium levels checked immediately after the infusion. The sponsor makes no comment about these specific levels and their significance.

In reviewing the clinical lab data listings, I also noted bicarb levels were checked at frequent intervals after dosing. It appears that baseline levels

dip by a small increment for some patients, while patient 16 had a level below the stated normal range. Again the sponsor does not comment on these levels.

Study 26

This was a 112 patient, double-blind, randomized, parallel study of an IV loading dose of fosphenytoin vs. an IV loading dose of phenytoin. Patients were randomized in a 4:1 ratio to fos vs phenytoin. The inclusion/exclusion criteria did not specify particular diagnostic categories of patients to be included; rather pts who required a loading dose of phenytoin were to be included. Broadly speaking, this would include pts who were in status epilepticus as well as many other patients.

Pts received equimolar amounts of fos or phenytoin. The bioequivalent infusion rates (based on free phenytoin levels) were used so that the time of infusion was approximately 7 minutes for fos and 20 minutes for phenytoin. The total dose was to be 20mg/kg phenytoin equivalents (PE) except for patients with baseline phenytoin levels or patients over 65 years of age who received 15mg/kg.

90 patients received Cerebyx while 22 received Dilantin. The study was started in April, 1995 and completed in June, 1995.

Roughly half the patients in each treatment group were epilepsy patients; roughly a third of the patients in each treatment group were neurosurgery patients. Only 2 patients with status epilepticus were entered and both were in the Cerebyx arm of the trial.

14% of Cerebyx patients had the infusion modified because of AEs; 2% had the infusion modified because of AEs and pump problems. 50% of Dilantin patients had the infusion modified because of AEs; 14% had the infusion modified because of AEs and pump problems. The predominant reason for modifying the infusion in Dilantin patients was the occurrence of local injection site pain. The predominant reason for modifying the infusion in Cerebyx patients was the occurrence of more generalized itching and tingling, especially in the groin and lower extremities.

TABLE 5. Study 982-26: All and Associated[a] Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM/ Adverse Events	IV Fosphenytoin N = 90				IV Dilantin N = 22			
	All		Associated		All		Associated	
ANY ADVERSE EVENT	81	(90)	75	(83)	18	(82)	18	(82)
NERVOUS SYSTEM[b]	69	(77)	63	(70)	17	(77)	17	(77)
Nystagmus	40	(44)	39	(43)	13	(59)	13	(59)
Dizziness	28	(31)	28	(31)	6	(27)	6	(27)
Somnolence	18	(20)	18	(20)	6	(27)	6	(27)
Ataxia	10	(11)	9	(10)	4	(18)	4	(18)
Stupor	7	(8)	7	(8)	1	(5)	1	(5)
Incoordination	4	(4)	4	(4)	1	(5)	1	(5)
Paresthesia	4	(4)	4	(4)	0	(0)	0	(0)
Extrapyramidal Syndrome	4	(4)	3	(3)	0	(0)	0	(0)
Tremor	3	(3)	1	(1)	2	(9)	2	(9)
Agitation	3	(3)	0	(0)	0	(0)	0	(0)
Hypesthesia	2	(2)	2	(2)	2	(9)	2	(9)
Dysarthria	2	(2)	2	(2)	0	(0)	0	(0)
Vertigo	2	(2)	2	(2)	0	(0)	0	(0)
Brain Edema	2	(2)	0	(0)	1	(5)	0	(0)
Neuropathy	2	(2)	0	(0)	0	(0)	0	(0)
Akathisia	1	(1)	1	(1)	0	(0)	0	(0)
Coma	1	(1)	1	(1)	0	(0)	0	(0)
Intracranial Hypertension	1	(1)	1	(1)	0	(0)	0	(0)
Abnormal Gait	1	(1)	0	(0)	0	(0)	0	(0)
Hemiplegia	1	(1)	0	(0)	0	(0)	0	(0)
Hypertonia	1	(1)	0	(0)	0	(0)	0	(0)
Reflexes Increased	1	(1)	0	(0)	0	(0)	0	(0)
Twitching	1	(1)	0	(0)	0	(0)	0	(0)
Anxiety	0	(0)	0	(0)	1	(5)	1	(5)
Euphoria	0	(0)	0	(0)	1	(5)	1	(5)
Speech Disorder	0	(0)	0	(0)	1	(5)	1	(5)
SKIN AND APPENDAGES[b]	45	(50)	43	(48)	1	(5)	1	(5)
Pruritus	44	(49)	43	(48)	1	(5)	1	(5)
Fungal Dermatitis	1	(1)	0	(0)	0	(0)	0	(0)
Rash	1	(1)	0	(0)	0	(0)	0	(0)

[a] Considered by the investigator to be definitely, probably, possibly related to treatment, or of insufficient information to determine relationship.

[b] The totals for this body system are less than the number of patients with adverse events because at least 1 patient had more than 1 adverse event.

TABLE 5. Study 982-26: All and Associated[a] Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Events	IV Fosphenytoin N = 90				IV Dilantin N = 22			
	All		Associated		All		Associated	
DIGESTIVE[b]	17	(19)	14	(16)	3	(14)	3	(14)
Nausea	8	(9)	6	(7)	3	(14)	3	(14)
Tongue Disorder	4	(4)	4	(4)	0	(0)	0	(0)
Dry Mouth	4	(4)	3	(3)	1	(5)	1	(5)
Vomiting	2	(2)	2	(2)	2	(9)	2	(9)
Rectal Disorder	1	(1)	1	(1)	0	(0)	0	(0)
Tenesmus	1	(1)	1	(1)	0	(0)	0	(0)
SPECIAL SENSES[b]	14	(16)	12	(13)	3	(14)	3	(14)
Tinnitus	8	(9)	8	(9)	2	(9)	2	(9)
Diplopia	3	(3)	3	(3)	0	(0)	0	(0)
Taste Perversion	3	(3)	2	(2)	0	(0)	0	(0)
Amblyopia	2	(2)	2	(2)	2	(9)	2	(9)
Deafness	2	(2)	1	(1)	0	(0)	0	(0)
Ear Disorder	1	(1)	1	(1)	0	(0)	0	(0)
Eye Disorder	1	(1)	0	(0)	0	(0)	0	(0)
Visual Field Defect	1	(1)	0	(0)	0	(0)	0	(0)
CARDIOVASCULAR[b]	13	(14)	12	(13)	4	(18)	4	(18)
Hypotension	7	(8)	7	(8)	2	(9)	2	(9)
Vasodilatation	5	(6)	5	(6)	1	(5)	1	(5)
Tachycardia	2	(2)	1	(1)	0	(0)	0	(0)
Hypertension	1	(1)	0	(0)	0	(0)	0	(0)
Palpitation	0	(0)	0	(0)	1	(5)	1	(5)
BODY AS A WHOLE[b]	13	(14)	8	(9)	2	(9)	2	(9)
Pelvic Pain	4	(4)	4	(4)	0	(0)	0	(0)
Asthenia	2	(2)	2	(2)	0	(0)	0	(0)
Back Pain	2	(2)	2	(2)	0	(0)	0	(0)
Headache	2	(2)	0	(0)	1	(5)	1	(5)
Overdose	1	(1)	1	(1)	0	(0)	0	(0)
Pain	1	(1)	0	(0)	1	(5)	1	(5)
Chills	1	(1)	0	(0)	0	(0)	0	(0)
Cryptococcosis	1	(1)	0	(0)	0	(0)	0	(0)
Death	1	(1)	0	(0)	0	(0)	0	(0)
Face Edema	1	(1)	0	(0)	0	(0)	0	(0)

[a] Considered by the investigator to be definitely, probably, possibly related to treatment, or of insufficient information to determine relationship.

[b] The totals for this body system are less than the number of patients with adverse events because at least 1 patient had more than 1 adverse event.

TABLE 5. Study 982-26: All and Associated[a] Adverse Events by Body System and Treatment Group

[Number (%) of Patients]

(Page 3 of 3)

BODY SYSTEM/ Adverse Events	IV Fosphenytoin N = 90				IV Dilantin N = 22			
	All		Associated		All		Associated	
BODY AS A WHOLE[b] (continued)								
Fever	1	(1)	0	(0)	0	(0)	0	(0)
Injection-Site Reaction	1	(1)	0	(0)	0	(0)	0	(0)
RESPIRATORY	3	(3)	0	(0)	0	(0)	0	(0)
Pneumonia	1	(1)	0	(0)	0	(0)	0	(0)
Sinusitis	1	(1)	0	(0)	0	(0)	0	(0)
Sputum Increased	1	(1)	0	(0)	0	(0)	0	(0)
METABOLIC AND NUTRITIONAL	2	(2)	0	(0)	1	(5)	1	(5)
Hyperglycemia	1	(1)	0	(0)	0	(0)	0	(0)
Hypokalemia	1	(1)	0	(0)	0	(0)	0	(0)
Peripheral Edema	0	(0)	0	(0)	1	(5)	1	(5)
HEMIC AND LYMPHATIC	2	(2)	0	(0)	0	(0)	0	(0)
Ecchymosis	1	(1)	0	(0)	0	(0)	0	(0)
Hypochromic Anemia	1	(1)	0	(0)	0	(0)	0	(0)
UROGENITAL	2	(2)	0	(0)	0	(0)	0	(0)
Urinary Tract Infection	1	(1)	0	(0)	0	(0)	0	(0)
Vaginal Moniliasis	1	(1)	0	(0)	0	(0)	0	(0)

[a] Considered by the investigator to be definitely, probably, possibly related to treatment, or of insufficient information to determine relationship.

[b] The totals for this body system are less than the number of patients with adverse events because at least 1 patient had more than 1 adverse event.

The AE profile in this study reveals pruritus in 50% of Cerebyx patients and 5% of Dilantin patients.

Of the 44 Cerebyx patients who reported pruritus, 6 reported severe intensity. 8 patients had pruritus continue for up to 1-2 hours. Not stated is the intensity of the pruritus for these last 8 patients. 5 patients had no stop time recorded for the pruritus. 4 were listed as recovered at the follow-up visit. One was listed as clinical outcome unknown.

The infusion was modified for 13/44 Cerebyx patients with pruritus. None of the patients with pruritus reported any additional skin reactions, fever, or other AEs suggestive of drug hypersensitivity or anaphylaxis.

The AE listing is attached.

9% of Cerebyx patients reported localized pain and/or burning at the injection site during infusion compared to 90% of Dilantin patients.

Cohort of Patients Adequately Loaded IV: All the new exposures in this safety update were IV, primarily at high doses and rates as a result of the Study 26 and Study 27 protocols. Therefore, there are currently 194 individuals in the safety database (38 volunteers and 156 patients) who received Cerebyx at doses >10mg/kg and rates > 100mg/min. Of these 194 individuals, 128 received Cerebyx at >15mg/kg and > 150mg/min. 66 received Cerebyx at $\geq$ 19.5mg/kg and $\geq$ 150 mg/min.

Sponsor's Table 11 summarizes the breakdown of AEs by dose and rate for the 128 patients exposed.

Sponsor's Table 12 summarizes the breakdown of AEs according to the reported intensity of the AEs.

Given the heterogenicity of the total population treated at the highest dose and rate (status epilepticus, neurosurgery, epilepsy), care must be exercised in extrapolating from these results.

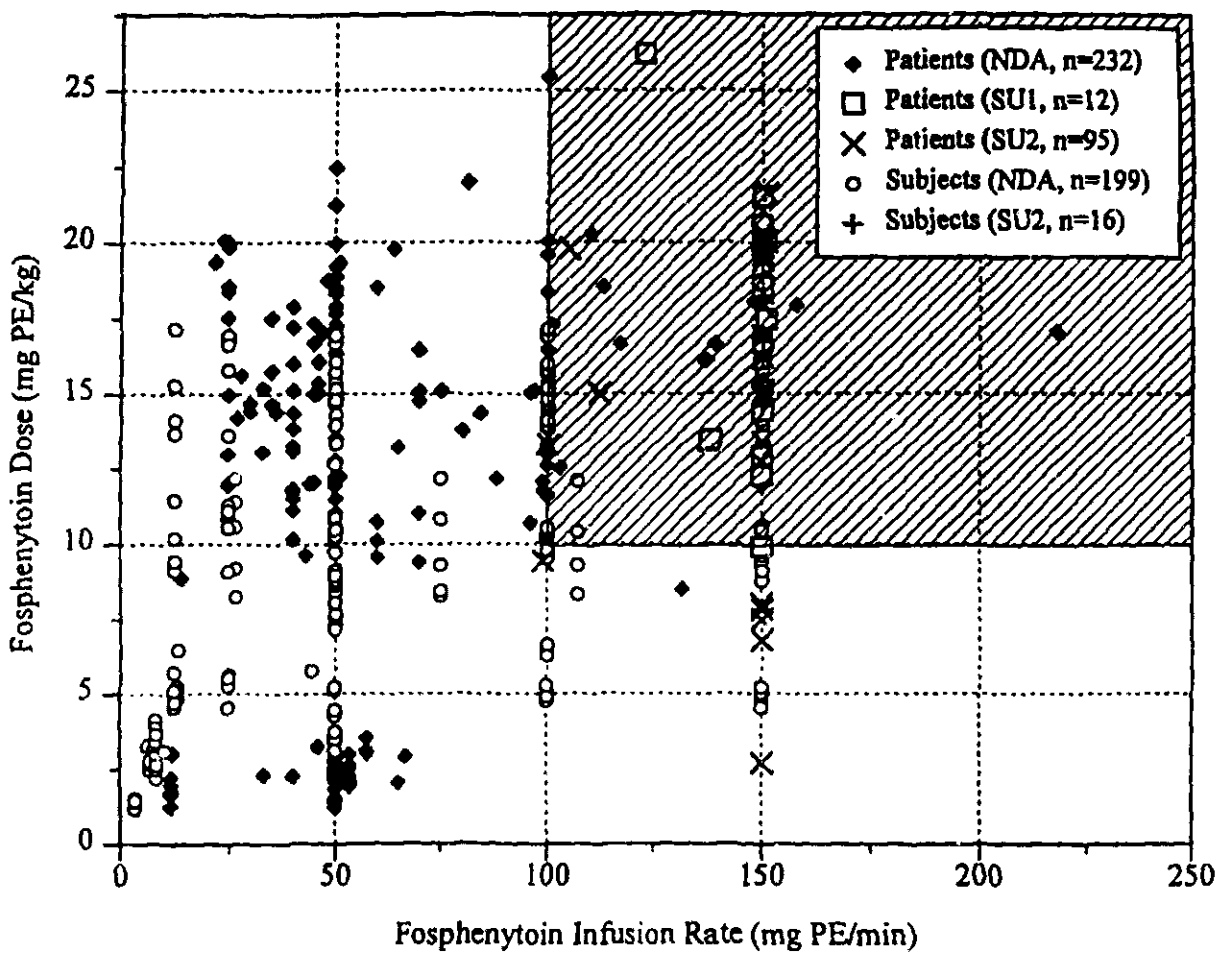

FIGURE 1. Subject and Patient Exposure to Fosphenytoin by Dose and Rate

TABLE 10. Number of Participants[a] Exposed to Fosphenytoin at High Doses and Rates

Dose (mg/kg)	Infusion Rate (mg/min)			
	≥100 to <150		≥150	
	SU1	SU2	SU1	SU2
≥10 to <15	19	24	15	25
≥15	21	32	35	128

[a] Total number of participants is less than total number of exposures because some subjects received multiple exposures to fosphenytoin.

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TABLE 11. Most Frequent Adverse Events[a] by Any IV Dose or Rate, Lower Doses or Rates, and Higher Doses and Higher Rates

[Number (%) of Participants]

BODY SYSTEM/ Adverse Event	IV Fosphenytoin at any Dose or Rate N = 490		IV Fosphenytoin at Lower Doses (<15 mg/kg) or Rates (<150 mg/min) N = 373[b]		IV Fosphenytoin at Higher Doses (≥15 mg/kg) and Higher Rates (≥150 mg/min) N = 128	
ANY ADVERSE EVENT	381	(77.8)	278	(74.5)	114	(89.1)
NERVOUS	296	(60.4)	213	(57.1)	94	(73.4)
Nystagmus	144	(29.4)	92	(24.7)	61	(47.7)
Dizziness	121	(24.7)	85	(22.8)	39	(30.5)
Paresthesia	81	(16.5)	65	(17.4)	21	(16.4)
Somnolence	54	(11.0)	32	(8.6)	22	(17.2)
Ataxia	44	(9.0)	23	(6.2)	21	(16.4)
BODY AS A WHOLE	143	(29.2)	111	(29.8)	34	(26.6)
Headache	50	(10.2)	39	(10.5)	12	(9.4)
Pain	25	(5.1)	12	(3.2)	13	(10.2)
DIGESTIVE	88	(18.0)	59	(15.8)	30	(23.4)
Nausea	41	(8.4)	25	(6.7)	16	(12.5)
SPECIAL SENSES	87	(17.8)	57	(15.3)	35	(27.3)
Tinnitus	47	(9.6)	26	(7.0)	21	(16.4)
SKIN AND APPENDAGES	113	(23.1)	62	(16.6)	53	(41.4)
Pruritus	103	(21.0)	54	(14.5)	51	(39.8)

[a] Most frequent adverse events are defined as those that occurred in ≥5% of fosphenytoin-treated subjects or patients.
[b] Includes 11 subjects who are also included in the higher dose/higher rate (N = 128) category.

RR- REG 720-03595
Second Safety Update
Fosphenytoin Sodium
Injection

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TABLE 12. Most Frequent Adverse Events[a] by Lower Doses or Rates, Higher Doses and Higher Rates, and Maximum Intensity

[Number (%)[b] of Patients or Exposures in Subjects)

Preferred Term	IV Fosphenytoin at Doses (<15 mg/kg) or Rates (<150 mg/min) N = 373[c]						IV Fosphenytoin at Doses (≥15 mg/kg) and Rates (≥150 mg/min) N = 128							
	Mild		Moderate		Severe		Mild		Moderate		Severe		Unknown	
Any Adverse Event	203	(73.0)	61	(21.9)	14	(5.0)	66	(57.9)	36	(31.6)	11	(9.6)	1	(0.9)
Nystagmus	84	(91.3)	8	(8.7)	0	(0.0)	38	(62.3)	23	(37.7)	0	(0.0)	0	(0.0)
Dizziness	67	(78.8)	16	(18.8)	2	(2.4)	19	(48.7)	18	(46.2)	2	(5.1)	0	(0.0)
Paresthesia	54	(83.1)	10	(15.4)	1	(1.5)	10	(47.6)	10	(47.6)	1	(4.8)	0	(0.0)
Somnolence	21	(65.6)	11	(34.4)	0	(0.0)	10	(45.5)	11	(50.0)	1	(4.5)	0	(0.0)
Ataxia	18	(78.3)	4	(17.4)	1	(4.3)	10	(47.6)	10	(47.6)	1	(4.8)	0	(0.0)
Headache	24	(61.5)	14	(35.9)	1	(2.6)	7	(58.3)	5	(41.7)	0	(0.0)	0	(0.0)
Pain	7	(58.3)	2	(16.7)	3	(25.0)	5	(38.5)	8	(61.5)	0	(0.0)	0	(0.0)
Nausea	18	(72.0)	6	(24.0)	1	(4.0)	11	(68.8)	4	(25.0)	1	(6.3)	0	(0.0)
Tinnitus	21	(80.8)	4	(15.4)	1	(3.8)	10	(47.6)	10	(47.6)	1	(4.8)	0	(0.0)
Pruritus	30	(55.6)	19	(35.2)	5	(9.3)	29	(56.9)	18	(35.3)	4	(7.8)	0	(0.0)

[a] Most frequent adverse events are defined as those that occurred in ≥5% of fosphenytoin-treated subjects or patients

[b] Percents are based on number of participants with the adverse event in the lower dose or rate, or higher dose and rate category

[c] Includes 11 subjects who are also included in the higher dose/higher rate (N = 128) category.

RR-REG 720-03593
Second Safety Update
Fosphenytoin Sodium
Injection

29

Sponsor's Discussion: In this second safety update, the sponsor acknowledges the occurrence of pruritus in Cerebyx-treated subjects and patients. The sponsor comments that other phosphate ester prodrugs, Decadron and Hydrocortone, cause a burning sensation in the groin area. The sponsor states that Foscavir in the treatment of CMV retinitis causes tingling. The sponsor draws attention to the fact that, in Study 26, infusions were interrupted more often with Dilantin than with Cerebyx. The sponsor acknowledges that interruptions require patients to be awake; the sponsor states that patients were, as a rule, awake in Study 26, although specific treatment group comparisons of level of consciousness are not presented.

My Comments: After reviewing the sponsor's references on Decadron and Hydrocortone, I am impressed by the similarities between the character and the location of the sensory disturbance that those drugs create and that Cerebyx creates. Specifically, Cerebyx, like Decadron and Hydrocortone, seems to cause a burning and itching which predominates in the groin area. The intensity of the disturbance seems less with Decadron and Hydrocortone, but the loading dose of these drugs would deliver only 1/20th-1/10th the phosphate that a loading dose of Cerebyx would deliver. Could phosphate alone cause this characteristic sensory disturbance ? If so, are there any intermediate steps required, for instance, the induction of hypocalcemia via calcium-phosphate precipitation ?

My answer to the last question would be, perhaps not. The sensory disturbance described in hypocalcemia is usually a tingling that localizes to the face and hands. While tingling is also described in Cerebyx-treated patients, burning and itching predominate in the descriptions provided. Further, the burning and itching with Cerebyx is often immediate in onset, suggesting a minimal number of steps to cause the phenomenon. Also, free calcium levels were checked in 5 subjects in Study 27 immediately after infusion and were normal. (Not stated was whether these same 5 subjects had sensory disturbances.)

The sponsor mentions Foscavir as another drug that causes sensory disturbances. My understanding is that Foscavir is not broken down to

phosphate, but rather is excreted unchanged in the urine. It is believed that Foscavir actually chelates calcium causing a transient hypocalcemia which, in turn, causes the characteristic sensory disturbance of hypocalcemia (tingling in the face and hands). Therefore, I do not think Foscavir-induced sensory phenomena are parallel to Cerebyx-induced sensory phenomena.

From Studies 26 and 27, I believe the sponsor could provide a much better description of the sensory disturbance caused by the SE dosing regimen of Cerebyx. Currently, I have only been provided narrative accounts for patients and subjects who had "serious" AEs. Patients who had "severe" but not "serious" sensory disturbances are of special interest. For these patients, I think we need to know the duration of sensory disturbance.

John Feeney, M.D.
Medical Reviewer
January 25, 1996

cc:
HFD-120
NDA 20-450
HFD-120/Leber/Katz/Feeney/Nighswander

APPENDIX E.2

NARRATIVES FOR DEATHS, SERIOUS ADVERSE EVENTS, AND WITHDRAWALS BECAUSE OF ADVERSE EVENTS THROUGH 09/15/95

Overall Listing of Deaths, Serious Adverse Events, and Withdrawals Because of Adverse Events

Study	Center/Patient	Indication	Death	Serious AE	Withdrawal	Narrative Number (ISS, Appendix F)	
Studies in Subjects							
982-003	003/016	HS		X	X	1	(SW)
982-011	011/010	HS		X	X	2	(SW)
982-012	012/006	HS		X		3	(S)
982-017	017/001	HS			X	4	(W)
Studies in Patients							
982-013	007/014	E		X	X	5	(SW)
	011/013[a]	E			X	6	(W)
982-014	001/006	N		X		7	(S)
	001/012	N	X	X		8	(DS)
	001/014	N	X	X	X	9	(DSW)
	005/003	N			X	10	(W)
	005/005	N	X	X		11	(DS)
	007/003	N	X	X	X	12	(DSW)
	007/027	N	X	X		13	(DS)
	009/002	N	X	X	X	14	(DSW)
	009/009[b]	N	X	X	X	15	(DSW)
	009/011	N	X	X	X	16	(DSW)
	009/027	N		X	X	17	(SW)
	009/028	N		X		18	(S)
982-015	003/005	N		X		19	(S)
	003/015	N	X	X	X	20	(DSW)
	003/018	N	X	X	X	21	(DSW)
	003/022	N			X	22	(W)
	009/001	N			X	23	(W)

HS = Healthy subjects; E = Epilepsy; N = Neurosurgery; D = Death; S = Serious adverse event; W = Withdrawal.

[a] Patient entered the study a second time at Center 10 as Patient 28 and was withdrawn again because of similar events.

[b] Patient had a serious adverse event and died prior to receiving study drug.

APPENDIX E.2

NARRATIVES FOR DEATHS, SERIOUS ADVERSE EVENTS, AND WITHDRAWALS BECAUSE OF ADVERSE EVENTS THROUGH 09/15/95
(Page 2 of 13)

Overall Listing of Deaths, Serious Adverse Events, and Withdrawals Because of Adverse Events

Study	Center/Patient	Indication	Death	Serious AE	Withdrawal	Narrative Number (ISS, Appendix F)	
Studies in Patients (continued)							
982-016	001/001	SE		X		24	(S)
	001/016	SE		X		31	(S)
	001/017	SE		X		32	(S)
	001/020	SE		X		33	(S)[c]
	002/006	SE	X	X		25	(DS)
	002/011	SE	X	X		26	(DS)
	002/013	SE	X	X		30	(DS)
	009/009	SE		X		27	(S)
	009/021	SE		X		[b]	(S)
	009/22	SE		X		[b]	(S)
	012/016	SE	X	X		34	(DS)[c]
982-021	002/003	LD			X	28	(W)
982-022	004/011	LD		X		29	(S)
982-026	001/009	LD	X	X	X	37	(DSW)[d]
	001/014	LD			X	38	(W)[d]
	001/015	LD			X	39	(W)[d]
	001/033	LD	X	X	X	40	(DSW)[d]
	001/049	LD	X	X	X	41	(DSW)[d]
	002/001	LD	X	X		35	(DS)[c]
	005/001	LD			X	42	(W)[d]
	007/002	LD		X		36	(S)[c]
	007/003	LD			X	43	(W)[d]
	007/004	LD			X	44	(W)[d]
	007/009	LD			X	45	(W)[d]
	007/018	LD			X	46	(W)[d]

SE = Status epilepticus; LD = Required loading dose; D = Death; S = Serious adverse event; W = Withdrawal.

[b] Occurred after data cut-off for the NDA (narratives in ISS, Section 9.2.2)

[c] Occurred during period covered by SU1

[d] Occurred during period covered by SU2

Study 982-13: A 5-Day Study of the Tolerance and Safety of IM Fosphenytoin

Investigators

1	Abou-Khalil	Tennessee	20
2	Dyken	Alabama	3
3	Garnett/Pellock	Virginia	24
4	Lai	Missouri	15
5	Leroy	Texas	18
6	Matsuo	Utah	17
7	Michie/Tipton	Florida	20
8	Ojemann	Washington	20
10	Ramsay	Florida	31
11	Singer	Florida	20
12	Verma	Michigan	20
13	Wilder	Florida	32
Total			240

A. Study Design

This was a 5-day, double-blind, placebo-controlled, parallel-group study of IM Fos. By protocol, adult pts were considered for inclusion if they were taking oral Dilantin for the treatment of epilepsy or seizure prophylaxis, had stable blood phenytoin levels, and were maintaining a record of their seizures.

Pts in one group (25% of total N) were to continue receiving their oral Dilantin dose along with IM placebo. Pts in the other group (75% of the total N) were to receive placebo orally along with IM Fos.

Sponsor's Table 3, a schedule of time and events, is attached. After each injection, subjective evaluations of any irritation produced by the injections were to be made by the patient and the investigator. Seizures were to be recorded. One week after the last injection, a final physical exam was to be performed.

A subset of pts at a single study site (N=24) was to have a more extensive PK evaluation. The rest of the pts had determinations made of plasma phenytoin levels immediately before double-blind treatment and again on the fifth day of treatment. The subset of 24 pts had to be on a QD regimen and had plasma samples collected on Day -1 before dosing and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 hrs post dosing. On Days 1-4, samples were collected before dosing. On Day 5, samples were collected before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, and 24 hrs post dosing. Samples were analyzed for total and free phenytoin levels and Fos levels.

Inclusion/Exclusion Criteria were as follows:

- Pts with epilepsy or recovering from neurosurgery
- 18 years of age and older
- On a stable dose of oral Dilantin for treatment or prophylaxis
- Oral regimen QD or BID
- Phenytoin levels between 10-20, with 2 samples between 1-4 weeks apart within 4 weeks of study entry which are within 30% of one another
- Have a written record of seizures for at least 28 days (if being treated for epilepsy)
- Not on more than 2 drugs to control seizures
- Absence of life-threatening disease

Injections were given in the gluteus maximus and could be divided into 2 equal injections given in separate locations if the dose required a large volume. The pt was to rate on a 4 point scale the extent of pain, itching, and burning immediately after injection and again at 5, 30, 60, and 120 min post-injection, and immediately prior to the next injection.

The attending investigator would examine the site of injection at 5 and 30 min, and 1 and 2 hr after injection and again immediately prior to the next injection. A subjective rating of injury and local irritation was to be made using a 4 point scale applied to the 4 symptoms: redness, swelling, tenderness, and necrosis.

The dose of oral and IM study medication could be adjusted to maintain therapeutic blood concentrations and to minimize phenytoin toxicity.

The protocol-specified analysis plan was vague beyond stating that local

irritation would be compared between groups. It was stated that analyses of both safety and efficacy would be stratified based on whether the drug was given as prophylaxis or as treatment for epilepsy.

The efficacy analysis was likewise vague other than to say that comparisons between treatment groups would be made for seizure control, looking at the treatment period as well as the immediate pre- and post-treatment periods.

"The sample size of 200 was not chosen based on statistical considerations. This number of pts, added to those in other studies, is intended to demonstrate safe passage of pts treated with Fos in a sample of over 500 pts and normal volunteers."

B. Subject Disposition and Baseline Comparison

The first pt entered the study on April 23, 1991 and the last pt completed the study on December 30, 1991. 240 pts were randomized; 5 pts in the Fos group did not receive all 5 days of dosing and 1 additional pt who did receive 5 days of dosing did not return for the follow-up visit.

By design, pts could receive medication QD or BID; in fact, all pts received their medication QD. One treatment group consisted of 179 pts. The other treatment group consisted of 61 pts. The two treatment groups were similar in demographic characteristics. 95% of pts in both groups carried a diagnosis of epilepsy; only 6 pts in one group and 3 pts in the other were neurosurgery pts who required seizure prophylaxis. The mean daily dose of Dilantin was 375mg, with a range of 200-500mg.

The two treatment groups were balanced with respect to the concurrent AED medications used. 70% of pts took no other AEDs. 9-10% of pts took concurrent phenobarb. 9-10% of pts took concurrent VPA. 7-8% of pts took concurrent carbamazepine.

174/179 pts in the Fos group received all 5 days of treatment. 61/61 pts in the Dilantin group received all 5 days of treatment.

During the treatment phase, 13 Fos pts had their dose adjusted. 5/13 had doses lowered because of AEs such as confusion, ataxia, dizziness, and

nystagmus. 2/13 had doses raised because of poor seizure control. 5/13 had dose adjustments because plasma levels were either too high (2) or too low (3); recall that the protocol called for levels during the treatment phase only in pts in the PK special study group. 1/13 had the dose lowered simply due to noncompliance.

2 pts withdrew because of AEs. 2 pts withdrew because of "administrative" reasons. A fifth pt in the Fos group did not receive all 5 doses, but completed the study visits.

Protocol variations that could impact on interpretation of local irritation were as follows:

nonalternating sides for medication injection in 75 pts
multiple injection sites in 7 pts
multiple injections for a given dose not of equal volume in 5 pts

In 26 pts, at least one phenytoin level during screen was less than 10. In 3 pts, the 2 plasma levels during screen were not within 30% of each other.

C. Results

Given the multiple tests for local irritation performed by both the pts and physicians, along with the multiple time points at which these tests were performed for each injection, and the 5 different injections, it is hard to envision a statistic that would capture all this data in a meaningful way. Suffice it to say that a visual screen of all the listings for local skin irritation reveal no clinically significant differences between Fos and placebo injections, other than a slight increase in mild to moderate itching within the first hour after injection.

No deaths occurred during the study. 2 pts withdrew from the Fos group because of AEs. 1 pt experienced a serious AE in the Fos group. The one serious AE reported was phenytoin toxicity. The pt recovered completely after withdrawal from the study; the investigator noted that the pt had taken some additional doses of Dilantin from her own supply on Days 1 and 2 of treatment. The other withdrawal was due to an allergic reaction and pruritus, with full recovery off treatment. (Recall that pts had been exposed to phenytoin chronically before entering the study; exposure to

Fos was not the pt's first exposure to phenytoin.)

The percent of pts reporting any AEs was slightly higher in the Fos group (68%) compared to the placebo group (62%).

There was a higher incidence of nystagmus, incoordination, headache, nausea, and pruritus in the Fos group.

During the study, 6 pts experienced AEs that were rated "severe" in intensity, 4 on Fos and 2 on placebo. In the Fos group, one pt was discussed above as the withdrawal for allergic reaction and pruritus. There was one case each of severe nausea, vomiting, and migraine. In the placebo group, there was one case of dizziness that responded to a reduced dose, and one case of local excision of a breast lesion.

The incidence of seizures during treatment differed between the Fos and placebo groups (18% vs 10%). In particular, Fos pts had a high incidence of partial complex seizures (11%) compared to placebo (2%). Two Fos pts required dose adjustments because of poor seizure control. Most pts experienced no seizures in either treatment group so that the sponsor's comparison of average number of seizures per day between treatment groups is not very instructive. The sponsor acknowledges that the latter is highly influenced by a single patient with a large number of seizures. The sponsor reports some additional analyses which compare change from baseline to treatment period or change from treatment period to post-treatment; no statistically significant differences were found.

Blood pressure, heart rate, and respiration rate were recorded in relation to Fos injections. No clinically important trends were noted in any of these parameters following Fos injection, although 2-3 pts were noted to have blood pressures as low as 90/60 30-60 minutes after Fos injection. Pt 11-13 who discontinued because of dizziness had a BP of 90/60 30 minutes post-dose with a pre-dose pressure of 110/70. No pressures lower than 90/60 were noted for any pt at any time.

To determine any trend toward abnormal lab values during the study, pts were categorized as to whether their lab values were below, within, or above normal range at baseline and at the end of treatment. Changes to low or high from the screening value to the first follow-up visit were summarized. The sponsor notes that no consistent differences or

clinically important trends were evident. Changes from normal at screen to low at f/u occurred for at least 10% of pts in either group for RBC count, WBC count, and calcium.

Detailed PK Analysis: At Center 3, evaluable data was available for 13 pts out of a targeted population of 24. The sponsor explains that for 7 of the remaining 11 pts, samples were collected in heparinized tubes which were later found to interfere with Fos measurements. The remaining 4 pts were in the oral Dilantin/IM placebo group and were therefore not included in the analyses. For the 13 available, samples had been drawn at baseline at numerous times in relation to oral dose administration; on day 5, samples again were drawn at numerous times in relation to IM Fos administration. The ratios for Day 5 (IM Fos)/Baseline (oral Dilantin) are as follows:

Total	Phenytoin	
	Cmax	1.21
	Tmax	0.66
	AUC	1.05
Free	Phenytoin	
	Cmax	1.32
	Tmax	0.42
	AUC	1.18

The increases in Cmax and AUC might be explained by the increased bioavailability of Fos (100%) relative to oral Dilantin (90%). The more marked increases in free phenytoin following IM Fos might be consistent with displacement of phenytoin from plasma protein binding sites by Fos.

Overall PK Analysis at All Centers: A trend analysis was used to determine if there were differences in trough concentrations between treatment groups over time. 20 pts who required changes in dosage during the study were excluded from the analysis; data were available for 165 Fos treated pts and 55 Dilantin treated pts. The results showed that the mean trough concentrations of total phenytoin provided by Fos increased slightly from the first day through the follow-up visit, while the mean trough levels provided by Dilantin orally tended to stay the same. The increase in trough levels seen with Fos may be consistent with the complete bioavailability of IM Fos.

D. Conclusions

The PK data from this trial needs further Biopharm review. Based on the sponsor's presentation of the data, it appears that an IM dose of Fos may be substituted for an equimolar oral dose of Dilantin, achieving plasma levels of total phenytoin and free phenytoin which are roughly 20% higher. The AE profile of IM Fos reflects an increased incidence of nystagmus, incoordination, nausea, and headache, all of which might be expected with higher phenytoin and free phenytoin levels. The increased incidence of pruritus with IM Fos is unexpected based on higher phenytoin levels alone, but would not preclude use of IM Fos.

Perhaps the pts who would benefit most by IM Fos would be chronically Dilantin-treated pts who have a transient 2-3 day gastrointestinal disturbance which prevents oral medication, but is transient and not expected to require IV access for hydration or caloric intake.

Because of the delayed Tmax of total phenytoin and free phenytoin after IM Fos, IM Fos is **not** an alternative route of phenytoin administration in pts with status epilepticus.

TABLE 3. Schedule of Study Procedures

Study Procedure	Patient Selection	Double-Blind Treatment Phase					Follow-up Visit	
		Day						
	-28 to -1	1 through 5					6	13
		Minutes From IM Injection						
		-15	5	30	60	120		
Medical History	X							
Current Medications	X							
Seizure History	X							
Physical Exam	X						X	X
Pregnancy Test	X							
Full Neuro Exam	X							X
Brief Neuro Exam		X					X	
Vital Signs	X	X		X	X	X	X	X
Record Seizures	X	X					X	X
Clinical Labs[a]	X						X	X
Drug Screen	X						X	X
Phenytoin Concentration	2X	X					X	
Patient Ratings		X	X	X	X	X	X	
Injection Site Exam		X	X	X	X	X	X	X
Global Evaluation								

[a] Hematology, blood chemistry, and urinalysis

TABLE 11. All and Associated Adverse Events by Body System and Treatment Group

[Number (%) of Patients]

(Page 1 of 3)

BODY SYSTEM/ Preferred Term	IM FOS/PO PBO N = 179				PO DIL/IM PBO N = 61			
	All		Associated		All		Associated	
ANY BODY SYSTEM	121	(67.6)	71	(39.7)	38	(62.3)	19	(31.1)
NERVOUS	77	(43.0)	51	(28.5)	26	(42.6)	13	(21.3)
Nystagmus	27	(15.1)	15	(8.4)	5	(8.2)	1	(1.6)
Tremor	17	(9.5)	12	(6.7)	8	(13.1)	5	(8.2)
Ataxia	15	(8.4)	6	(3.4)	5	(8.2)	0	(0.0)
Incoordination	14	(7.8)	10	(5.6)	3	(4.9)	1	(1.6)
Somnolence	12	(6.7)	10	(5.6)	6	(9.8)	6	(9.8)
Dizziness	9	(5.0)	8	(4.5)	2	(3.3)	1	(1.6)
Paresthesia	7	(3.9)	3	(1.7)	2	(3.3)	2	(3.3)
Reflexes decreased	5	(2.8)	1	(0.6)	3	(4.9)	2	(3.3)
Depersonalization	2	(1.1)	2	(1.1)	0	(0.0)	0	(0.0)
Abnormal gait	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Confusion	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Dysarthria	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Hyperkinesia	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Hypertonia	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Stupor	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Vertigo	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Reflexes increased	1	(0.6)	0	(0.0)	3	(4.9)	0	(0.0)
Nervousness	1	(0.6)	0	(0.0)	2	(3.3)	1	(1.6)
Anxiety	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypesthesia	0	(0.0)	0	(0.0)	2	(3.3)	2	(3.3)
BODY AS A WHOLE	45	(25.1)	18	(10.1)	12	(19.7)	4	(6.6)
Headache	16	(8.9)	5	(2.8)	3	(4.9)	1	(1.6)
Asthenia	7	(3.9)	5	(2.8)	2	(3.3)	1	(1.6)
Accidental injury	6	(3.4)	1	(0.6)	4	(6.6)	1	(1.6)
Back pain	6	(3.4)	1	(0.6)	0	(0.0)	0	(0.0)
Pain	4	(2.2)	0	(0.0)	1	(1.6)	1	(1.6)
Abdominal pain	3	(1.7)	3	(1.7)	1	(1.6)	0	(0.0)
Infection	3	(1.7)	0	(0.0)	3	(4.9)	0	(0.0)

TABLE 11. All and Associated Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Preferred Term	IM FOS/PO PBO N = 179				PO DIL/IM PBO N = 61			
	All		Associated		All		Associated	
BODY AS A WHOLE (continued)								
Flu syndrome	3	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Allergic reaction	2	(1.1)	2	(1.1)	0	(0.0)	0	(0.0)
Injection site reaction	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Malaise	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Overdose	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
DIGESTIVE	15	(8.4)	6	(3.4)	1	(1.6)	0	(0.0)
Nausea	8	(4.5)	5	(2.8)	0	(0.0)	0	(0.0)
Vomiting	5	(2.8)	2	(1.1)	0	(0.0)	0	(0.0)
Constipation	3	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspepsia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhea	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
HEMIC AND LYMPHATIC	15	(8.4)	12	(6.7)	3	(4.9)	2	(3.3)
Ecchymosis	13	(7.3)	11	(6.1)	3	(4.9)	2	(3.3)
Leukocytosis	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES	10	(5.6)	4	(2.2)	0	(0.0)	0	(0.0)
Pruritus	5	(2.8)	4	(2.2)	0	(0.0)	0	(0.0)
Rash	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin discoloration	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Contact dermatitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Maculopapular rash	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pustular rash	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Sweating	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR	7	(3.9)	4	(2.2)	0	(0.0)	0	(0.0)
Hypertension	3	(1.7)	1	(0.6)	0	(0.0)	0	(0.0)
Migraine	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Palpitation	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Syncope	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Postural hypotension	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

TABLE 11. All and Associated Adverse Events by Body System and Treatment Group
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Preferred Term	IM FOS/PO PBO N = 179				PO DIL/IM PBO N = 61			
	All		Associated		All		Associated	
MUSCULOSKELETAL	4	(2.2)	3	(1.7)	3	(4.9)	2	(3.3)
Leg cramps	3	(1.7)	3	(1.7)	2	(3.3)	2	(3.3)
Joint disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Arthralgia	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
RESPIRATORY	4	(2.2)	0	(0.0)	2	(3.3)	0	(0.0)
Pharyngitis	1	(0.6)	0	(0.0)	1	(1.6)	0	(0.0)
Dyspnea	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Lung disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Sinusitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinitis	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
SPECIAL SENSES	4	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)
Amblyopia	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Diplopia	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Edema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral edema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
ENDOCRINE	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroid disorder	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
UROGENITAL	1	(0.6)	0	(0.0)	1	(1.6)	0	(0.0)
Breast neoplasm	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Fibrocystic breast	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Impotence	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)
SURGERIES/PROCEDURES	1	(0.6)	0	(0.0)	2	(3.3)	0	(0.0)
Surgeries/Procedures	1	(0.6)	0	(0.0)	2	(3.3)	0	(0.0)

Study 982-14: An Open-Label Study of the Tolerance and Safety of IM Fosphenytoin Given as a Single Loading Dose Followed by a Maintenance Regimen For Up To 2 Weeks

Investigators

1	Boucher	Memphis, TN	30
5	Matsuo	Salt Lake City, UT	5
6	Michie	Cape Coral, FL	20
7	Dean	Winston-Salem, NC	30
8	Ramsay	Miami, FL	2
9	Smith	St.Louis, MO	31
Total			118

A. Study Design

The study was intended to be a safety study. The projected enrollment was 150 patients.

Patients were to be candidates for neurosurgery or patients who had already undergone neurosurgery. Open-label treatment was to consist of a single loading dose followed by maintenance dosing for at least 3 days and for a maximum of 7 days (changed by amendment to 14 days). Patients were to return 2-4 days after the last injection for follow-up exams and procedures. A subset of patients at a single site (n=10) were to have PK determinations performed at various timepoints following injections.

Inclusion/exclusion criteria dictated that patients be 12 years of age or older. Pts were not to be have terminal illnesses or other life-threatening diseases.

To be excluded were pts with hypotension, bradycardia, and A-V block. Pts were excluded if they took any AED except benzodiazepines within 1 week prior to screen.

No medications were specifically excluded during the study. Any IV medications other than the study medication were to be administered at a

site different from that used for study drug.

By protocol the study drug could be administered either QD or BID as deemed appropriate by the investigator to achieve therapeutic concentrations of at least 10-20 microgms/mL. A protocol amendment required QD dosing only. Page 7 of the protocol implies that the loading dose would be 8-12 mg/kg PE.

The dosing administration could be divided and given in separate locations on the buttock.

During the treatment period, a trough blood phenytoin was to be drawn each day, prior to the patient receiving the first daily dose of study medication.

B. Subject Disposition and Baseline Comparison

The study was conducted between July 1991 and April 1992.

The study population included 78 males and 40 females, 93 whites and 25 blacks. The mean age was 48 years.

The pts were seriously ill neurosurgery pts who were victims of trauma to the head or other neurological emergencies, the most common of which were motor vehicle accidents and gunshot wounds. Over 1/5 pts were unconscious when they entered the study, and over 1/2 pts had a level of consciousness that was lethargic or worse.

110 pts completed treatment. 80 pts completed the follow-up assessments. 8 pts withdrew, 6 for admin reasons and 2 for AEs.

118 patients were given a loading dose between 8-21.6 mg/kg PE. Maintenance doses ranged from 1.7-17.2 mg/kg. Maintenance doses were given either QD or BID. 64 pts received QD doses, 45 pts received BID doses, and 9 pts received both QD and BID doses.

While the maximum treatment duration was extended by protocol amendment from 7 days to 14 days, only 5 pts received treatment for 8 days or greater.

C. Results

Eight pts withdrew from the study, 2 for administrative reasons and 6 because of AEs. Only 1/6 experienced an event that was considered drug related, an erythematous rash. At the follow-up visit, most of the rash had resolved.

Four pts who withdrew from the study died. Three other pts died after completing the study.

At any one timepoint, a maximum of 3 pts experienced mild irritation at the injection site.

Note that the AE data was grouped across the entire study and was not separated according to loading vs maintenance dosing. Altogether, 75% of pts reported AEs; only 8% of pts overall had AEs that were considered associated with study drug. The most frequent AEs were fever, somnolence, and nystagmus. 5% of pts experienced at least one seizure during open-label treatment; without a comparative treatment group, it is hard to interpret this finding.

Ten pts experienced serious AEs, but none of these were considered associated with study drug.

Changes from baseline in laboratory parameters occurred not infrequently during this study. However, given the population of seriously ill trauma patients requiring neurosurgery, no inferences can be made from the lab data.

For each patient studied, the mean trough phenytoin concentration for the study duration was > 10. Recall that daily trough concentrations were measured and doses adjusted to keep the daily levels > 10.

D. Conclusions

In a seriously ill neurosurgical population, the sponsor has demonstrated that plasma levels of phenytoin > 10 can be achieved and maintained. No safety concerns obviously related to Fos arose during the conduct of the study, but the natural tendency in this population is to attribute all AEs to

the underlying condition or the treatment of the underlying condition. Mild to moderate AEs will be overshadowed by more serious AEs in this population.

No efficacy data arises from this study. The occurrence of seizures in some patients despite plasma levels of phenytoin > 10 was documented, but is not surprising given the severity of the underlying conditions.

Study 982-15: A Study of the Tolerance and Safety of IV Fosphenytoin Given as a Single Loading Dose Followed by a Maintenance Regimen For Up To 2 Weeks

Investigators

1	Passini	Charlotte	4
2	Gallagher	Augusta, GA	1
3	Boucher/Feler	Memphis, TN	27
4	Dean	Winston-Salem	6
5	Kramer	Englewood, CO	10
6	Michie/Tipton	Cape Coral, FL	15
7	Newmark	Houston, TX	6
8	Schmitz/Young	Lexington, KY	12
9	Miller/Parks	Jackson, MS	10
10	Smith	St.Louis, MO	25
Total			116

A. Study Design

This was a double-blind, parallel-group, active control trial in patients requiring a loading dose of phenytoin to prevent or control seizures. Pts who met the inclusion/exclusion criteria were randomized in a 1:3 ratio to receive either parenteral Dilantin or Fosphenytoin.

The objectives of the study were 1) to evaluate the safety and tolerance of multiple IV doses of Fos for seizure prophylaxis in neurosurgery patients and 2) to obtain descriptive PK data for Fos in this patient population.

The study had 3 phases:

1. Screening phase
2. Treatment phase, Days 1-14
3. Follow-up phase for 2-4 days following the last IV dose

The treatment phase included a loading dose on Day 1 followed by daily IV maintenance infusions. "At the prestudy investigators meeting, the

minimum exposure requirement was defined as 72 hours, i.e. a loading dose followed by 2 days of maintenance dosing."

Pts at Center 5 had serial blood samples drawn over a 24 hour period beginning on the day of loading dose to determine total and free phenytoin concentrations in plasma.

Inclusion/exclusion criteria required that pts be 12 years of age or older. Patients were to require neurosurgery or were to have undergone neurosurgery. Pts were to be scheduled for neurosurgery within 14 days of entry into double-blind treatment.

To be excluded were pts with hypotension, bradycardia, and A-V block. Pts were excluded if they took any AED except benzodiazepines within 1 week prior to screen.

No medications were specifically excluded during the study. Any IV medications other than the study medication were to be administered at a site different from that used for study drug by using a second IV line.

By protocol, study drug could not be administered at rates greater than 50 mg/min either for loading or maintenance. The study drug could be administered either QD or BID as deemed appropriate by the investigator.

B. Subject Disposition and Baseline Comparison

The study was conducted between July 1992 and February 1993.

In general, patients were seriously ill neurosurgery patients who were suffering from head trauma or other neurological emergencies. With rare exceptions, patients underwent neurosurgical procedures on Study Day 1.

88 pts received IV Fos while 28 pts received IV Dilantin. The loading dose of Fos was given as a total dose between 7.3-22.4 mg/kg PE at infusion rates between 14-51 mg/min PE. Dilantin was given as a total dose between 7.8-19.8 mg/kg at infusion rates between 21-51 mg/min.

Maintenance doses of Fos were given as total doses of 1.2-23 mg/kg PE at infusion rates between 3.1-62.1 mg/min PE. Maintenance Dilantin was given as total doses of 1.3-18.4 mg/kg at infusion rates between 5.1-50

mg/min.

No patients received concurrent antiepileptic drugs during the screening phase of the study. Thus, patients should not have had baseline levels of phenytoin or any other AED. During the treatment phase, 4 pts received phenytoin in an unblinded fashion (3 Fos, 1 Dilantin), 3 pts received diazepam, and 2 pts received lorazepam.

Concurrent meds, other than AEDs, were in large part dictated by the individual's neurosurgery status. 108 pts actually had surgery during the study. 27/108 had surgery before beginning treatment with study drug. 79/108 had neurosurgery during the study. 2/108 had surgery after completing the study. Thus, 44% of pts were taking CNS agents at screen and this increased to 96% during double-blind treatment. The most common CNS agents were acetaminophen, fentanyl, codeine, and morphine.

To further complicate all this, we are told that small numbers of pts received BID maintenance dosing instead of QD, while similarly small numbers of pts received maintenance dosing as QD medication some days and BID medication other days.

14 pts withdrew from the study, 4 because of AEs and 10 for administrative reasons. Only 4 pts in each treatment group were treated for more than 7 days.

C. Results

Because the loading dose of Fos was not given at the bioequivalent rate of administration, this study cannot provide comparable safety data between an IV loading dose of Fos and an IV loading dose of Dilantin.

Comparable safety data between IV maintenance regimens of IV Fos and IV Dilantin is provided. One death occurred in each treatment group, unrelated to the treatment itself. One serious AE occurred in the Fos group and 2 serious AEs occurred in the Dilantin group; none were deemed related to the underlying treatment. Among AEs deemed associated with treatment, there was only 1 severe AE and this occurred in the Fos group: severe ataxia.

Among a listing of all AEs, the obvious discrepancies between treatment

groups occur for injection site reaction, injection site pain, and pruritus. The trend is for more local reactions with Dilantin and more generalized pruritus with Fos.

Seizures were so rare in both treatment groups that no meaningful statement about the anticonvulsant properties of either treatment can be made.

The sponsor (p 49 of the study report) presents changes in vital sign data between screening and 2 hours post loading dose for the 2 treatment groups. There are no obvious differences between treatment groups.

Changes seen in laboratory parameters during the study were felt to be most consistent with the population being studied, i.e. ill neurosurgery patients.

PK data was also accrued which demonstrates roughly equivalent trough levels of phenytoin with both the IV Fos and IV Dilantin regimens. During treatment, dose was adjusted by the investigators based on plasma phenytoin monitoring. The extrapolation of this might be that IV Fos can be used to achieve and maintain therapeutic plasma phenytoin concentrations *while monitoring trough plasma phenytoin levels.*

On page 65 of the study report, the sponsor summarizes changes in rates of infusion. Presumably, these changes pertain primarily to the loading doses administered. 17% of Fos pts and 36% of Dilantin pts required decreases in rates. Note, however, that the bioequivalent rate of Fos administration for IV loading was not given. Thus, a comparison of proportions of pts requiring dose reductions under the conditions of bioequivalence might have resulted in very different results.

The same problem in comparing groups arises when comparing groups for dose reductions due to injection site burning and itching. 5% of Fos pts required this while 18% of Dilantin pts required this.

TABLE 16. Most Frequent Adverse Events With IV Administration to Neurosurgical Patients (Study 982-015)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 88		Dilantin N = 28	
NERVOUS				
Nystagmus	12	(13.6)	4	(14.3)
Neuropathy	9	(10.2)	4	(14.3)
Reflexes Increased	7	(8.0)	0	(0.0)
Dizziness	6	(6.8)	3	(10.7)
Somnolence	6	(6.8)	3	(10.7)
Speech Disorder	5	(5.7)	1	(3.6)
BODY AS A WHOLE				
Fever	11	(12.5)	6	(21.4)
Face Edema	7	(8.0)	4	(14.3)
Injection-Site Reaction	6	(6.8)	5	(17.9)
Infection	6	(6.8)	2	(7.1)
DIGESTIVE				
Constipation	11	(12.5)	3	(10.7)
Nausea	9	(10.2)	4	(14.3)
Vomiting	6	(6.8)	5	(17.9)
CARDIOVASCULAR				
Tachycardia	7	(8.0)	2	(7.1)
Hypotension	6	(6.8)	2	(7.1)
SKIN AND APPENDAGES				
Pruritus	5	(5.7)	0	(0.0)
SURGERIES/PROCEDURES				
Surgeries/Procedures	9	(10.2)	3	(10.7)
RESPIRATORY				
Pneumonia	6	(6.8)	6	(21.4)
UROGENITAL				
Urinary Retention	7	(8.0)	3	(10.7)
MUSCULOSKELETAL				
Myasthenia	7	(8.0)	2	(7.1)
METABOLIC AND NUTRITIONAL				
Hypokalemia	8	(9.1)	2	(7.1)

Study 982-16: An Open-Label Safety and Tolerance Study of a Single IV Loading Dose of Fosphenytoin in Status Epilepticus

Investigators

1	Alldredge/Gelb	San Francisco	3
2	Allen/Runge	Charlotte, NC	18
4	Dean	Winston-Salem, N	2
5	Turnbull et al	Chicago, IL	6
6	Kriel/Langendorf	Minneapolis	3
7	Lai/Allen	Kansas City, KS	0
8	Maria/Legarda	Gainesville, FL	9
9	Matsuo et al	Salt Lake City, UT	9
10	Parks/Carlton	Jackson, MS	1
11	Pellock	Richmond, VA	1
12	Unwin/Leroy	Dallas, TX	0
13	Uthman/Wilder	Gainesville, FL	2
Total			54

A. Study Design

This was an open-label, single dose study in status epilepticus.

The objectives of the study were to 1) establish the safety of two rates of IV Fos in pts with status and 2) obtain descriptive PK data.

By protocol, the first 10 patients would receive Fos up to a maximum rate of 100 mg PE/min. If that was well tolerated, subsequent patients would receive rates up to a maximum of 150 mg/min. On Feb 10, 1993, data from 14 patients who received Fos at 100 mg/min PE were reviewed by Parke-Davis in consultation with a panel of noncompany neurologists. The panel unanimously recommended that the rate of Fos administration could be increased to 150 mg/min PE as provided in the protocol.

Status was defined as 2 or more consecutive seizures without regaining consciousness or a single seizure of at least 10 minutes duration; patients with partial status or absence status were excluded.

Inclusion/exclusion criteria required that pts be 5 years of age or older. There were no restrictions on AED use prior to study entry. Likewise, there were no restrictions on concurrent medication to treat the episode of status.

The protocol required that "if two IV lines are available, study medication should be administered through one line and all other medications through the other. If only one line is available, it is important to clear the IV line with normal saline between the administration of other medications and study drug."

During administration, vital signs were to be recorded every 5 minutes. Continuous ECG recording was to be performed during infusion. If systolic blood pressure dropped by 20 mmHg, the investigator could slow the infusion rate. If the absolute SBP dropped below 70, the investigator was to stop the infusion; once the BP returned to an acceptable level, the infusion could be restarted at 50% the original rate.

The goal of the study was to enroll between 20-100 pts between July and December 1992.

B. Subject Disposition and Baseline Comparison

54 patients were enrolled at 10 centers by September 1, 1994. There were 32 males and 22 females, 23 whites and 23 blacks. The mean age was 39 years of age with a range of 15 years to 75 years.

26% of patients had status precipitated by AED withdrawal or noncompliance (i.e. had the potential to have low, but measurable levels of phenytoin already present **prior to IV loading**). The sponsor notes that only 43 pts had usable plasma drug-concentration data; of these, 16 had measurable phenytoin concentrations prior to Fos infusion. The mean level for these pts was 6 with a range from 0.12 up to 15.

Six pts (11%) had partial status or absence status in violation of the protocol. The other patients all had generalized status, either primary generalized or secondarily generalized.

In 42/54 (78%) of pts, benzodiazepines were given prior to administration of Fos.

35 patients received loading doses at rates of 100 mg/min. (Recall that 150 mg/min is the rate considered bioequivalent to standard Dilantin loading doses). 18 pts received loading doses at rates > 150 mg/min.

All but 4 pts received total loading doses of 10 mg/kg or greater.

C. Results

Unfortunately, safety data is presented for the entire group of 54 patients; it would be helpful to see a review of adverse events only for the 12 patients who were dosed as per the proposed labeling. On page 36 of the study report, the sponsor presents a brief review entitled "Adverse Events by Rate of Administration." Here the sponsor states that the 5 most frequent AEs appeared to occur at similar frequencies for pts at faster rates (41%) compared with slower rates (45%). In this section, the sponsor does not address the fact that the post hoc separation of pts into high rate/low rate groups does not control for baseline levels of AEDs, especially phenytoin.

No patients withdrew for AEs. 3 patients died after completing the study but all were considered unrelated to Fos. The 8 most frequent adverse events were nystagmus, ataxia, headache, agitation, dysarthria, somnolence, vomiting, and pruritus.

Of note in safety data accrued after the cutoff date for this report is the occurrence of two cases of postictal psychosis, both beginning 3 days after status was treated with Fos. One patient had a previous, less severe case of psychosis after status; the other patient had not experienced previous post-ictal psychosis. A sensation of itchiness followed the psychosis in one patients.

60% of patients had a > 20 mm Hg drop in systolic blood pressure; only 4% had a symptomatic drop in SBP. The sponsor states that, "While the magnitude of decreases in blood pressure were substantial in some patients, no changes in infusion rate or interventions (eg, Trendelenburg positioning, IV fluids, or medications) were required to treat any hypotensive symptoms."

Status continued beyond 30 minutes post infusion of Fos in only 3 patients. 2 of these had other explanations besides lack of efficacy i.e. subdural and anoxic brain insult post CPR. **Patient 8, Center 9 had a gradual decline in seizures over 45 minutes. The infusion rate for this patient was 90 mg/min PE; no plasma levels are available for this patient during the first 20 minutes of treatment raising the question whether a faster infusion rate would have been more effective.**

Study 982-21: A Single-Dose Study of the Tolerance and Safety of IV Fosphenytoin

Investigators

1	Wilder	Florida	21
2	Fischer	Illinois	23
3	So	Minnesota	8
Total			52

A. Study Design

This was a double-blind, parallel-group, active control trial in patients requiring a loading dose of phenytoin to prevent or control seizures. Pts who met the inclusion/exclusion criteria were randomized in a 1:3 ratio to receive either parenteral Dilantin or Fosphenytoin.

Inclusion/exclusion criteria required that pts be 12 years of age or older and require a loading dose of phenytoin. Pts whose condition was serious or life-threatening were not considered appropriate candidates for the study. In particular, patients in status epilepticus were excluded. Neurosurgery patients who required acute treatment were also excluded.

The inclusion criteria required that patients be able to evaluate the extent of pain, burning and itching experienced as a result of the infusion.

The anticipated enrollment was 60 patients, 20 from each of 3 centers.

During the infusion, vital signs were to be recorded every 5 minutes and ECG was to be monitored continuously. After the infusion, vital signs were to be recorded every 15 minutes for 2 hours.

The rate of infusion was not to exceed 50 mg/min PE. By protocol, the investigator was to consider slowing the rate if SBP dropped by 20 mmHg or greater. If SBP dropped to an absolute of 70mmHg, the infusion was to be stopped; once SBP was acceptable, the infusion could be restarted at half the previous rate.

By protocol amendment, the maximum rate was increased to 100mg/min PE for Fos patients.

B. Subject Disposition and Baseline Comparison

39 pts received IV Fos while 13 pts received IV Dilantin.

The majority of pts required a loading dose because of new onset seizures or because their baseline phenytoin levels had dropped below the therapeutic range due to noncompliance or prescribed dosage change.

Fos was given as a total dose between 480-1500 mg/kg PE at infusion rates between 40-103 mg/min PE. Dilantin was given as a total dose between 290-1000 mg/kg at infusion rates between 20-51 mg/min.

Because of the design of the study, a true comparison between randomized groups cannot be made. In addition to the variable of interest, Dilantin vs Fos, there were 4 additional variables that were not adequately controlled, to include:

1. total dose in PE
2. infusion rate (recall that the bioequivalent infusion rate for Fos is 3 X faster in PE than the rate for Dilantin)
3. presence or absence of measurable baseline levels of phenytoin
4. when present, the actual values for baseline phenytoin levels

10/13 Dilantin pts (77%) received 800-1000 mg PE while 23/39 Fos pts (50%) received 800-1000 mg PE or greater. The rate was about 50 mg/min PE for Dilantin, but only 18/39 (50%) of Fos pts received 100 mg/min or greater (100-150 mg/min is the bioequivalent rate when based on free phenytoin levels).

Therefore, at this point, the question would be, of the 23 pts who received 800 mg PE or greater, what percent of these received a rate of 100 mg/min or greater. One might guess that only 10-12 Fos pts are available to compare to the 10-12 Dilantin pts (certainly not *randomized* groups at this point); we have not even introduced the additional variable of background phenytoin levels at baseline.

To further complicate all this, we are told that 7/39 Fos pts (18%)

required changes in rate compared with 6/13 Dilantin pts (46%). The reason for the rate changes are as follows:

Fos	
Hypotension	2
Generalized burning or itching	4
Infusion pump problem	1
Dilantin	
Hypotension	1
Localized pain or burning at inj. site	5

C. Results

There were no deaths in either treatment group. Three withdrawals occurred, all in the Dilantin group. There was 1 withdrawal for AE; there were 2 withdrawals for "lost-to-f/u." No AEs in either treatment group were rated "serious."

Because of the multiple variables discussed above, any comparison between groups with regard to AEs is really inappropriate. Suffice it to say that the pattern of AEs seen in the Fos group raised only one unusual concern, the occurrence of pruritus in 30% of Fos pts vs 0% of Dilantin pts.

Looking only at Fos pts who received a total of 1000 mg PE at rates of 100 mg/min PE or greater, I identified 15 Fos pts in the category. Of these "high-dose, high-rate" pts, 3/15 or 1/5 had a rate change during the infusion because of an AE. One pt had hypotension, 1 had itching, and 1 had burning.

D. Clinical Labs

No clinically important differences are noted between groups and no clear trends toward abnormal values are evident.

E. Vital Signs

The sponsor's discussion of vital signs seems flawed since they have chosen to compare baseline to the 2-hour visit. (See Sponsor's Tables 20

and 21.) In fact, the vitals of interest are those at 5, 15, and perhaps 30 minutes.

Sponsor's Table 22 shows the incidence of decreases in systolic BP > 20 mm Hg: 7 Fos pts (18%) and 4 Dilantin pts (31%). However, the percentages are misleading because the true denominators for comparison are obscured by variable rates, total doses, and baseline phenytoin levels.

2 pts on Fos and 1 on Dilantin required rate changes due to hypotension. One of these Fos pts had a 26mmHg drop in SBP without symptoms. The other Fos pt had an 18mmHg drop with severe dizziness and moderate vertigo. The Dilantin pt had a 22mmHg drop with mild vertigo.

F. Infusion Sites

At the follow-up exam, investigators classified the overall appearance of the infusion sites. The majority of pts in both treatment groups tolerated the infusions, with no differences between groups noted.

Immediately after the infusion, 50% of Dilantin pts reported some pain and 83% reported some burning. By comparison, 2.6% of Fos pts reported some pain and 10% reported some burning. Except for 2 Fos pts who reported pain 2 hours after the infusion, both pain and burning had resolved for all pts in each treatment group by the end of double-blind treatment.

Investigators rated erythema, swelling, tenderness, necrosis, and bruising on a 4 point scale. Essentially no differences between treatment groups emerged.

F. Conclusions

Because the 2 drugs were mixed and administered the same way during this trial, nothing was learned about relative ease-of-use.

Rates were faster for Fos on average, but the sponsor's discussion avoids the issue that *where rate is important,* Fos must be given faster than it was in this study and may, under those conditions of use, be associated

with more AEs (both local and systemic) than were seen here. Rate is not important for maintenance loading and, in that clinical situation, the ability to administer a drug faster may not necessarily be an advantage.

This study provides some safety information in support of a subacute IV loading dose of Fos in non-emergent situations where the physician wishes to achieve therapeutic levels of phenytoin more rapidly than could be achieved by the oral route. Any comparison between the Fos loading and Dilantin loading was obscured by the study design as discussed above.

TABLE 15. Most Frequent Adverse Events With IV Administration to Patients With Epilepsy (Study 982-021)
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Fosphenytoin N = 39		Dilantin N = 13	
NERVOUS				
Nystagmus	18	(46.2)	5	(38.5)
Dizziness	10	(25.6)	5	(38.5)
Ataxia	7	(17.9)	2	(15.4)
Vertigo	4	(10.3)	3	(23.1)
Paresthesia	4	(10.3)	0	(0.0)
Tremor	3	(7.7)	0	(0.0)
Neuropathy	3	(7.7)	0	(0.0)
Somnolence	2	(5.1)	1	(7.7)
Speech Disorder	2	(5.1)	2	(15.4)
BODY AS A WHOLE				
Headache	7	(17.9)	1	(7.7)
Pain	5	(12.8)	1	(7.7)
Reaction Unevaluable	4	(10.3)	1	(7.7)
Chills	2	(5.1)	0	(0.0)
Chest Pain	2	(5.1)	0	(0.0)
CARDIOVASCULAR				
Hypotension	3	(7.7)	1	(7.7)
SKIN AND APPENDAGES				
Pruritus	12	(30.8)	0	(0.0)
SPECIAL SENSES				
Amblyopia	4	(10.3)	3	(23.1)
Ear Disorder	2	(5.1)	0	(0.0)

Study 982-22: An Open-Label Study of the Safety and Tolerance of an IM Loading Dose of Fosphenytoin

Investigators

1	Leppik	Minneapolis, MN	5
2	Barkley	Detroit, MI	6
3	Ramsay	Miami, FL	28
4	Wilder	Gainesville, FL	14
5	Garnett/Pellock	Richmond, VA	7
Total			60

A. Study Design

The study was intended to be a safety study. The projected enrollment was 60 patients.

Patients were to require a loading dose of phenytoin for the treatment or prophylaxis of seizures. Open-label treatment was to consist of a single loading dose, minimum 10 mg/kg PE. This was followed by a 3-hour observation period. Patients were to return in 2-7 days for follow-up exams and procedures.

Inclusion/exclusion criteria dictated that patients be 12 years of age or older. Pts were not to be in serious or life-threatening condition. This excluded patients in status epilepticus from the study.

Not excluded were pts already being treated with phenytoin. Prior phenytoin usage was to be assessed when determining dosing requirements. If that information was unavailable, the investigator was to use clinical judgment to decide on a dose.

The dosing administration could be divided and given in separate locations on the buttock.

B. Subject Disposition and Baseline Comparison

The study was conducted between August 1992 and February 1993.

60 patients (34 male, 26 female) entered the study. 57 completed all the follow-up assessments. 32 pts were white; 24 were black; 1 was Asian. The mean age was 43 years with a range 16-80 years.

The reasons for loading dose were as follows:

Noncompliance	11
First treatment with phenytoin	18
Decreased phenytoin level (unknown reason)	13
Decreased phenytoin level (prescribed dose reduction)	9
Other reason	9

Therefore, IM loading in the face of absent plasma phenytoin occurred in about 27 patients. The other 33 patients had the potential to have low but measurable levels of phenytoin and might therefore have received downward adjusted doses (based on the clinical judgment of the investigator). AEDs taken within 3 days of study entry included phenytoin in 27 patients. Only 23 patients took no AEDs within 3 days of study entry.

A review of concurrent AEDs taken from day of Fos loading to follow-up follows:

None	10
Phenytoin	47
Carbamazepine	10
VPA	10
Lorazepam	5
Phenobarbital	2
Clorazepate	2
Methsuximide	1
Acetazolamide	1

This list reminds us that the follow-up assessments done after the day of Fos dosing will be obscured by the use of these other drugs and, in fact, might be more representative of these AEDs than the Fos itself.

The doses of Fos ranged from 350 to 1500mg (3.6 to 20.2 mg/kg) PE. 22

patients received a loading dose of 12 mg/kg or greater. An additional 25 pts received a loading dose between 10-12 mg/kg. The actual doses were between a gram and 1600 mg for 16 pts; 20 pts received between 800 to 1000 mg. Note that the 12 pts who received less than 10 mg/kg of Fos were actually in violation of the protocol requirement that pts receive at least 10 mg/kg.

Doses were given as a single injection for 28 pts. 28 pts had their doses divided into 2 injections. 4 pts received 3-4 injections.

C. Results

No patient died during the study. Withdrawals in the true sense of the word could not occur since the Fos was given as a loading dose.

Only one patient experienced serious AEs: arrhythmia, neuropathy, stupor, and tachycardia. This was also the only pt who experienced AEs that were graded severe in intensity. He was a 74 year old man with a history of a stroke with complex partial seizures. He received IM Fos on Day 1. On Day 4, he experienced an irregular pulse, deterioration in neurological status, stuporous condition, and tachycardia. None of these were considered related to study medication by the investigator. The pt had not yet recovered from these AEs by the end of the study.

66% of pts experienced some AEs. Most of these were considered associated with use of Fos. Almost all these AEs were considered mild in intensity.

Nystagmus was the most common AE, occurring in 47% of pts. Dizziness and ataxia occurred in 17% and 13% of pts respectively.

Evaluation of injection sites revealed that only 3 pts had mild injection site irritation 3 hours after IM dosing. 4 pts had mild irritation 2-7 days later at the follow-up visit. Only 1 pt had mild irritation at both time points. The sponsor states that no relationship was found between the dose or the number of injections and the tendency toward this mild irritation.

D. Conclusions

This study demonstrated no drug-related serious AEs, either systemically or locally at the injection site, when Fos was given IM at relatively high doses. 47 pts received 10 mg/kg or greater. However, only 28 pts received the entire loading dose at a single injection site and some of these may have received less than 10 mg/kg. Because of this last point, this study would probably best support the safety of IM Fos at comparable doses *with the total dose divided and given at two separate injection sites*.

Note that patients who required an emergent loading dose of phenytoin were excluded from this study. In particular, pts with status were excluded. Thus, this study would not support the efficacy of IM Fos in emergent situations. Likewise, there is no data that I am aware of to support use of IM Fos loading over PO Fos loading. In fact, IM Fos loading would probably only have a role in non-emergent settings where patients could not tolerate PO feedings. This might occur in patients chronically treated with AEDs (especially phenytoin) who develop transient gastrointestinal illnesses that preclude continued oral medication and result in dropping plasma AED levels.

At a minimum, although this study was designed to support the safety of IM **loading**, the data from this study can be used to support the safety of IM **maintenance** dosing. That is, if the higher doses given in this study were tolerated, the lower doses necessary for IM maintenance dosing should have a wider safety margin.

Review and Evaluation of Pharmacology and Toxicology Continuation of Review # 1

Drug: -9653-010

Category:

Anticonvulsant; prodrug for phenytoin.

Summary:

It was pointed out in our team meeting for this new drug that the *in vivo* hydrolysis o -9653 occurs in 2 steps, producing one mole of formaldehyde for each mole of prodrug. In the initial clinical Phase I trial, the top dose of 2250 mg would produce 5.5 mmoles of HCHO. The possible hazard from this burden will be discussed from several different veiwpoints below. All calculations are gross approximations, based on available information.

1. OSHA has adopted a permissible exposure level for toxic effects of formaldehyde other thar. cancer of 3 ppm as an 8 hour time weighted average, anu 10 ppm maximum peak concentration for 30 minutes in an 8 hour period (Third Annual Report on Carcinogens, USDHHS Public Health Service, September, 1983, page 73). It has been reported that workers exposed to formaldehyde at a concentration of 7 mg/m^3 developed blood levels of 0.6 - 4.0 mg/l. The duration of exposure was not given (J.Piotrowski, Exposure Tests for Organic Compaounds in Industrial Toxicology, Gant Printing Office, DC, 1977, p.122). [1m^3 = 1000 l; wt. of air = 1.293 gms/l at 0^{0}C + 760 mm Hg; therefore 7 mg/m^3 = 7 mg/1.293 kg = 5.4 mg/kg = 5.4 ppm in air]

   Since 5.4 ppm of HCHO → a maximum of 4 mg/l in blood, the 10 ppm maximum allowed by OSHA would → approximately 7.4 mg HCHO/liter or 0.25 meq HCHO/l in blood. This figure should more or less represent the maximal allowable blood level of HCHO according to OSHA. If we then assume that the 5.5 mmoles of HCHO that are split from the prodrug all appear in the circulation (ave. volume 5 liters) the concentration would be 33 mg/l or 1.1 meq/l, or approximately 4 fold higher than the OSHA level allowed. However, this is a very crude estimate since the data are not readily available for taking the time factor allowed under the OSHA limit into consideration.

2. There is a great deal of information in the literature that suggests that it is formic acid that is repsonsible for the ocular toxicity and acidosis seen following acute methanol poisoning (methanol → formaldehyde → formate). This toxicity would be of greater concern when dealing with a drug to be used acutely than would potential carcinogenicity. Although a role for HCHO has not been clearly ruled out, experiments in monkeys suggest that the resultant formate levels are of more concern.

In a model in rhesus monkeys for methanol ocular toxicity and metabolic acidosis, formate blood and CSF levels of 7 to 34 meq/l were associated with optic disc edema, morphological alterations in optic nerve and swelling of oligodendroglial cytoplasm (Martin - Amat, Hayreh, Baumtach et al, Arch Ophthalmol., 95, 1847-50, 1851-58, 1859-61; Martin-Amat, et.al., TAP, 45, 201-208, 1978). Pretreatment with folate increased the metabolism of formate and decreased the toxicity (McMartin et al, JPET, 201, 564-572, 1977). In the proposed clinical trial, if we assume the 5.5 meq of HCHO goes to 5.5 meq of formate, with a blood concentration of 1.1 meq/l, there is a minimum of a 7-fold safety factor before ocular toxicity occurred in the monkey (which is thought to metabolize HCHO like the human).

3. It has been reported that the mechanism for ocular toxicity caused by methanol is the inhibition of cytochrome oxidase by formate (Nicholls, BBRC, 67, 610-616, 1975). Since cytochrome oxidase activity is low in white matter, it has been suggested that its activity may be critical in that tissue. The Ki values determined for formate inhibition of cytochrome oxidase are between 5 and 30 m M (above reference plus Martin-Amat, Arch Ophthol., 95, 1847-50, 1977). Based on this data, blood levels of formate of 1.1 m M would be somewhat lower then those expected to produce toxicity.

4. In dogs and cats administered 35 mg/kg (1.2 meq/kg) of formaldehyde by i.v. infusion, a blood HCHO concentration of 25 mg/l (0.83 meq/l) was produced which declined to about 1 mg/l by 1 hour after the infusion. (4 x as much HCHO was in erythrocytes as in plasma). The peak plasma concentration of formate, however, was 144 mg/l (3.1 meq/l) at the end of the infusion, which declined with a $T_{1/2}$ of 1.5 hours. Toxicity was not addressed (G. Malorney et al, Naunyn - Schmiedebergs A.E.P.P., 250, 419-436, 1965). These data would suggest that peak levels of the possibly more toxic metabolite, formate, might be approximated as follows for top dose in the clinical trial:

   5.5 meq of HCHO (155 mg) = 3 mg/kg in a 50 kg person. If 35 mg/kg of i.v. HCHO → 144 mg/l of formate, 3 mg/kg or HCHO may result in peak blood levels of formate of 12 mg or 0.26 meq/l. (This is assuming comparable relative blood levles to body weight in humans and animals. Actually, dogs may have slightly larger blood volume/kg of body weight than humans, so the estimate for humans is possibly on the low side. The assumption for comparable metabolism is also made).

This figure is considerably lower than the Ki for formate inhibition of cytochrome oxidase and it is about 25-30 fold lower than the lowest levels of formate associated with ocular toxicity in monkeys (see numbers 2 and 3 above). If instead, we examine the blood HCHO concentration using these data, an i.v. dose of prodrug that yields 5.5 mmoles of HCHO (0.11 mmoles/kg) would be expected to result in a peak blood concentration of HCHO of 0.08 mmoles/liter, or 1/3 of the maximal allowable HCHO exposure according to OSHA.

Evaluation and Recommendations:

The above approximations are extremely crude, but they do provide some data for evaluating the risk involved from a drug which will be used acutely that is metabolized to produce a mole of formaldehyde for every mole of drug.

Based on OSHA limits for exposure to formaldehyde, the guestimate is that the top dose of prodrug planned in the rising dose trial (2250 mg) would result in anywhere from 1/3 of 4 times the maximal allowable blood level of formaldehyde. If we assume that formate is responsible for the expected acute toxicty (occular and acidosis), there may be anywhere between a 7 fold and a 30 fold safety factor, based on toxicity observed in monkeys and blood levels of formate measured after i.v. administration of HCHO to dogs. If we believe that formate toxicity occurs through cytochrome oxidase inhibition, there is at least a small margin of safety based on the Ki.

In any case, it is a close call, and there are a couple of precautions that might be considered. Monitoring of blood formic acid, blood pH, bicarbonate and pCO_2 is recommended. Since folinic acid pretreatment hastens the elimination rate, a supplement of 2 mg, p.o., might be given the day before the trial. However, if it is considered that this is an appropriate time to determine whether or not formate levels in blood are detectable (since in practice there would not be time to give folinic acid) I would recommend careful monitoring for formate levels at all doses before proceeding to the next higher dose. SRD is May 4, so sponsor should be phoned.

Glenna G. Fitzgerald

Glenna G. Fitzgerald Ph.D., M.D.

cc: Orig.IND
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/GFitzgerald
rd/pjd/5/15/86:ft/5/16/86
doc 0471f

December 20, 1995

Review and Evaluation of Pharmacology and Toxicology

NDA: 20-450

Sponsor: Parke-Davis Pharmaceutical Research
Ann Arbor, MI 48105

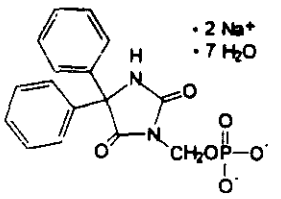
Drug: Cerebyx (fosphenytoin sodium)

Chemical Name: 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

Molecular Formula: $C_{16}H_{13}N_2O_6PNa_2$

Code name(s): ACC-9653; CI-982

Structure:



Mol. Wt.: 406.3

Category: Parenteral antiepileptic; prodrug of phenytoin for use in status epilepticus and neurosurgery

Related IND(s):

Table of Contents

All pivotal toxicology studies and all genetic and reproductive toxicity studies contain GLP statements. Studies were conducted by Parke-Davis,

Drug lot numbers are given with the individual studies.

I. PHARMACODYNAMICS

Anticonvulsant Activity

A) EFFECTS ON MES-INDUCED SEIZURES IN MICE (RR 740-02904, NDA Vol. 1.9).

1. After iv dosing with phenytoin (8 mg/kg) or fosphenytoin (11.9 mg/kg), no appreciable anticonvulsant activity was seen for either drug until 10 min, when 50% (4/8) of phenytoin-treated mice were protected from tonic hindlimb extension (THE) and 13% (1/8) of fosphenytoin-treated mice were protected (**Table I.1**).
2. Peak activity was reached for both compounds at 30 min when 63% (5/8) of phenytoin-treated and 88% of fosphenytoin-treated mice were protected (**Table I.1**). In addition to reducing the incidence of MES-induced THE, phenytoin and fosphenytoin reduced seizure duration.
3. When dose-response determinations were made at 10 and 30 min (**Table I.2**), both drugs exerted dose-dependent protection from MES-induced THE. The iv ED50 values (95% confidence limits) were 8.3 mg/kg (6.1-11.2) at 10 min and 6 6 mg/kg (5.1-8.0) at 30 min after dosing with phenytoin, compared to 10.8 mg/kg (8.4-17.5) at 10 min and 6.8 mg/kg (6.1-7.5) at 30 min after dosing with fosphenytoin (doses expressed as phenytoin equivalents). Neither vehicle was active. Based on statistical comparisons of the dose-response curves and potency ratios, the anticonvulsant potencies of fosphenytoin and phenytoin against MES-induced THE were not significantly different at either time point, although there were apparent differences in low dose activity and onset of action.
4. The ED50 values for iv phenytoin and fosphenytoin were in agreement with those reported in the literature for oral (9.0 and 12.8 mg/kg), sc (7.2 mg/kg), and ip (9.5 mg/kg) administration of phenytoin to mice and for oral (11.8 mg/kg PE) and ip (10.3 mg/kg PE) administration of the prodrug to mice.

Table I.1 TIME COURSE OF ANTI-CONVULSIVE ACTIVITY OF PHENYTOIN AND ACC-9653 IN MES-INDUCED THE-SEIZURES IN MICE

	MINUTES AFTER INJECTION									
	PHENYTOIN (8 mg/kg, IV)					ACC-9653 (11.9 mg/kg, IV)				
	5	10	30	60	120	5	10	30	60	120
Percent of mice proteced from THE-seizures	13	50	63	38	63	0	13	88	38	25
Duration of THE-seizures (seconds)	10.5* ± 1.0	12.3 ± 1.0	9.2* ± .2	9.2* ± 1.0	8.8 ± 2.0	10.9 ± .8	10.5 ± .9	10.8 –	10.2* ± .9	9.4* ± .5

Eighty mice were used in this study; eight at each time point with each drug. Duration values represent the mean ± S.E. of THE-seizure durations in unprotected animals.
* Indicates a significant difference from the corresponding value at the same time point in vehicle-treated mice (Table 1).

Table I.2 DOSE-REPONSE STUDY OF THE ANTI-CONVULSIVE ACTIVITY OF PHENYTOIN AND 9653 IN MES-INDUCED THE-SEIZURES IN MICE

PHENYTOIN			9653		
	Minutes After Dosing			Minutes After Dosing	
	10	30		10	30
Dose mg/kg IV	% Protected From THE-Seizures		Dose mg/kg IV	% Protected From THE-Seizures	
2	0	13	3	0	0
3	13	25	4.4	13	0
4.5	13	13	6.7	0	0
6.8	38	63	10.1	25	50
10.1	63	88	15.0	38	100
15.2	88	100	22.5	75	100

One hundred and twelve mice were used in this study; eight at each time point with each drug dose.

Cardiovascular effects

A) ANTIARRHYTHMIC ACTIVITY IN VITRO AND IN VIVO (RR 740-02905, Vol. 9).

In vitro, fosphenytoin had not antiarrhythmic effect in acetylstrophanthidin-treated guinea pig right atria at concentrations up to 400 uM, while phenytoin restored rhythmic beating in 4 of 7 atria at a mean EC50 of 20 uM. *In vivo*, fosphenytoin and phenytoin exerted similar antiarrhythmic activity, respectively converting oubain-induced tachycardia in 87 and 100 % of animals after an infusion time of 8.5 and 7 min, at administered doses of 24.3 and 14.1 mg/kg, and plasma levels of 18 and 29.5 ug/ml of phenytoin. This indicates that fosphenytoin has no direct antiarrhythmic action, but is similar to phenytoin under *in vivo* conditions, presumably due to enzymatic conversion to phenytoin.

B) HEMODYNAMIC EFFECTS IN ANESTHETIZED DOGS (RR 740-02906, Vol. 9).

1. Fosphenytoin (60 mg/kg) infused over 2 min (infusion rate of 20 mg/kg/min) produced marked reductions in systolic (50%) and diastolic (60%) blood pressure, heart rate (25%), and LvdP/dt (70%). The maximum effects were observed 10 min after termination of infusion and had returned toward normal by 60 min. After rapid infusion of an equimolar dose of phenytoin (40 mg/kg), changes in CV parameters were comparable to those seen after fosphenytoin (**Figures I.1 & I.2**). Effects on CV parameters appeared somewhat more pronounced after fosphenytoin (diastolic BP was significantly lower in fosphenytoin group at 4 min); however, 3 of the phenytoin animals died within 4 min from onset of infusion, while all 6 fosphenytoin dogs recovered.
2. Plasma levels of fosphenytoin were highest at the end of the infusion, while peak levels of formed phenytoin were seen at about 8 min after the end of infusion (**Figure I.3**). Peak plasma phenytoin levels (free levels not determined) were reached more rapidly after infusion of phenytoin than after fosphenytoin, although maximal levels achieved were similar.
3. Fosphenytoin (31 mg/kg) infused over 15, 20, or 30 min produced significant reductions in systolic (25%) and diastolic (35%) blood pressure, HR (10%), left ventricular contractility

(LvdP/dt, 20-45%), and cardiac output (20-40%) at all three infusion rates (**Figures I.4 and I.5**). The maximum effects were comparable at each infusion rate and the maximum effects were observed at the end of each infusion period. In each group, pressures had returned to normal by 60 min. There were no significant effects on systolic blood pressure, heart rate, left ventricular end diastolic pressure, or cardiac output. Comparable changes in CV parameters were seen when an equimolar dose of phenytoin (21 mg/kg) was infused over 30 min.

4. Analysis of plasma samples showed that maximum levels of fosphenytoin occurred at the end of the infusion period (**Figure I.6**). Peak fosphenytoin levels of 106, 82, and, 72 ug/ml were attained after infusion over 15, 20, and 30 min, respectively. The maximum levels of phenytoin were also observed at the end of the infusion period. Peak levels of phenytoin were 35, 29, and 31 ug/ml after infusion of fosphenytoin over 15, 20, and 30 min, respectively. Plasma levels declined rapidly thereafter. After infusion of phenytoin, plasma levels of phenytoin were maximal (33 ug/ml) at the end of infusion, and declined thereafter.

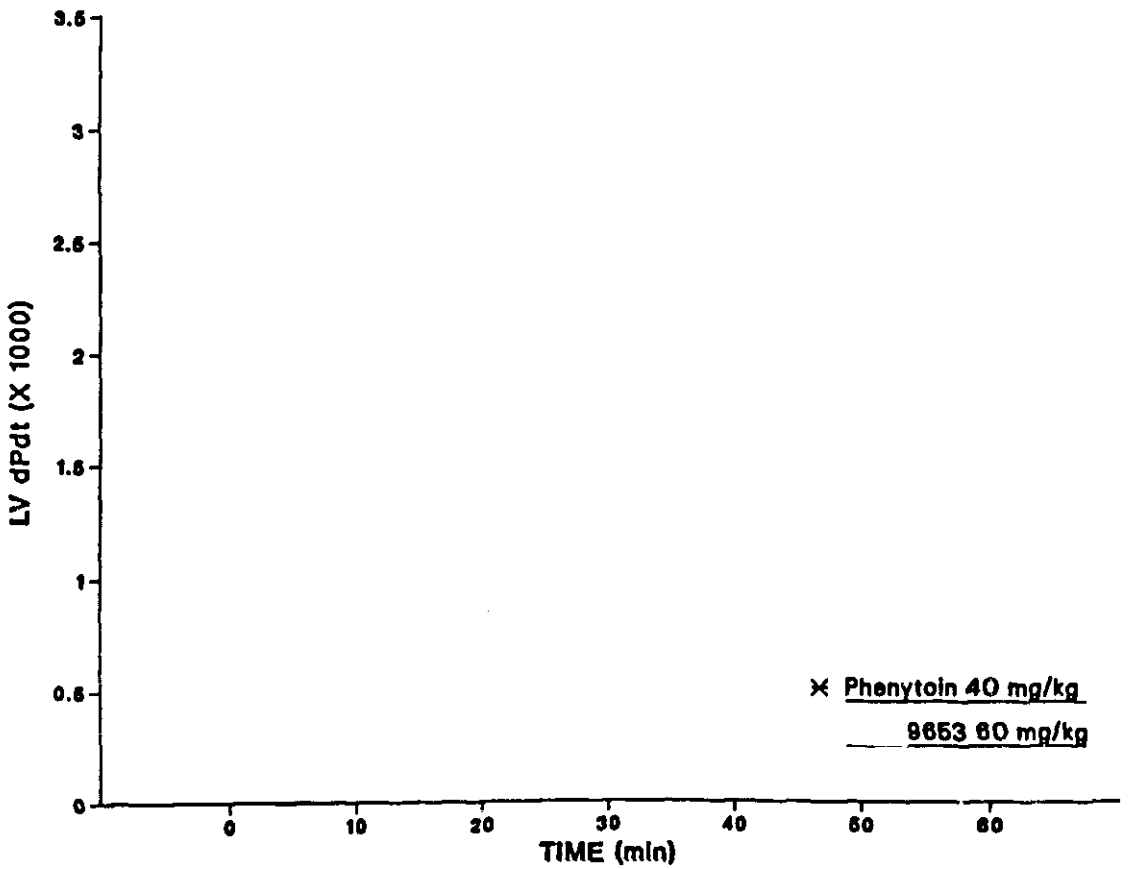


Figure I.1. Effect of fosphenytoin, 60 mg/kg, or phenytoin sodium, 40 mg/kg, infused iv over 2 min on LvdP/dt in anesthetized dogs. Values are the mean ± SEM (N=6).

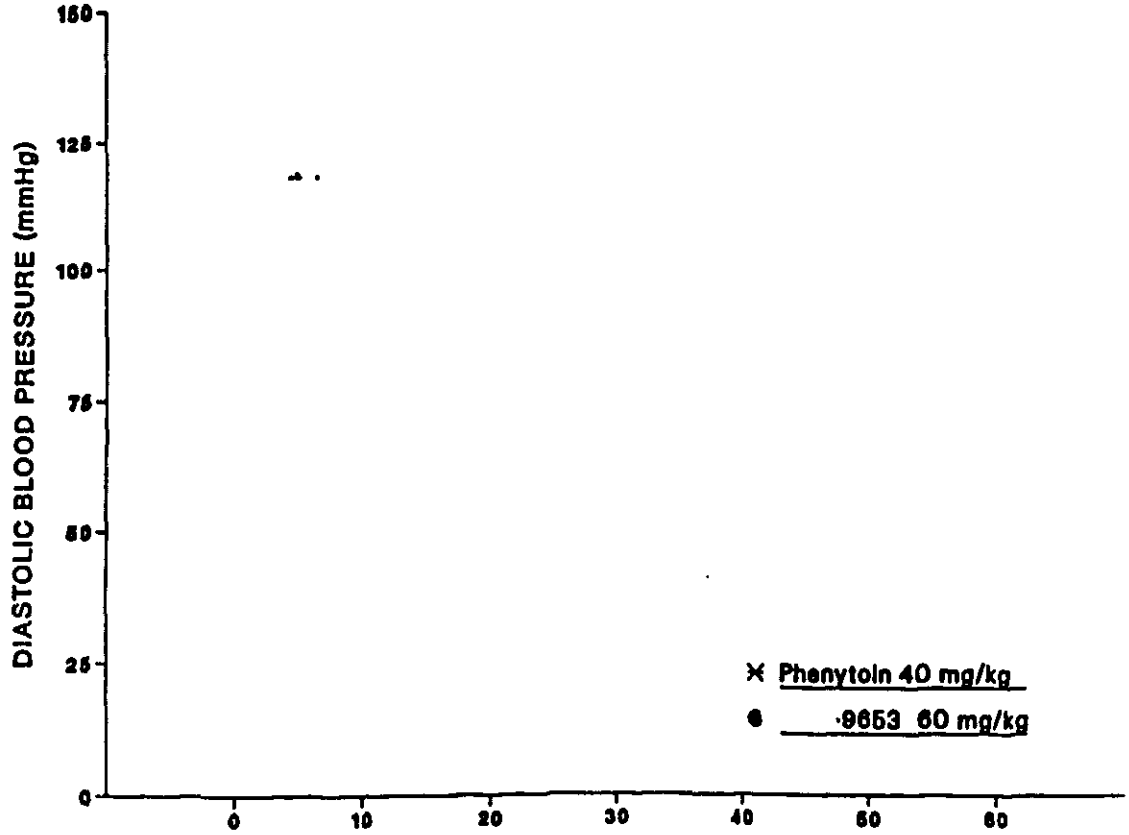


Figure I.2. Effect of fosphenytoin, 60 mg/kg, or phenytoin sodium, 40 mg/kg, infused iv over 2 min on diastolic blood pressure in anesthetized dogs. Values are the mean ± SEM (N=6).

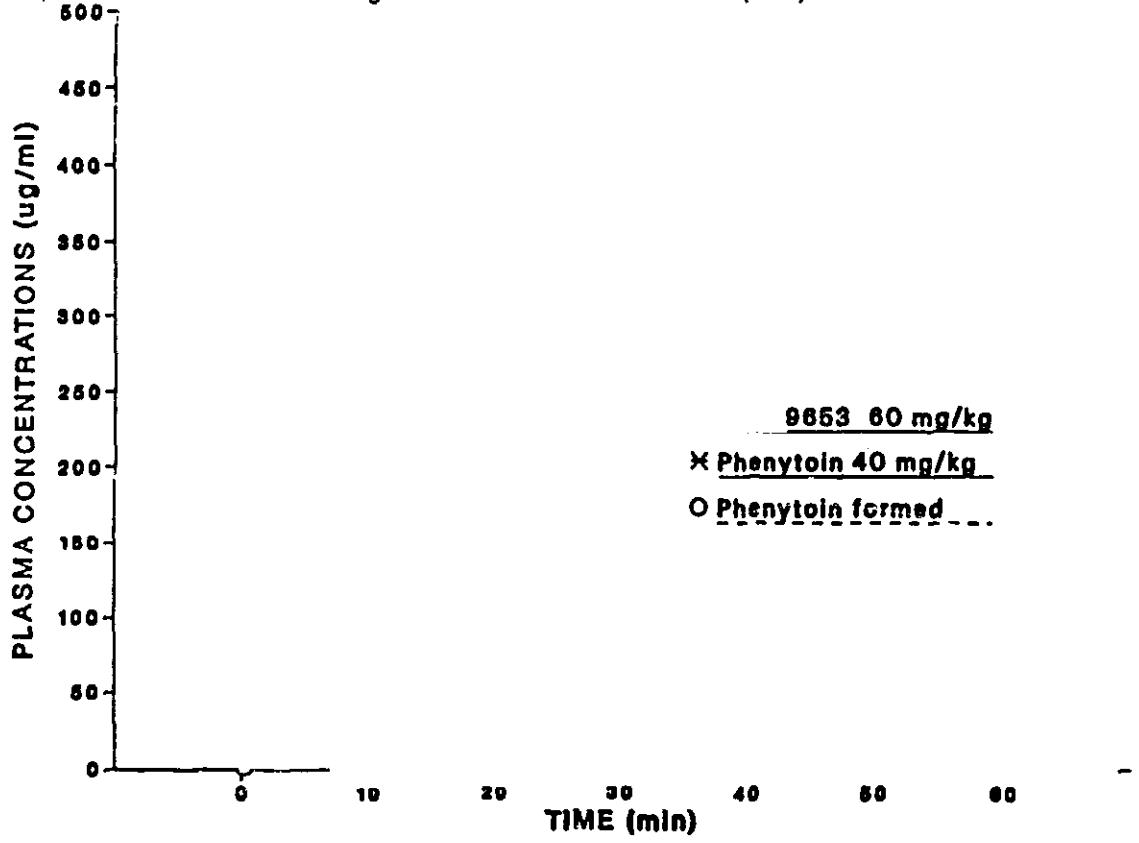


Figure I.3. Plasma levels of fosphenytoin or of the phenytoin formed following infusion of fosphenytoin, 60 mg/kg, infused iv over 2 min and of phenytoin following infusion in an equimolar amount of phenytoin sodium, 40 mg/kg, iv, over 2 min. Values are the mean of 6 determinations.

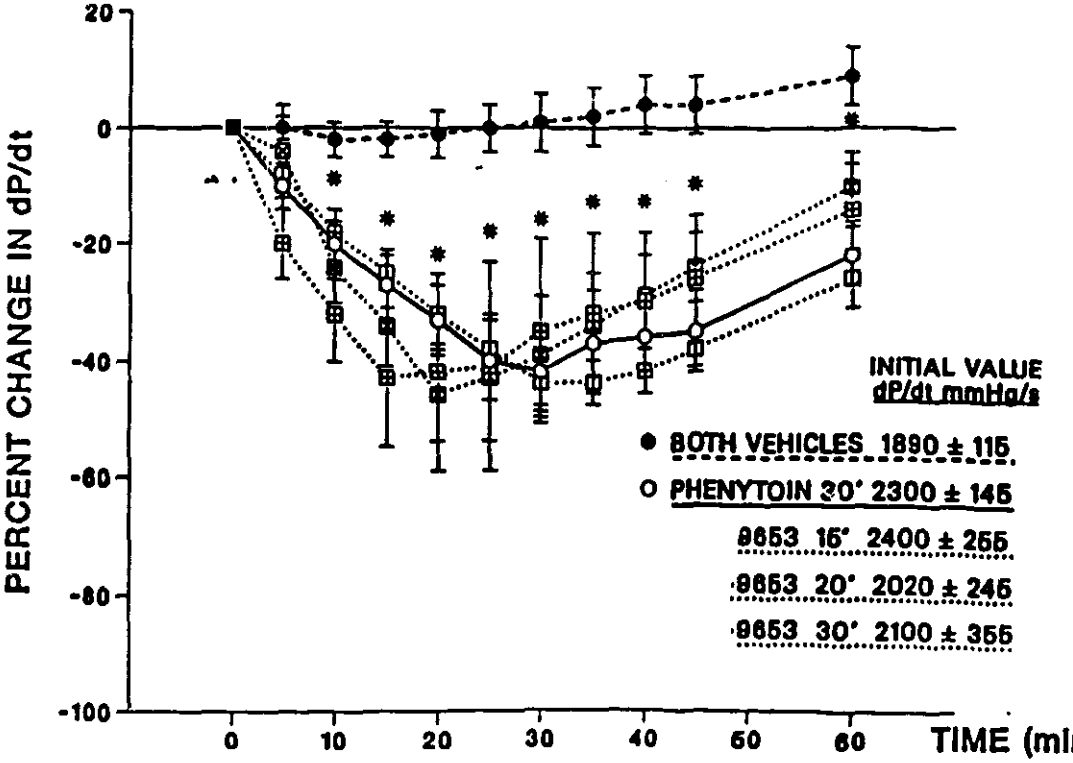


Figure I.4. Effects of fosphenytoin, 31 mg/kg, infused over 15, 20, or 30 min, of phenytoin sodium, 21 mg/kg, infused over 30 min, or of vehicles alone on LvdP/dt in anesthetized dogs. The vehicle data represent the combined mean data from the phenytoin vehicle (propylene glycol, alcohol; N=4) and the fosphenytoin vehicle (TRIS; N=3) treated animals. All values are mean ± SEM. Asterisks indicate values significantly different from comparable vehicle values, $p<0.05$.

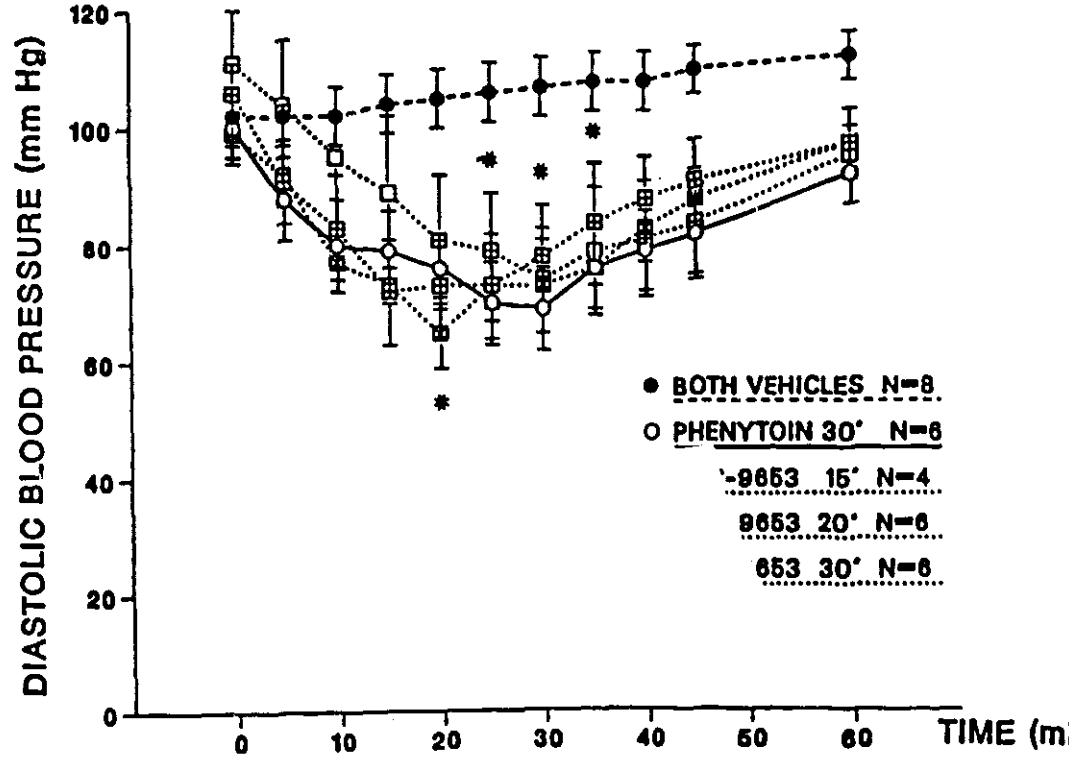


Figure I.5 Effects of fosphenytoin, 31 mg/kg, infused over 15, 20, or 30 min, of phenytoin sodium, 21 mg/kg, infused over 30 min, or of vehicles alone on diastolic blood pressure in anesthetized dogs. The vehicle data represent the combined mean data from the phenytoin vehicle (propylene glycol, alcohol; N=4) and the fosphenytoin vehicle (TRIS; N=3) treated animals. All values are mean ± SEM. Asterisks indicate values significantly different from comparable vehicle values, $p<0.05$.

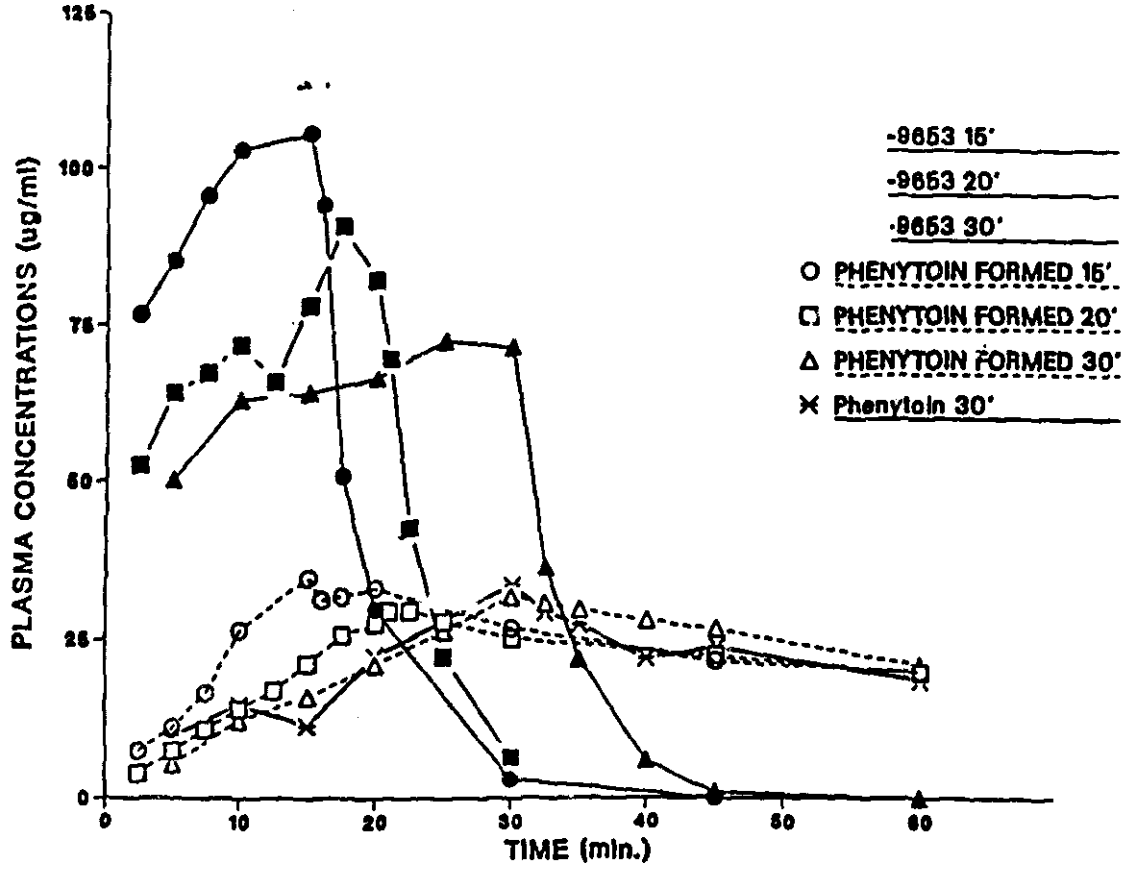


Figure I.6. Plasma levels of fosphenytoin and/or phenytoin following iv infusion of fosphenytoin, 31.5 mg/kg, over 15, 20, or 30 min or of phenytoin sodium, 21 mg/kg, iv over 30 min. All values are the mean ± SEM of 2- 6 samples.

C) EFFECTS ON GUINEA PIG ATRIA IN VITRO (RR 740-02907, Vol. 9).

1. Fosphenytoin and phenytoin both produced concentration-dependent decreases in the rate of spontaneous beating in right atrial preparations and both produced complete arrest.
2. Arrest occurred at a much lower concentration of phenytoin (100 uM) than of fosphenytoin (3000 uM). The EC50's for depression of spontaneous rate were 41 uM (11 ug/ml) for phenytoin and 535 uM (217 ug/ml) for fosphenytoin.
3. Both drugs produced similar concentration-dependent reductions in contractile force in electrically driven left atria (**Figure I.7**) . The EC50 for cardiodepression was similar for each: 98 uM (27 ug/ml) for phenytoin and 105 uM (43 ug/ml) for fosphenytoin. The vehicles depressed developed contractile force <20% at their highest concentrations.
4. This study indicated that under *in vitro* conditions in which less than 1% of phenytoin was present fosphenytoin had a cardiac depressant effect similar to that of phenytoin in guinea pig left atrial preparations. The difference between effects on left and right atria is unexplained. Thus, the prodrug is a myocardial depressant under certain experimental conditions. The relevance of this finding to *in vivo* administration is unknown.

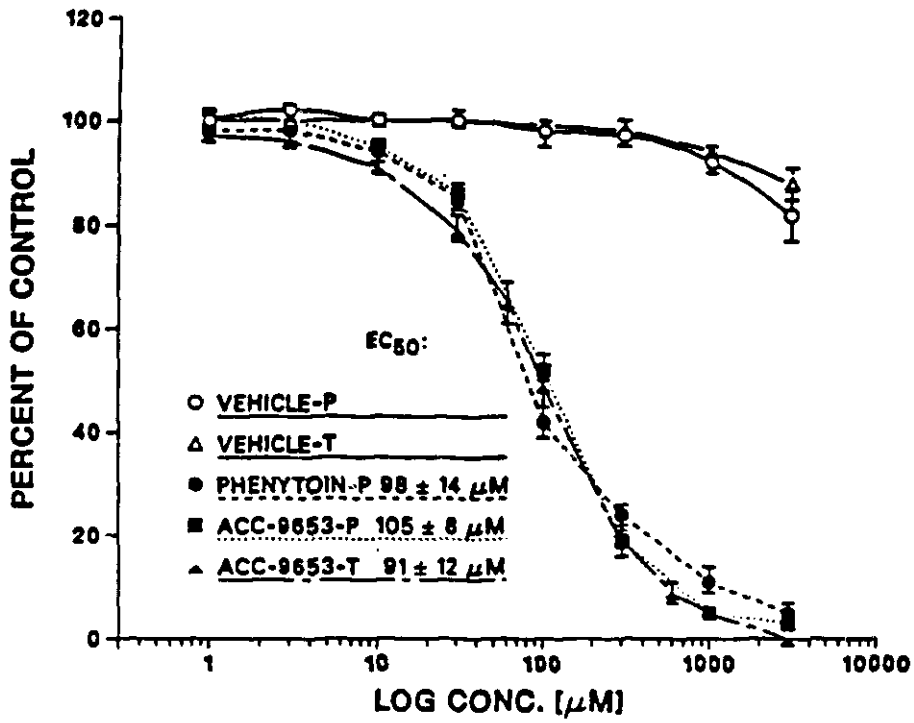


Figure I.7 Effects of ACC-9653 and phenytoin in guinea pig left atria. The mean ± SE values of percent of initial developed force for N=4 (vehicles) or N=8 (each drug) atria are plotted versus the molar concentration of each drug or equivalent vehicle volume. ACC-9653 was examined after dissolution in vehicle-T and vehicle-P; the solid squares represent ACC-9653 in vehicle-P, while the solid triangles represent ACC-9653 in vehicle-T. Phenytoin is represented by solid circles whereas vehicle-P is represented by open circles; the open triangles represent vehicle-T and the values shown in the legend indicate the EC_{50} ± 95% confidence limits for causing cardiodepression for each drug.

II. ADME

Single-dose absorption and pharmacokinetics

A) BLOOD LEVELS AFTER IM ADMINISTRATION TO RATS (RR 764-01612, Vol. 1.10).

Groups of 4 male rats (CD-Sprague-Dawley) were given 115, 250, 370, or 500 mg/kg of fosphenytoin or 77, 169, 250, or 337 mg/kg of phenytoin (equimolar doses) by im injection. Blood samples were collected from each rat at 0.5, 1.5, 3, 6, and 24 hr post-dose. Analysis was by HPLC.

Peak blood concentrations of fosphenytoin were achieved at 30 min after im administration and averaged 9.6, 12.5, 21.4, and 19.6 ug/ml after doses of 115, 250, 370, and 500 mg/kg, respectively. Blood levels of fosphenytoin were still quantifiable at 6 hr in the 3 highest dose groups. Blood concentrations of phenytoin after im fosphenytoin peaked at 90 min and averaged 42.3, 112, 127, and 153 ug/ml at the respective doses. Corresponding peak levels after phenytoin administration were 14.9, 20.1, 31.2, and 33.2 ug/ml at 30 min after dosing. Thus, fosphenytoin administration resulted in phenytoin levels 5-6X higher than those produced by an equimolar dose of phenytoin, indicating greater bioavailability of phenytoin after im administration of fosphenytoin.

B) PHENYTOIN PHARMACOKINETICS AND BIOAVAILABILITY AFTER IV ADMINISTRATION OF EQUIMOLAR DOSES OF PHENYTOIN OR FOSPHENYTOIN TO DOGS (RR 764-01606, Vol. 10).

Five dogs were administered equimolar iv doses of phenytoin (10 mg/kg) or fosphenytoin (14.8 mg/kg) in a two-way crossover study designed to compare the pharmacokinetics and bioavailability of phenytoin after each drug (**Table II.1**). Analysis was by HPLC.

After iv administration of fosphenytoin, fosphenytoin t1/2, Vd, and AUC values averaged 2.6 min, 150 ml/kg, and 255 ug min/ml, respectively. The Cl of 40.2 ml/min/kg approximates the hepatic blood flow in dogs, which would be consistent with metabolism to phenytoin by phosphatases present in tissues such as kidney and liver. Conversion of fosphenytoin to phenytoin was rapid in dogs; the formation t1/2 averaged 0.42 min and the peak phenytoin levels (mean 6.98 ug/ml) were reached at 3.3 min. During the first 30 min after administration of phenytoin, phenytoin levels were higher than after administration of fosphenytoin, but levels were similar thereafter. The elimination t1/2, Cl, Vd, and AUC of phenytoin were not significantly different after iv administration of fosphenytoin and phenytoin sodium. The bioavailability of phenytoin after iv fosphenytoin administration averaged 97.7%

Table II.1. Pharmacokinetic Parameters of Phenytoin in Dogs after IV Administration of 14.8 mg/kg of Fosphenytoin or an Equimolar Dose of Phenytoin Sodium

Phenytoin Parameters*	IV Fosphenytoin	IV Phenytoin
Formation t1/2(min)	0.42 ± 0.42	---
Elimination t1/2 (min)	137 ± 24.5	118 ± 15.2
Clearance (ml/min/kg)	7.35 ± 1.36	7.11 ± 1.09
Vd (ml/kg)	1409 ± 53.3	1197 ± 122
AUC (ug min/ml)	1399 ± 255	1433 ± 223
Tmax (min)	3.28 ± 2.63	---
Cmax (ug/ml)	6.98 ± 0.27	---

* Data expressed as Mean ± SD of 5 dogs

Analysis of 48-hr urine samples collected after administration of phenytoin or fosphenytoin indicated similar metabolite elimination profiles. The glucuronide conjugate of 5-(m-hydroxyphenyl)-5-phenylhydantoin (m-HPPH) was the major metabolite identified in urine, accounting for 58.4 and 56.1% of the dose after fosphenytoin and phenytoin, respectively. Less than 5% of the dose was eliminated as phenytoin and 5-(p-hydroxyphenyl)-5-phenylhydantoin after administration of either compound, and fosphenytoin was not detected in 24 and 48-hr urine samples.

C) PHENYTOIN PHARMACOKINETICS AND RELATIVE BIOAVAILABILITY AFTER IM ADMINISTRATION OF PHENYTOIN OR FOSPHENYTOIN TO DOGS (RR 764-01601, Vol. 1.10).

Five dogs were administered equimolar im doses of phenytoin (10 mg/kg) or fosphenytoin (14.8 mg/kg) in a two-way crossover study to compare the pharmacokinetics and bioavailability of phenytoin after each (**Tables II.2 and II.3**). Samples were analyzed by HPLC.

After im administration, fosphenytoin levels reached a mean peak of 20.4 ug/ml at 9 min, then rapidly decreased such that fosphenytoin was not detectable in plasma after 120 min (**Table II.3**). The absorption and elimination t1/2 values averaged 3.2 and 17.4 min, respectively. The appearance of phenytoin in the plasma was fairly rapid after im administration of fosphenytoin. The formation t1/2, Cmax, and tmax were 24.7 min, 6.8 ug/ml, and 76.9 min, respectively (**Table II.2**). The corresponding values after im administration of an equimolar dose of phenytoin were 17.4 min, 2.16 ug/ml, and 68.1 min for the absorption t1/2, Cmax, and tmax, respectively. The elimination t1/2 and apparent volume of distribution of phenytoin after fosphenytoin administration averaged 164 min and 1058 ml/kg, respectively, which were significantly different than corresponding values of 369 min and 4086 ml/kg, respectively, obtained after im phenytoin. The differences probably reflect precipitation and deposition of phenytoin at the injection site.

The AUC values obtained after administration of phenytoin were substantially lower when compared to the phenytoin AUCs after fosphenytoin administration. From 0 to 720 min, the AUC values averaged 2091 and 960 ug.min/ml after fosphenytoin and phenytoin sodium, respectively. When extrapolated to infinity, the corresponding AUC values averaged 2236 and 1336 ug.min/ml, respectively. These findings show that the bioavailability of phenytoin administered as fosphenytoin was increased compared to im phenytoin sodium, and that the relative bioavailability was time dependent, again indicating that phenytoin was retained at the injection site and slowly released.

Table II.2. Pharmacokinetic Parameters of Phenytoin in Dogs after IM Administration of 14.8 mg/kg of Fosphenytoin or an Equimolar Dose of Phenytoin Sodium

Phenytoin Parameters*	IM Fosphenytoin	IM Phenytoin
Absorption/Formation t1/2(min)	24.7 ± 10.2	17.4 ± 18.7
Elimination t1/2 (min)	164 ± 46.7	369 ± 97.4
Clearance (ml/min/kg)	4.66 ± 0.94	8.2 ± 2.91
Vd (ml/kg)	1058 ± 127	4086 ± 626
$AUC_{0-\infty}$ (ug•min/ml)	2236 ± 557	1336 ± 419
Tmax (min)	76.9 ± 23.8	68.1 ± 57.5
Cmax (ug/ml)	6.83 ± 0.89	2.16 ± 0.38

* Data expressed as Mean ± SD of 5 dogs

Analysis of 48-hr urine samples collected after administration of phenytoin or fosphenytoin indicated similar metabolite elimination profiles. Approximately 58% of the dose was recovered in 48-hr cumulative urine after dosing with fosphenytoin and about 47.4% of the dose was recovered after phenytoin. The major metabolite was the glucuronide conjugate of 5-(m-hydroxyphenyl)-5-phenylhydantoin (m-HPPH), which accounted for 90% of the material recovered in urine in both cases.

D) FOSPHENYTOIN AND PHENYTOIN PHARMACOKINETICS AND BIOAVAILABILITY AFTER IV OR IM ADMINISTRATION OF FOSPHENYTOIN TO DOGS (RR 764-01609, Vol 10).

Fosphenytoin (14.8 mg/kg) was administered iv to 5 dogs, and PK parameters (HPLC analysis) were compared to those determined in the previous im study (**Table II.3** and **II.4**).

After iv administration, fosphenytoin levels averaged 220 ug/ml at 0.6 min after dosing, then rapidly declined in a biphasic manner. The distribution and elimination t1/2 averaged 1.8 and 9.5 min, respectively. The absorption t1/2, Cmax, and tmax after im administration were 3.2 min, 20.4 ug/ml, and 9.1 min, respectively. The elimination t1/2 and Vd were greater than the corresponding iv values. The bioavailability of im fosphenytoin was 100% based on AUCs.

Table II.3. Pharmacokinetic Parameters of Fosphenytoin in Dogs after an IM or IV Dose of 14.8 mg/kg

Fosphenytoin Parameters*	IM Fosphenytoin	IV Fosphenytoin
Absorption or Distribution t1/2(min)	3.22 ± 1.53	1.79 ± 0.16
Elimination t1/2 (min)	17.4 ± 6.22	9.52 ± 2.33
Clearance (ml/min/kg)	21.9 ± 3.21	22.10 ± 3.37
Vd (ml/kg)	544 ± 180	299 ± 82.5
AUC (ug·min/ml)	688 ± 100	685 ± 109
Tmax or T1 (min)	9.13 ± 2.79	0.63 ± 0.35
Cmax or C1 (ug/ml)	20.4 ± 8.52	220 ± 43.7

* Data expressed as Mean ± SD of 5 dogs

Conversion of fosphenytoin to phenytoin was rapid after iv administration. The formation t1/2 averaged 1.3 min, and peak phenytoin levels (mean 7.7 ug/ml) were seen at an average of 9 min after iv administration of fosphenytoin. Absorption of fosphenytoin and conversion to phenytoin was prolonged by im administration; the formation t1/2 averaged 24.7 min, and the peak phenytoin concentration of 6.8 ug/ml (comparable to iv Cmax) was reached after 77 min. The elimination t1/2, Vd, and Cl of phenytoin were similar for the two routes. Based on the AUCs, the bioavailability of phenytoin was 100% after im administration of fosphenytoin.

Table II.4. Pharmacokinetic Parameters of Phenytoin in Dogs after an IM or IV Dose of 14.8 mg/kg of Fosphenytoin

Phenytoin Parameters*	IM Fosphenytoin	IV Fosphenytoin
Formation t1/2 (min)	24.7 ± 10.2	1.25 ± 0.36
Elimination t1/2(min)	164 ± 46.7	194 ± 55.9
Clearance (ml/min/kg)	4.66 ± 0.94	4.75 ± 1.11
Vd (ml/kg)	1058 ± 127	1266 ± 102
AUC (ug·min/ml)	2236 ± 557	2220 ± 617
Tmax (min)	76.9 ± 23.8	9.01 ± 1.83
Cmax (ug/ml)	6.83 ± 0.89	7.67 ± 0.62

* Data expressed as Mean ± SD of 5 dogs

Distribution, Metabolism, and Elimination

A) TISSUE DISTRIBUTION IN RATS (RR 764-01600, Vol. 1.10).

The tissue distribution of 14C-fosphenytoin was examined in 36 male rats after a single iv bolus dose of 10 mg/kg. The distribution of total radioactivity into various tissues was very rapid. For blood, heart, kidneys, liver, lungs, and spleen the highest amount of total radioactivity was seen within the first 5 min. The highest levels in brain, carcass, eyes, intestines, skin/hair, stomach, testes, and urinary bladder occurred at 20, 20, 30, 90, 30, 10, 60, and 60 min, respectively. The highest levels of radioactivity in the intestines, kidneys, liver, carcass, and skin/hair averaged 52.1, 1.9, 14.5, 32.6, and 22.1% of the dose, respectively. Only 0.2% of the dose was found in the brain at 5 and 60 min after dosing, and the amount of radioactivity declined rapidly thereafter.

Rapid elimination of total radioactivity was observed from blood and all tissues. At 24 hr the highest radioactivity was in the carcass and intestines (2.1 and 4.7% of the dose, respectively); the radioactivity in all other tissues including blood was less than 1% of the dose. At 48 hr after dosing, less than 1.4% of the dose remained in all tissues. The tissue/blood total radioactivity ratio was above 1 or close to 1 in the heart, intestines, kidneys, liver, lungs, and stomach over the entire study period. The highest tissue/blood ratios were in intestines> stomach> liver> urinary bladder> kidneys> lungs.

Radio-HPLC analysis of blood, intestines, kidney, and liver samples showed three radioactive peaks, which were identified as a mixture of p-HPPH glucuronide and an unknown metabolite, p-HPPH, and phenytoin, based on their retention times after beta-glucuronidase treatment. In brain, the radioactive peak corresponding to p-HPPH glucuronide was absent. m-HPPH was not detected in blood or any of the 4 tissues examined. The prodrug was rapidly converted to phenytoin. At 5 min after dosing, fosphenytoin was not detectable in brain, intestines, kidneys, and liver, and only a trace amount was detected in blood. The tissue/blood ratio for phenytoin was above one in liver, kidneys, and intestines, and was close to one in brain at several of the later time points after administration. Pharmacokinetic parameters were determined after the concentration-time profiles of phenytoin in blood, brain, intestines, kidneys and liver had been fitted to appropriate pharmacokinetic models. The elimination half-lives of phenytoin in blood, brain, intestines, kidneys, and liver were determined to be 72.8, 59.8, 52.6, 90.1, and 70.3 min, respectively. The elimination t1/2 for blood agrees very closely with published data (Varia and Stella).

B) MASS BALANCE AFTER IV ADMINISTRATION TO RATS (RR 764-01608, Vol. 1.10).

The metabolism and excretion of 14C-fosphenytoin were studied in 10 male rats following iv administration of 10 mg/kg. At 24 hr after dosing, 86.9% of the dose was recovered, with 46.7% in urine and 40.2% in feces. Cumulative urinary and fecal excretion of radioactivity over 72 hr averaged 51.7% and 47.7% of the dose, respectively. These results are consistent with what has been reported for DPH. In the 24 hr urine sample, a large fraction of the radioactivity was in the form of polar metabolites. In contrast, 24-hr fecal samples contained more non-polar metabolites. In the 24-48 and 48-72 hr urine and fecal samples, a larger percentage of the dose was eliminated as nonpolar metabolites. When separated by HPLC, the polar fraction was found not to contain any unchanged fosphenytoin. Three radioactive peaks were detected in this fraction; the major urinary metabolite was a glucuronide conjugate of p-HPPH. Two additional peaks were not identified. One major and two minor metabolites were detected in the nonpolar fraction of urine. The major metabolite was identified as p-HPPH, and one of the minor metabolites was phenytoin. One nonpolar metabolite remained unidentified. The nonpolar fraction of feces contained the same unknown minor metabolite detected in urine and a major metabolite identified to be p-HPPH. So, fosphenytoin was cleared entirely by metabolism; only a trace amount of phenytoin was recovered in urine;> 40% of the dose was recovered in urine and feces as the glucuronide conjugate of p-HPPH. Metabolism appears identical to that of phenytoin, ie, ring oxidation and glucuronidation, followed by renal and biliary excretion of the metabolites.

C) IN VITRO HYDROLYSIS IN HUMAN, DOG, AND RAT BLOOD AND TISSUES (RR 764-01597, Vol. 1.11).

In vitro conversion of fosphenytoin to phenytoin was examined in rat, dog, and human tissues and whole blood. Incubation of fosphenytoin with whole blood and various tissues from rats resulted in the rapid disappearance of prodrug with a concomitant appearance of equimolar amounts of phenytoin. Kidneys, small intestines, and liver exhibited the highest phosphatase activity. Dog and human blood hydrolyzed the drug much more slowly. Mean *in vitro* half-lives of fosphenytoin in rat, dog, and human whole blood were 5.89, 321, and 189 minutes, respectively. Faster prodrug conversion was observed in dog tissue homogenates, with the small intestine, kidney, and liver again the most active in mediating hydrolysis of the prodrug. *In vitro* studies with partially purified alkaline phosphatase (bovine liver and dog intestines) and acid phosphatase (bovine) revealed that fosphenytoin was a better substrate for alkaline than for acid phosphatase.

D) PLASMA PROTEIN BINDING OF FOSPHENYTOIN (RR 764-01620, Vol. 1.11).

The protein binding of 14C-fosphenytoin to dog and human plasma was determined by the ultrafiltration method. Mean percentages of fosphenytoin (at a concentration of 20 ug/ml) bound to human and dog plasma proteins were 95.7 and 91.3%, respectively, indicating that the drug is highly protein bound at therapeutic concentrations. Albumin accounted for 88% of the fosphenytoin binding to human plasma proteins. Varying the concentrations of albumin from 25 to 50 mg/ml significantly increased the % fosphenytoin bound from 81 to 90.5. Binding of 20 ug/ml to human alpha-acid glycoprotein (0.2 to 2 mg/ml) was independent of protein concentration, with percent bound averaging 13.2%. Binding of fosphenytoin to human albumin, 40 mg/ml, decreased linearly from 81 to 67% when concentrations of fosphenytoin increased from 6 to 200 ug/ml.

The effect of fosphenytoin on the plasma protein binding of phenytoin was studied by coincubating DPH at various concentrations of fosphenytoin (7.5-500 ug/ml). Phenytoin binding decreased with increasing fosphenytoin concentrations. At a DPH concentration of 5 ug/ml, the free fraction of phenytoin increased from 4 to 18% when the fosphenytoin concentrations increased from 7.5 to 500 ug/ml. These results indicate that at high concentrations, fosphenytoin may enhance the pharmacological or toxicological effects of phenytoin by displacing DPH from its binding sites.

Drugs highly bound to albumin, such as phenylbutazone, sulfisoxazole, or warfarin, can displace fosphenytoin from binding sites on albumin. When toxic concentrations of AEDs such as PHB, DPH, or VPA were added to plasma, the drugs significantly increased (5-20%) the free fraction of fosphenytoin. Diazepam, phenytoin, and carbamazepine at a concentration of <10 ug/ml did not change the free fraction of fosphenytoin. Since fosphenytoin has little intrinsic pharmacological effect, the changes in free fraction should have no clinical significance. Addition of fosphenytoin at equimolar concentrations to carbamazepine, phenobarbital, or VPA resulted in small but significant displacement of these drugs from its plasma binding sites. The degree of displacement of diazepam or carbamazepine was not enhanced by increasing the concentration of fosphenytoin 30-80-fold. The slight increase in free fraction of these drugs caused by fosphenytoin is unlikely to have clinical significance.

Toxicokinetics

A) TOXICOKINETICS IN RATS FOLLOWING SINGLE IM OR IV DOSES (RR 764-02096, Vol. 1.11).

Plasma *phenytoin* concentrations were determined in serial blood samples collected for 32 hr after administration of single im or iv doses of 150 mg/kg fosphenytoin to Wistar rats (5/sex). While peak plasma levels were greater after iv administration, concentration-time profiles appeared similar between routes after Cmax was reached. Phenytoin mean Cmax values following im fosphenytoin were 50-60% lower than those after iv fosphenytoin (**Table II.5**). Mean tmax values were 10-15X greater after im administration. Elimination t1/2 averaged 2.4 (im) and 5.3 (iv) hr in males and (18 (im) and 21 (iv) hr in females. Mean AUC values were 331 (im) and 404 (iv) ug hr/ml in males and 649 (im) and 611 (iv) in females. Thus, sex differences in phenytoin pharmacokinetics were seen, peak phenytoin levels were reduced after im administration relative to iv administration, and total phenytoin exposure was similar following im or iv administration of the same dose.

Table II.5. Mean (%RSD) Pharmacokinetic Parameters of Phenytoin following IM or IV Bolus Administration of 150 mg/kg of Fosphenytoin to Male and Female Rats (N=5/sex)

Parameters	Male		Female	
	IM	IV	IM	IV
Cmax (ug/ml)	39.8 (15.9)	108 (8.3)	47.4 (18.6)	95.4 (4.9)
tmax (hr)	0.9 (20.8)	0.08 (0.0)	1.3 (46.7)	0.08 (0.0)
t1/2 (hr)	2.4 (27.5)	5.3 (35.8)	17.9 (117)	21.0 (64.2)
AUC (ug hr/ml)	331 (57.2)	404 (32.4)	649 (27.5)	611 (42.7)

B) TOXICOKINETICS IN DOGS FOLLOWING SINGLE IM AND IV DOSES (RR 764-02035, Vol. 1.11).

Phenytoin kinetics were determined after single im or iv doses of 50 mg/kg fosphenytoin to beagle dogs (**Table II.6**). Serial blood samples were collected for 32 hr after dosing. Mean Cmax and tmax values following im fosphenytoin were approximately 21% lower (21.3 ug/ml for im versus 26.8 for iv)

and 100% longer (1.2 hr for im versus 0.6 hr for iv) than those following iv fosphenytoin. Once Cmax was attained, plasma phenytoin concentration-time profiles were similar for both routes. Mean elimination t1/2 values were essentially the same following im (2.8 hr) and iv (3 hr) administration. Mean AUC values following im and iv administration were also comparable, averaging 159 and 163 ug hr/ml, respectively. There was no gender difference in pharmacokinetics in dogs.

Table II.6. Mean (%RSD) Pharmacokinetic Parameters of Phenytoin following IM or IV Bolus Administration of 50 mg/kg of Fosphenytoin to Beagle Dogs (N=3/sex)

Parameters	IM	IV
Cmax (ug/ml)	21.3 (12.8)	26.8 (18.4)
tmax (hr)	1.2 (34.9)	0.6 (125)
t1/2 (hr)	2.8 (19.1)	3.0 (16.9)
$AUC_{0-\infty}$ (ug•hr/ml)	159 (28.9)	163 (27.0)

III. TOXICOLOGY

A) ACUTE IV TOXICITY IN MICE, RATS, RABBITS, AND DOGS (RR's 745-01722, 745-01726, 745-01727, 745-01725, 745-01721, 745-01728, 745-01729; Vol. 1.12)

Results of acute iv toxicity studies comparing fosphenytoin to phenytoin in mice (5/sex/group), rats (5/sex/group), rabbits (6/sex), and dogs (2/sex) are presented in **Table III.1**. Rodents were administered a single dose, while non-rodents received rising doses, allowing one or more days for recovery between doses. Doses were administered either as an iv injection or a 30 min iv infusion.

The acute toxicity of fosphenytoin was similar to that of equimolar doses of phenytoin when both drugs were administered by iv infusion. However, when administered by bolus injection phenytoin was more potent than fosphenytoin, probably because of the more gradual rise in peak phenytoin levels with the later compound. Clinical signs were similar for both and included ataxia, prostration, convulsions, and hypokinesia in both rodent and non-rodent species. Tremors and dyspnea were commonly observed in rodents, while struggling, salivation, and vomiting/retching were seen in dogs. When administered to rats by 30 min infusion, both drugs produced rigid hindlimbs, while only fosphenytoin produced this finding after rapid iv bolus injection. In general the times of onset and recovery of toxic effects were similar for both compounds except following rapid iv injection to rats. Under these conditions, toxic effects were observed immediately after dosing with phenytoin but only after mean lag times of 4 to 14 min with fosphenytoin. Necropsies of rats, rabbits and dogs revealed no macroscopic pathology which could be attributed to drug treatment.

Since phenytoin is commonly administered to children, the acute toxicities of fosphenytoin and phenytoin were compared in weanling (4 week old) and neonatal (7 days) rats. When administered by 30 min iv infusion to weanlings, the compounds produced similar toxic signs, which included ataxia, prostration, hypokinesia, sedation, piloerection, dyspnea, hypopnea, tremors, and convulsions (few fosphenytoin rats only). The phenytoin and fosphenytoin MLD's in weanling rats were similar to those obtained in adult rats. Because iv injections could not be made in neonates, both neonatal and weanling rats were administered fosphenytoin or phenytoin ip. It was concluded from this study that the acute toxicities of the two drugs were similar following ip administration, but that both were more toxic (lethal) in neonates.

B) ACUTE IM TOXICITY IN RATS AND DOGS (RR 745-01738, RR 745-01742; Vol. 1.12)

The acute toxicities of fosphenytoin and phenytoin were also compared after im administration to rats (3/sex/dose) and dogs (3/sex). Clinical signs were noted in rats within 40 to 60 min postdose with both compounds. Ataxia and prostration were observed in rats with fosphenytoin doses 1/2 and 1/3 lower, respectively, on a molar basis, than those phenytoin doses producing the same signs. Deaths occurred between 3 and 19 hr postdose with fosphenytoin doses ≥ 247 mg/kg (phenytoin equivalents), while no deaths occurred with phenytoin doses up to 337 mg/kg **(Table III.2)**. In dogs, sedation and emesis occurred with both compounds, while prostration, ataxia, and convulsion were seen only with fosphenytoin. Struggling during dosing, presumably resulting from pain, was seen only with phenytoin. No deaths occurred in dogs at doses of up to 50 mg/kg of either compound. In a separate PK study in rats, whole blood phenytoin concentrations were consistently 5 to 6 times higher after administration of fosphenytoin than with equimolar doses of phenytoin (see PK section, above). Thus, the greater solubility and resultant higher blood levels presumably accounted for the increased systemic toxicity of fosphenytoin seen in both rats and dogs. In both species, phenytoin caused injection site necrosis while no necrosis was observed with fosphenytoin.

Table III.1. Summary of Acute IV Toxicity Studies of Fosphenytoin and Phenytoin

Species	Route	Drug	Results (mg/kg phenytoin equivalents)		
			NOAEL	MTD	MLD
Mouse	IV infusion	Fosphenytoin	33.3	63.3	156
		Phenytoin	<33	63	192
Rat	IV bolus	Fosphenytoin	50	153	213
		Phenytoin	<45	45	90.4
Rat	IV infusion	Fosphenytoin	<50	153	242
		Phenytoin	<45	210	275
Rat (weanling)	IV infusion	Fosphenytoin	33.3	120	258
		Phenytoin	33	120	297
Rat (weanling)	IP	Fosphenytoin	60	ND	352
		Phenytoin	60	ND	339
Rat (neonate)	IP	Fosphenytoin	100	ND	180
		Phenytoin	102	ND	224
Rabbit	IV infusion	Fosphenytoin	40	40	ND
		Phenytoin	27	40.5	ND
Dog	IV bolus	Fosphenytoin	13.3	26.7	ND
		Phenytoin	6	24	ND
Dog	IV infusion	Fosphenytoin	13.3	26.7	ND
		Phenytoin	12	24	ND

Table III.2. Comparison of Acute IM Toxicity of Fosphenytoin and Phenytoin in Rats and Dogs

Species	Route	Drug	Results (mg/kg phenytoin equivalents)		
			NOAEL	MTD	MLD
Rat	IM	Fosphenytoin	33.3	167	278
		Phenytoin	34	337	>337
Dog	IM	Fosphenytoin	33.3	33.3	ND
		Phenytoin	6.7	> 50	ND

C) FOUR-WEEK IV TOXICITY IN RATS (RR 250-01648, Vol. 1.14).

1. Treatment

Four groups of 18 Wistar rats/sex were given daily iv (bolus) doses of vehicle or fosphenytoin (30, 60, and 150 mg/kg) for 4 weeks. Ten rats/sex/grp were euthanized at the completion of dosing, and 5/sex/group were sacrificed after a 4 week recovery period (week 8). Three rats/sex/group were sacrificed 15 min postdose during week 3 for determination of whole blood and plasma phenytoin concentrations. All animals were observed daily for signs of toxicity. Body weight and food consumption were determined weekly. Detailed physical and ophthalmoscopic exams were performed pretest and at termination (week 4 or 8). Samples for hematology, biochemistry, and urinalysis were obtained prior to termination. Selected organs were weighed, and tissues from control and HD groups and liver and injection sites from all groups were examined microscopically. Liver from selected control and HD animals were evaluated by EM.

Drug lot #: CM 345120

2. Clinical Signs and Mortality

a) Ataxia or hypoactivity were observed infrequently in 1 and 2 MD males, respectively. Ataxia and hypoactivity were seen throughout the treatment phase in all HD animals. Salivation was noted in 3 MD and 14 HD rats. Urinary staining and dyspnea occurred in both sexes at the HD. The incidence of injection-related skin sores was similar in treated and control groups.
b) No animals died during the study.

3. Body weight and food consumption

a) BW was decreased 18% in HD males, with a 32% reduction in weight gain during the dosing period. In the recovery period, BW gain was higher in HD males and there were no statistically significant differences at week 8.
b) Food consumption was 14% lower in HD males and 10% higher in HD females compared to controls.

4. Physical and Ophthalmoscopic exams

No significant treatment-related effects.

5. Hematology

Small decreases in RBCs, HGB, and HCT and an increase in MCHC were seen in HD females at week 4 compared to controls (not considered toxicologically significant).

6. Clinical Chemistry

a) Increases (30-60%) in alanine aminotransferase and alkaline phosphatase activities were observed in HD males and females.
b) A 48% decrease in triglyceride concentration was seen in HD males at 4 weeks.
c) Urea was slightly decreased in all treatment group males at 4 weeks (15% at HD).

7. Urinalysis

No TR effects.

8. Organ weights -

Statistically significant increases in absolute and relative liver weight were noted at 4 weeks in treated females at all doses. Relative liver weights were also increased in HD males, but absolute weights were lower than controls. Relative liver to BW ratios were increased at 8 weeks in HD males and females, but there were no differences in absolute liver weights.

9. Gross Pathology

Treatment-related changes in the skin at the tail injection sites were noted in HD rats at 4 weeks and 8 weeks.

10. Histopathology

Changes in the liver and injection sites were seen in treated males and females at week 4.

a) Liver -The incidence of periportal cytoplasmic vacuolization of hepatocytes was increased in treated males (minimal to mild) and females (mild to moderate). No liver abnormalities were observed in the recovery groups. 4 week liver tissue from selected control and HD group animals exhibited no evidence of hepatocellular injury by EM; however, glycogen deposition was increased in treated animals, particularly in a females having the greatest periportal vacuolization.

b) Skin - Cutaneous necrosis and inflammation were increased at the injection sites of treated males and females at 4 weeks. No changes were noted at 8 weeks.

11. Plasma concentrations

Phenytoin concentrations at 15 min postdosing were proportional to dose and similar in plasma and whole blood of males and females (**Table III.3**).

Table III.3. Plasma and Whole Blood Phenytoin Concentrations in Rats Given Fosphenytoin IV for 4 Weeks

Fosphenytoin Dose (mg/kg)	Plasma Concentration (ug/ml)*			
	Plasma		Whole Blood	
	Male	Female	Male	Female
30	7.34 ± 0.85	10.9 ± 1.75	7.85 ± 0.24	10.7 ± 0.79
60	18.4 ± 4.24	21.2 ± 0.91	19.0 ± 3.67	22.4 ± 1.27
150	54.6 ± 1.10	51.0 ± 0.91	55.1 ± 2.12	55.5 ± 1.04

* Samples obtained 15 min postdose from 3 animals/sex/group during week 3; values are mean ± standard.

D) 13 WEEK IM TOXICITY IN RATS (RR 745-01744, conducted by IRDC, Vol. 1.15).

1. Treatment

Fifteen Sprague Dawley (Charles River CD) rats/sex/group were randomly assigned to each of five treatment groups, to receive either normal saline (controls), phenytoin sodium (positive control; 100 mg/kg in 40% propylene glycol and 10% ETOH), or fosphenytoin (30, 60, or 150 mg/kg in 0.1 M TRIS buffer) by intramuscular injection, once daily, for 13 weeks. Ten rats/sex/group were designated as main study animals and the remaining 5/sex/group were used for pharmacokinetic studies. The phenytoin and HD fosphenytoin groups received approximately equimolar doses. Because of excessive mortality, the phenytoin group was terminated during week 9, and all tests scheduled for termination were carried out at that time.

Drug lot #: Z86-7-10

2. Observed signs

Decreased activity, leaning to one side, excessive salivation, and dilated pupils were observed in HD fosphenytoin animals. Only excessive salivation was observed in the MD group. The phenytoin group exhibited decreased activity, excessive salivation, swollen hindlimbs, and autocanibalism of hind limbs.

3. Mortality

In the phenytoin group, 8/15 male and 10/15 female rats died by week 8. In the fosphenytoin groups, deaths occurred in 1/15 LD females, 1/15 MD females, 2/15 HD males and 1/15 HD females. One saline control female died. Only the phenytoin group and HD fosphenytoin group deaths were considered treatment-related; the others were thought to be related to the blood collection procedure.

4. Body Weights and Food Consumption

a) BWs for males and females in both the HD fosphenytoin group and the phenytoin group were lower than those in the saline control group throughout the treatment period.

b) Food consumption (g/animal) for HD fosphenytoin group males was consistently lower than saline controls. However, when calculated relative to BW, food consumption values (g/kg) for both male and female HD animals were generally higher than those for the control group. Food consumption in the LD and MD fosphenytoin groups was slightly (<10%) lower than controls. In the phenytoin group, both absolute and relative consumption were reduced compared to controls.

5. Hematology (routine hematology, serum chemistry and urinalysis tests were conducted on all main study rats during week 6 and at termination)

No treatment-related effects on hematology were observed among any of the fosphenytoin-treated groups. Significant decreases in RBCs, HGB and HCT, and increases in WBCs observed in phenytoin-treated rats were attributed to hemorrhage and infection secondary to autocannibalism induced by the local irritation of im phenytoin.

6. Clinical Chemistry

a) Aspartate and alanine aminotransferase and alkaline phosphatase levels were

elevated in the HD fosphenytoin group (≅ about 2-fold for all 3 in M & F). Only slight increases in alkaline phosphatase levels were noted in the phenytoin group.

b) Non-fasted glucose concentrations (from samples collected 2 hr after dosing) were significantly elevated (4-fold compared to saline) in the HD fosphenytoin group. Phenytoin had previously been shown to induce hyperglycemia, presumably by inhibiting insulin release, and glucose was elevated about 2-fold in the phenytoin group at 9 weeks in the current study. A hyperglycemic effect has also been previously shown for fosphenytoin. The hyperglycemia was no longer evident by the time routine blood samples were collected 24 hr later.

7. Urinalysis

Glucosuria was observed in both the phenytoin and HD fosphenytoin groups.

8. Organ Weights

a) Absolute and relative liver weights were elevated in MD and HD fosphenytoin groups, primarily in females (70-80% in HD females). In contrast, absolute and relative (to brain) liver weights were decreased in the phenytoin group.

b) Relative adrenal weights were increased in phenytoin group animals, and absolute adrenal weights were increased in the HD fosphenytoin group.

c) Thymus weights were significantly decreased in HD fosphenytoin males and females, while relative thymus weights were significantly decreased in phenytoin group females.

9. Gross Pathology

Macroscopic evidence of tissue irritation at injection sites was observed in the phenytoin- and fosphenytoin-treated groups. Changes in the phenytoin group consisted of pockets of fibrous material, nodules, necrosis, thickened tissue, and abscesses. The lesions were bilateral and the intensity was moderate to severe. Also, 10/15 males and 8/15 females in this group had missing toes or foot parts from their rear limbs. In fosphenytoin groups, changes included necrosis, hemorrhage or discolored areas, and pale, firm areas. The lesions were unilateral or bilateral, focal, and varied from mild to severe. The changes in the fosphenytoin groups were dose-related, and no signs of autocannibalism were seen.

10. Microscopic Pathology

a) Injection site - Microscopic evidence of injection site irritation, consisting of hemorrhage, inflammation, necrosis, mineralization, and thrombosis, was seen in both the phenytoin and fosphenytoin groups. The response was dose-dependent in the fosphenytoin groups, and the changes were reportedly somewhat less severe than in the phenytoin group.

b) Liver - Increased intracytoplasmic vacuolization of hepatocytes was observed in HD fosphenytoin animals (8/10 males, 9/10 females). This was thought to be due to glycogen accumulation. Single cell hepatocyte necrosis was observed in the phenytoin group animals (3/10 males, 3/10 females).

c) Thymus - Thymuses of rats in the phenytoin and HD fosphenytoin groups showed trace to moderate lymphoid depletion (correlated with decreases in thymus weights; considered stress-related).

d) A few animals in the phenytoin and HD fosphenytoin groups had cortical cell vacuolization or hypertrophy of the adrenals. This was also considered stress-related.

11. Plasma Drug Concentrations

Blood samples were collected from rats designated for blood level studies immediately prior to, and at 30, 60, and 120 min after dosing on study days 1, 42, and at termination (**Table III.4**).

At equimolar doses, peak phenytoin levels were about 3-4 times higher following fosphenytoin administration than after phenytoin injection. Absorption of phenytoin was apparently prolonged, since significant levels were measured in this group prior to dosing on day 42.

Table III.4. Plasma Fosphenytoin and Phenytoin Concentrations in Rats Given Fosphenytoin or Phenytoin IM for 13 Weeks

Fosphenytoin Dose (mg/kg phenytoin equivalents)	Plasma Concentration (ug/ml)*			
	Fosphenytoin		Phenytoin	
	Male	Female	Male	Female
20	< 0.1	< 0.1	8.42 ± 1.40	7.53 ± 1.22
40	0.782 ± 0.85	0.319 ± 0.65	14.3 ± 4.88	18.0 ± 4.67
100	2.10 ± 1.25	3.19 ± 2.38	46.7 ± 16.5	48.9 ± 6.64
Phenytoin 100 mg/kg	NM	NM	15.2 ± 10.2	23.8 ± 1.36

* Samples obtained 30 min postdose from 5 animals/sex/group, on day 91 (week 13) from animals given fosphenytoin and on day 42 (week 6) from animals given phenytoin; values are mean ± standard.
NM = not measured

E) FOUR-WEEK IV TOXICITY IN DOGS (RR 745-01970, Vol. 1.18)

1. Treatment

Four groups of beagle dogs (4/sex/group) were given daily iv bolus doses of fosphenytoin at 0 (vehicle-0.1 M Tris buffer, pH 8.8), 15, 30, or 50 mg/kg for 4 weeks. Three animals in each group were sacrificed after 4 weeks; the remaining dog in each group was sacrificed after a 4 week recovery period. Animals were observed daily for signs of toxicity and systemic effects. Body weights were recorded pretest, weekly, and at termination. Food consumption was assessed daily by visual inspection. Physical and ophthalmoscopic exams were performed pretest and at weeks 4 and 8. Blood pressure measurements and ECG were performed pretest, before and 60 mi. after dosing on day 1 and during week 4, and at 8 weeks. Hematological, clinical chemistry and urinalysis determinations were made pretest and at weeks 4 and 8. Blood samples for determination of phenytoin concentrations were collected 30 min after dosing during week 2. Complete necropsies were performed on all animals at termination after 4 or 8 weeks.

Drug lot #: CM 344120

2. Clinical Signs and Mortality

a) Salivation, emesis, mucoid feces were observed in all treatment groups (D-R).
b) Erythema of the gums and/or muzzle after dosing was seen in MD and HD dogs.
c) All HD males and 2 HD females exhibited ataxia, and hypoactivity and tremors occurred sporadically in HD animals.
d) No significant signs were observed during the recovery period.
e) No unscheduled deaths occurred.

3. Body Weight and Food Consumption

There were no significant drug-related effects on body weights or food consumption.

4. Physical and Ophthalmoscopic exams

No significant treatment-related effects.

5. Blood Pressure and ECG

There were no significant treatment-related changes.

6. Hematology and Bone Marrow

No drug-related alterations in hematologic parameters or bone marrow data were observed.

7. Clinical Chemistry

A D-R increase in serum alkaline phosphatase ($\bar{x}$ 2.5-3X C at HD) was seen in treated dogs compared to pretest and control values. These returned toward normal during the recovery period, but were still elevated at 8 weeks.

8. Urinalysis

No treatment-related changes.

9. Organ Weights

a) D-R increases in liver weights occurred in treated dogs (absolute x̄+25-30% at HD).
b) Mandibular salivary gland weights were increased in HD males and MD and HD females.
c) Small (10%) increases in absolute and relative heart weights were seen in MD and HD males.

10. Gross Pathology

No TR changes were noted.

11. Histopathology

a) Two HD males had minimal diffuse hypertrophy of mandibular and parotid salivary gland acini which correlated with salivation noted clinically and increased salivary gland weights. These changes were not seen in females.
b) No differences in the incidence or severity of injection site alterations were noted between vehicle controls and treated groups.

12. Plasma concentrations

Mean plasma and whole blood phenytoin concentrations increased proportionately with dose. Plasma and whole blood phenytoin concentrations were similar and were equivalent between sexes at each dose (**Table III.5**).

Table III.5. Plasma and Whole Blood Phenytoin Concentrations in Dogs Given Fosphenytoin IV for 4 Weeks

Fosphenytoin Dose (mg/kg)	Plasma Concentration (ug/ml)*			
	Plasma		Whole Blood	
	Male	Female	Male	Female
15	6.43 ± 0.33	6.76 ± 0.41	6.54 ± 0.31	6.95 ± 0.07
30	13.4 ± 0.99	13.2 ± 0.19	13.7 ± 0.30	13.8 ± 0.40
50	22.2 ± 1.47	24.0 ± 2.90	23.5 ± 0.69	23.8 ± 2.46

* Samples obtained 30 min postdose from 4 animals/sex/group during week 2; values are mean ± standard.

F) 13 WEEK IM TOXICITY IN DOGS (RR 745-01740, conducted by IRDC, Vol. 1.19).

1. Treatment

Fosphenytoin was administered im to beagle dogs at dose levels of 15, 30, and 60 mg/kg/day for 13 weeks. A negative control group was administered saline, and a positive control group received phenytoin sodium on the same regimen. The phenytoin dose was 40 mg/kg, which was equimolar to the high fosphenytoin dose. All groups contained 4 males and 4 female dogs.

Drug lot #: Z86-7-10

2. Clinical Signs

Ataxia, decreased activity, and mucoid diarrhea were observed in the HD fosphenytoin group. Emesis and ptyalism were seen in all fosphenytoin-treated dogs in a dose-related manner. Ataxia, emesis, and diarrhea were observed in the phenytoin group with incidences intermediate between that seen in the MD and HD fosphenytoin groups. Other observations made in phenytoin-treated dogs include the inability to bend rear legs, thinness, swollen legs, and loss of appetite. Dogs in this group also struggled and vocalized during dosing. Both phenytoin and fosphenytoin groups exhibited swelling at the injection sites.

3. Mortality

All study animals survived until termination.

4. Body Weight and Food Consumption

BW gain was increased in male fosphenytoin group dogs (1.5X saline controls at HD) and slightly decreased in phenytoin group males and females compared to saline controls. Food consumption was decreased in HD females and in phenytoin group males and females.

5. Ophthalmoscopic Examination

No treatment-related ophthalmoscopic abnormalities were detected.

6. Physical Examination

Signs of injection site irritation were noted in the phenytoin group only.

7. Cardiovascular Examination

No cardiovascular abnormalities were detected at one month or at the end of the study.

8. Hematology (pre-study and at 1, 2, and 3 months)

No changes in hematologic values were noted in the analysis of blood samples. However, one HD fosphenytoin female had an elevated myeloid/erythroid ratio (M/E = 6.1) in the bone marrow smear performed post mortem, indicative of depressed erythrogenesis. All other hematologic parameters were normal for this dog, however.

9. Clinical Chemistry (pre-study and at 1, 2, and 3 months)

Alkaline phosphatase levels were elevated in the phenytoin group males and females (≈ 2-3-

fold C), in HD fosphenytoin group males and females (2-3X C), and in MD fosphenytoin females (+60% compared to C). Creatine phosphokinase (CPK) values were elevated in MD and HD fosphenytoin males (2X C), in HD fosphenytoin group females (2X C), and in phenytoin group females (2-3X C). AST and ALT were increased in phenytoin group females (2 X). BUN was decreased in phenytoin group males and females (-30-40%).

10. Urinalysis (pre-study and at 1, 2, and 3 months)

The urinalysis values for all groups were normal.

11. Organ Weights

A dose-related increase in liver weights occurred in fosphenytoin group males (+35% at HD) and females (+28% at HD). Liver weight was also increased in the PC group (+28% M, 14% F).

12. Macroscopic Pathology

Injection site changes were observed in dogs from the phenytoin group and from the MD and HD fosphenytoin groups. These were more extensive and severe in the phenytoin group and consisted of abscesses, fibrous tissue masses, and multiple hemorrhages. Only 2 females in the MD fosphenytoin group and 2 males and 2 females in the HD group had tissue changes consisting of discolored fat and muscle, edema between muscles, and petechial hemorrhage.

13. Microscopic Pathology

a) Injection site - Microscopic changes were observed at the injection site in the phenytoin group and in the HD and MD fosphenytoin groups. Abnormalities seen at the injection site in phenytoin treated dogs included hemorrhage, inflammation, necrosis, thrombosis, mineralization and abscess formation. Injection site changes in the fosphenytoin groups were reportedly much less severe.

b) Livers of 1 male and 1 female from the phenytoin group and of all females from the HD fosphenytoin group showed diffuse increases in intracytoplasmic vacuolization of hepatocytes.

14. Plasma Drug Levels

Blood samples were collected from each animal 30 min before and at intervals up to 3 hr after dosing on days 1, 42 and at termination (**Table III.6**). Peak fosphenytoin levels were seen 10-15 min after administration. Rapid conversion to phenytoin was demonstrated by the appearance of phenytoin levels by 5 min after dosing. Phenytoin levels peaked at approximately 60 min after prodrug administration. Peak phenytoin levels in the phenytoin group were consistently about 3 times lower than those in the equimolar fosphenytoin group.

Table III.6. Plasma Fosphenytoin and Phenytoin Concentrations in Dogs Given Fosphenytoin or Phenytoin IM for 13 Weeks

Fosphenytoin Dose (mg/kg phenytoin equivalents)	Plasma Concentration (ug/ml)			
	Fosphenytoin*		Phenytoin**	
	Male	Female	Male	Female
10	13.7 ± 5.91	20.2 ± 10.9	6.24 ± 0.59	6.34 ± 0.81
20	28.1 ± 12.9	21.7 ± 8.09	12.1 ± 0.90	11.2 ± 1.32
40	60.6 ± 7.18	51.4 ± 12.8	27.5 ± 3.47	28.7 ± 11.0
Phenytoin 40 mg/kg	NM	NM	6.67 ± 1.57	9.97 ± 1.65

* Samples obtained 10 min postdose from 4 animals/sex/group on day 91 (week 13); values are mean ± standard.
**Samples obtained 60 min postdose from 4 animals/sex/group on day 91 (week 13); values are mean ± standard.
NM = not measured

IV. SPECIAL TOXICITY

A) VENOUS AND PERIVASCULAR IRRITATION IN RABBITS (RR 745-10724, Vol. 1.20).

When administered as a 30-min iv infusion (0.05 ml/min) into the right ear or as a 0.1 ml perivascular injection into the left ear, fosphenytoin at concentrations of 10, 25, or 50 mg/ml was no more irritating than the saline control at either site. A concentration of 75 mg/ml resulted in higher (50%) irritation scores than the saline control at both sites. Phenytoin concentrations of 16.9, 33.7, and 50 mg/ml produced significantly greater microscopic irritation than did the saline control at the venous site and concentrations of 33.7 and 50 mg/ml produced significantly greater irritation at the perivascular site. The three highest doses of phenytoin were only slightly more irritating than their undiluted vehicle (40% propylene glycol, 10% alcohol, water - pH adjusted to 12 with NaOH). The irritation produced by phenytoin and its vehicle included a high incidence of thrombosis, which was not seen in the fosphenytoin groups.

B) LOCAL IRRITATION AFTER ACUTE IM INJECTION OF RABBITS (RR 745-01737, Vol. 1.20).

Microscopic irritation scores (slight to moderate) were not different among injections sites for saline, phenytoin vehicle, and phenytoin (50 mg/ml). Irritation scores (minimal to mild) at fosphenytoin vehicle (0.1 M Tris buffer, pH adjusted to 8.8 with HCl) or fosphenytoin (25, 50, 75, or 100 mg/ml) sites were statistically lower than those for saline control and phenytoin.

C) LOCAL IRRITATION AFTER DAILY IM INJECTION OF RABBITS FOR FIVE CONSECUTIVE DAYS (RR 745-01741, Vol. 1.20).

When a 1 ml volume was injected im into the hindlimb of rabbits daily for 5 consecutive days, fosphenytoin concentrations of 50, 75 and 100 mg/ml produced concentration-dependent irritation compared to saline controls (increased serum creatine kinase and irritation scores). Based on macroscopic scores and effects on serum CK, phenytoin at 50 mg/ml was more irritating than equimolar concentrations of fosphenytoin. Irritation produced by the undiluted phenytoin vehicle was comparable in severity to that seen with formulated phenytoin at a concentration of 50 mg/ml.

D) HYPERGLYCEMIC EFFECTS IN RATS (RR 745-01734, Vol. 1.20).

Fosphenytoin (150 mg/kg) or phenytoin (100 mg/kg) were administered by 30 min infusions to 10 rats/group, and multiple blood and urine samples were collected over a 48 hr period. Serum glucose concentrations in the fosphenytoin and phenytoin groups were elevated by 30 min after dosing and peaked at about 400 mg/dL at 1 hr. Levels were significantly increased for 4-6 hr after dosing. Glucose levels in both groups had returned to normal by 24 hr. Urine glucose levels increased during the first 12 hr after dosing in both groups compared to saline controls and returned to normal during the second 12 hr. Effects on glucose were comparable for the two drugs.

E) CNS TOXICITY IN MICE (RR 745-01736, vol. 1.20).

6 mice/group received single ip injections of equimolar doses of fosphenytoin or phenytoin sodium solution. Saline and vehicle controls were included. Fosphenytoin at 50 mg/kg or phenytoin at 33 mg/kg produced no effects. Dose-related CNS toxicity, including decreased respiration, prostration, piloerection, tremors, ataxia, sedation, decreased pupil response, reduced righting reflex, decreased grip strength, decreased body temperature, and death (at 2 highest doses), were observed after doses of 100, 200, 500, or 1000 mg/kg of fosphenytoin or 69, 134, 337, or 675 of phenytoin. Responses to equimolar doses of fosphenytoin and phenytoin were similar, but there was a suggestion of quantitatively greater effects with fosphenytoin. These differences may have been due to differences in absorption after ip administration.

F) CARDIOVASCULAR TOXICITY IN DOGS (RR 745-01735, Vol. 1.20).

The cardiovascular effects of fosphenytoin, phenytoin, and their respective vehicles (0.1 M Tris buffer, pH 8.8 and 40% propylene glycol, 10% alcohol, pH 12) were compared following iv bolus (3 sec) injection to anesthetized female dogs (4/group). A saline control was also included. The phenytoin dosage (18 mg/kg) used in the study was considered to represent a clinically effective dose for treatment of status epilepticus, which would normally be infused over 20-30 min. The fosphenytoin dose (27 mg/kg) was equimolar. Heart rate, left ventricular dP/dt at 40 mmHg (LVdP/dt), left ventricular end diastolic pressure (LVEDP), mean arterial pressure (MAP), and Lead II electrocardiograms were recorded at frequent intervals for 1 hour after dosing. Blood samples for determination of drug concentrations were collected at each interval.

Since there were no differences in CV parameters among the three control groups, data from these were pooled. Lead II ECG recordings were similar among groups. A slight increase in QT interval was seen in both treated groups, but this effect was not considered biologically significant. Intravenous phenytoin resulted in decreases in heart rate (80% of baseline), LvdP/dt (max -55% compared to C), and MAP (-40% compared to C) and a significant increase in LVEDP (2-3-fold). Effects on LVdp/dt and LVEDP lasted 3-5 min, while changes in MAP gradually returned toward baseline over the 60-min observation period and HR remained low up to 1 hr (**Figures IV. 1 and IV.2**). Peak phenytoin levels in blood occurred at 30 sec after dosing (49 ug/ml) and gradually decreased to 14 ug/kg at 60 min (**Table IV.1**). Fosphenytoin resulted in more gradual decreases in HR (80% of baseline), LvdP/dt (max -36% compared to C), and MAP (-40% compared to C and baseline). These changes peaked at 2-3 min and then slowly returned toward baseline (HR remained low at 1 hr). Effects on LVEDP were variable and did not appear to be as pronounced as those produced by phenytoin administration. Phenytoin blood levels rose more slowly after fosphenytoin administration, peaking at 5 min after dosing (22 ug/ml). Effects on CV parameters appeared to correlate with phenytoin blood levels in both cases. The major difference between drugs was in effects on LVEDP. The less pronounced effects seen after fosphenytoin presumably reflect the lower peak blood level of phenytoin resulting from its administration.

Table IV.1

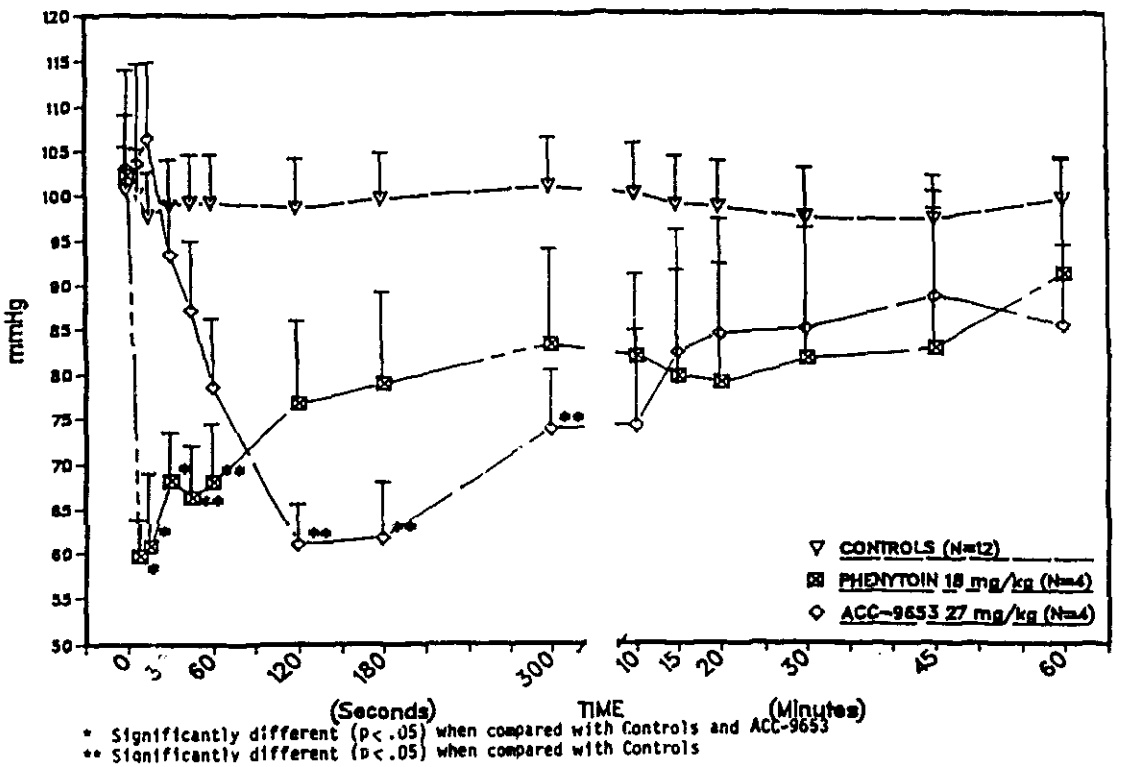
Mean 9653 and Phenytoin Blood Levels (µg/mL)

Time	Phenytoin 18 mg/kg Mean	SD	N	9653 27 mg/kg 9653 Mean	SD	N	Phenytoin Mean	SD	N
Baseline	BQL[a]	-	4	BQL[a]	-	4	BQL[a]	-	4
5 Seconds	41.6	54.3	3	194	66.9	4	6.5	0.4	4
15 Seconds	47.8	30.1	3	258	68.2	4	2.5	1.6	4
30 Seconds	49.4	17.3	4	241	28.0	4	5.5	1.3	4
45 Seconds	39.9	12.5	4	179	31.1	4	8.9	2.2	4
60 Seconds	34.2	8.3	4	188	13.9	4	10.4	1.0	4
2 Minutes	41.3	4.6	4	104	16.2	4	16.3	2.0	4
3 Minutes	37.7	3.8	4	86.7	9.0	4	19.5	1.5	4
5 Minutes	33.2	2.2	4	35.9	6.0	4	22.1	1.3	4
10 Minutes	28.1	3.1	4	11.1	2.5	4	20.5	1.5	4
15 Minutes	21.8	1.1	4	4.1	1.2	4	17.0	1.9	4
20 Minutes	20.9	2.1	4	1.5	0.6	4	15.8	0.8	4
30 Minutes	17.8	2.3	4	0.4	0.2	4	14.5	2.6	4
45 Minutes	14.9	2.8	4	0.2	0.1	4	10.7	2.1	4
60 Minutes	13.8	3.5	4	0.1	0.2	4	10.5	2.1	4

[a] BQL=Below Quantifiable Limit (0.1 µg/mL)

Figure IV.1

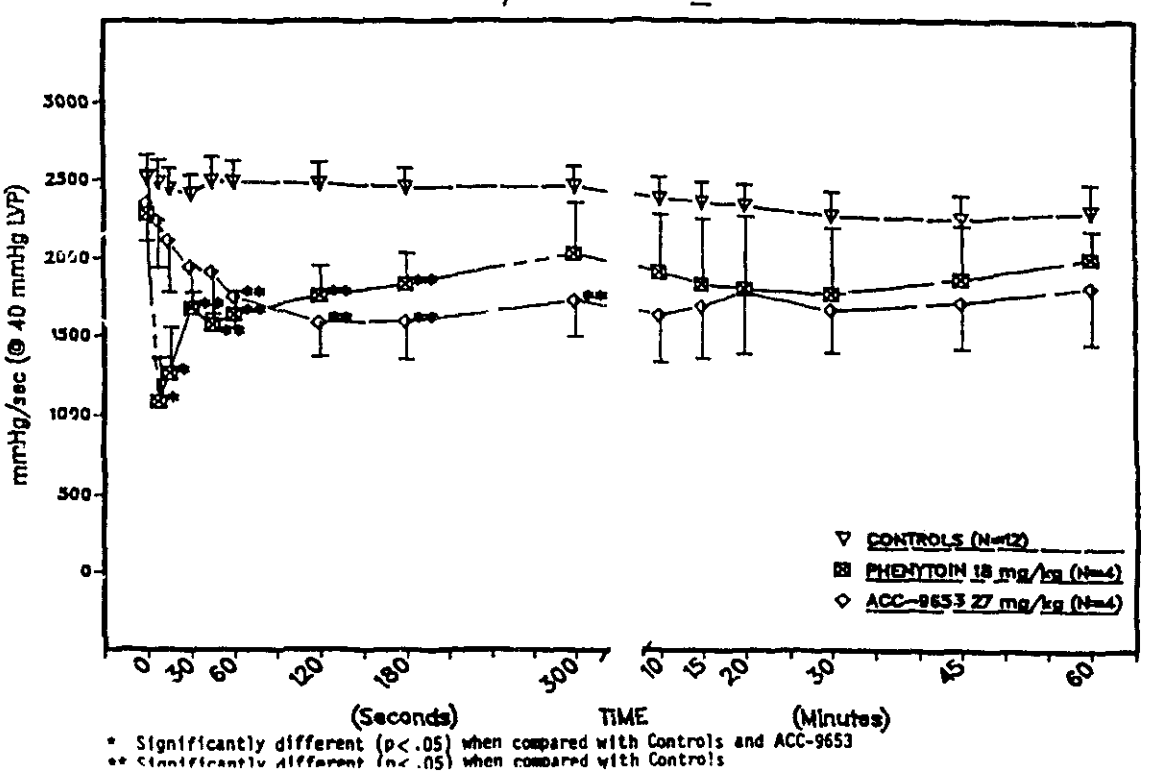
CARDIOVASCULAR TOXICITY EVALUATION
OF -9653 AND PHENYTOIN
MAP Means ± S.E.M.



* Significantly different ($p < .05$) when compared with Controls and ACC-9653
** Significantly different ($p < .05$) when compared with Controls

Figure IV.2

CARDIOVASCULAR TOXICITY EVALUATION
OF 9653 AND PHENYTOIN
LV dP/dT Means ± S.E.M.



* Significantly different ($p < .05$) when compared with Controls and ACC-9653
** Significantly different ($p < .05$) when compared with Controls

G) IN VITRO EFFECTS ON HUMAN BLOOD (RR 745-01746, Vol. 1.20).

Washed cell and plasma from blood collected from 4 human donors were mixed with various concentrations of fosphenytoin and phenytoin and compared to positive controls for hemolysis and plasma protein flocculation by measuring hemoglobin concentration or optical density. Fosphenytoin produced little hemolysis (<0.7%) at any of the concentrations tested (0.15 - 75 mg/ml). Phenytoin produced only slight hemolysis (<3.6%) at concentrations up to 5 mg/kg, but essentially complete hemolysis was seen at 10, 20, and 50 mg/ml. Fosphenytoin produced no plasma protein flocculation at any concentration tested. Phenytoin produced mild flocculation at 20 mg/ml but none at lower or higher concentrations, indicating that this may have been an anomalous result. No explanation for the difference in hemolytic effects was provided.

H) POTENTIAL RISK ASSOCIATED WITH SYSTEMIC FORMALDEHYDE (RR-MEMO 745-01786, Vol. 1.31)

Formaldehyde is generated during the conversion of fosphenytoin to phenytoin by tissue phosphatases (t1/2 approximately 8 min in humans). The theoretical maximum dose of formaldehyde, assuming complete, instantaneous conversion after an iv dose of 2100 mg fosphenytoin (said to be maximum human iv dose), and based on a 1:1 molar ratio, would be 155.3 mg (5.17 mmol) or 3.1 mg/kg (50 kg BW). The theoretical maximal rate of exposure to formaldehyde was calculated as 0.22 mg/kg/min, based on a fosphenytoin infusion rate of 150 mg/min. (The proposed maximum dose and rate are now 30 mg/kg and 225 mg/min, respectively.)

The pharmacokinetics of formaldehyde and its major metabolite formate were modeled using data from a published report (McMartin et al., Biochem Pharmacol 28:645-649, 1979) in which formaldehyde (30 mg/kg) was administered iv to monkeys. Using this model, peak formaldehyde and formate concentrations resulting from first order input of 3 mg/kg formaldehyde, with a formation half-life of 8 min, were simulated (**Figures IV. 3** and **IV.4**). Peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 min. Maximal formate levels were predicted to be 0.08 mmol/L, which is below the baseline levels measured in 2 monkeys in the same published study (0.18 and 0.27 mmol/L). These are worst case simulations analogous to a bolus dose of 2100 mg of fosphenytoin. Background levels of formate in humans have been reported in the literature to be 3 to 19 mg/L (0.07 to 0.4 mM). Elevations in formate levels were expected to be transient, since an elimination t1/2 of about 11 min was predicted. Metabolic acidosis and other characteristics of methanol poisoning reported in 2 monkeys following administration of a high dose of methanol (3 g/kg) were associated with plasma formate levels of 6.4 and 10.5 mmol/L (McMartin et al., above). Plasma formate levels measured in 4 healthy volunteers following administration of 1200 mg of fosphenytoin by iv infusion over 30 min were not significantly different from those observed in a placebo group (N=5) or from baseline levels, which averaged about 25 mg/L. It is thought that endogenous production of formaldehyde during normal metabolism in humans amounts to about 36 g/day in a 50 kg person; thus, the estimated maximal amount of formaldehyde added as a result of fosphenytoin administration (3.1 mg/kg) represents about 0.5% of the daily body burden due to metabolism.

Since the theoretical maximum dose of formaldehyde represents only a fraction of the total body burden from normal metabolism, and since the PK simulations indicated that formaldehyde concentrations would exceed background levels for a relatively short time, the sponsor considers the potential risks associated with formaldehyde exposure as a result of fosphenytoin administration to be negligible.

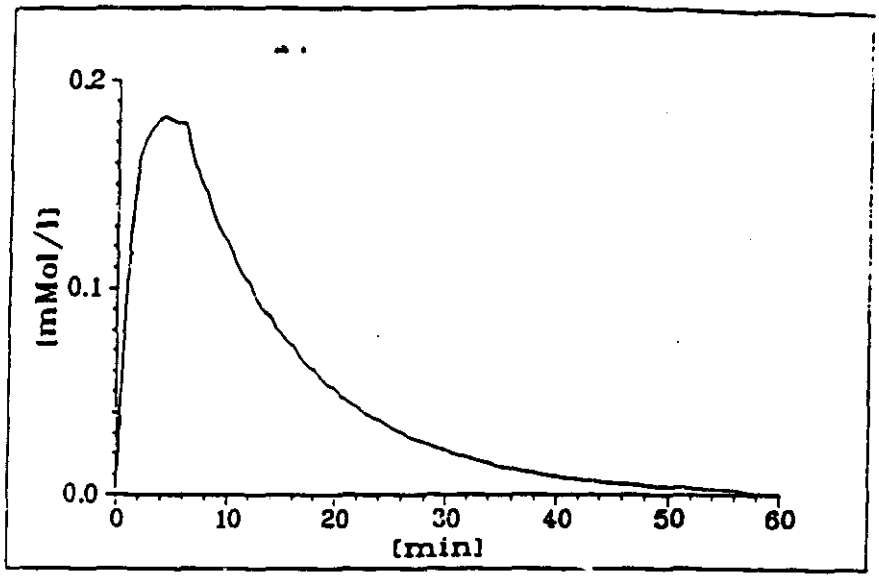


Figure IV.3 Simulated blood formaldehyde concentrations following a 3-mg/kg (0.1 mM/kg) dose of formaldehyde generated by a first order process (formation half-life = 8 minutes). This simulation would be analogous to a bolus intravenous dose of 2100 mg fosphenytoin in a 50-kg human.

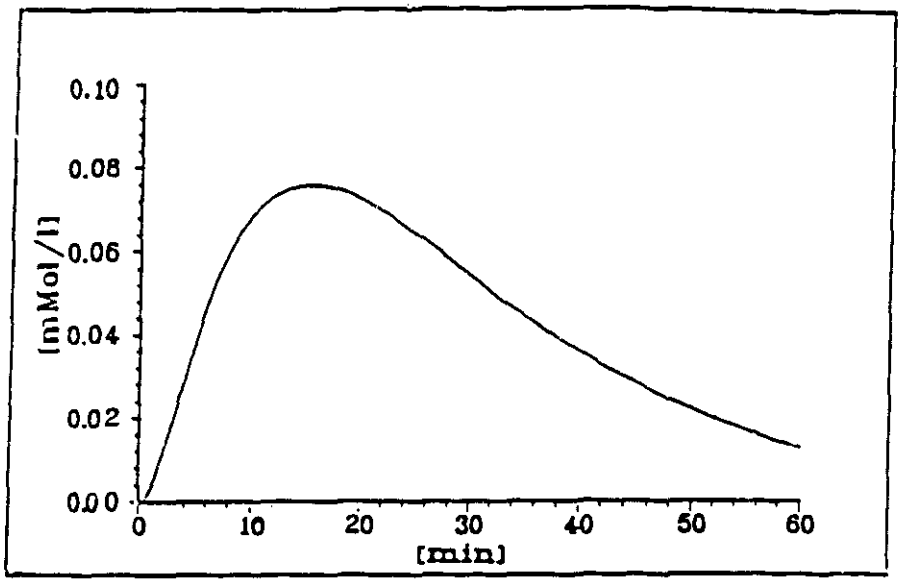


Figure IV.4 Simulated blood formate concentrations following a 3-mg/kg (0.1 mM/kg) dose of formaldehyde generated by a first order process (formation half-life = 8 minutes). This simulation would be analogous to a bolus intravenous dose of 2100 mg fosphenytoin in a 50-kg human.

V. GENETIC TOXICOLOGY (Vol. 1.31)

A) AMES TEST (RR 745-01958)

Fosphenytoin was tested with Salmonella strains TA-98, TA-100, TA-1535, TA-1537, and TA-1538, both with and without metabolic activation. In initial rangefinding tests, no toxicity to the background lawn occurred, by either plate incorporation or preincubation methods, over concentrations ranging from 0.5 to 5000 ug/plate. No increase in revertants occurred for any strain in these tests. Confirmatory tests were performed by the plate incorporation method in triplicate with concentrations ranging from 312.5 to 5000 ug/plate. The positive controls produced appropriate increases in revertant frequency with each strain, and all background frequencies were within historical ranges. No toxicity to the background lawns occurred. Statistically significant trends were seen in TA-100, with and without activation, and with TA-98 without activation; however, the increases were relatively small and not considered biologically significant. The sponsor pointed out that greater (statistically significant) increases in revertant frequency were seen with placebo (Tris buffer vehicle) in both of these strains. The maximum response with TA-100 was 1.4-fold the background level at 5000 ug/plate without activation, while the maximum increase with TA-98 was 1.7X the background at 625 and 1250 ug/plate without activation.

Drug lot: CM 344120

B) MUTATION ASSAY IN V79 CHINESE HAMSTER LUNG CELLS (RR 745-01935)

V79 Chinese hamster lung cell cultures were exposed to fosphenytoin for 3 hr in the presence and absence of S9. The concentrations ranged from 100 to 4000 ug/ml in both studies. In dose range-finding for cytotoxicity, the high concentration produced no effect on cell survival in the absence of S9, but in the presence of S9 there was a 89% reduction in cell survival at 4000 ug/ml.

In the 2 nonactivated mutation (HGPRT locus) assay trials, the presence of fosphenytoin did not produce an increase in mutant frequency. The positive control (ethyl methanesulfonate) produced appropriate increases in both trials (>4X background), but the magnitude of the response differed markedly between trials (68.2 and 836.4 mutants/10^6). All background frequencies were within the acceptable range (0-15 mutants/10^6).

In both activation trials, the positive control (benzo(a)pyrene) produced appropriate increases in mutant frequency, and background frequencies were within the acceptable range. Cell viability was reduced by about 40-50% (relative to vehicle controls) at the maximum fosphenytoin concentration in both trials. In trial 1, there was a significant quadratic trend due to an increase in mutation frequency at two intermediate drug concentrations (23 and 24 mutants/10^6 at 1000 and 2000 ug/ml, respectively, versus 11 mutants/10^6 in vehicle controls). Although not significant by linear dose trend analysis, the effect met other criteria for a positive assay, ie, mutant frequency at least 2X vehicle control at two or more contiguous drug concentrations and exceeding 20 mutants per 10^6 viable cells with at least one concentration. In trial 2, however, no effect on mutation frequency was seen in fosphenytoin exposed cultures.

Drug lot: CM 344120

C) CHROMOSOME ABERRATION IN V79 CHINESE HAMSTER LUNG CELLS (RR 745-02101)

Fosphenytoin, at concentrations up to 4000 ug/ml (high concentration arbitrarily chosen in the absence of cytotoxicity or insolubility), was tested for its ability to induce structural chromosome aberrations (SCA) in cultured V79 Chinese hamster lung cells.

In assays performed without S9 activation, with fosphenytoin concentrations from 500 to 4000 ug/ml, there was a statistically significant increase in the percentage of cells with aberrations at the 12 hr harvest time after exposure to 4000 ug/ml (8.5% vs 2.5% in vehicle control; 14 and 15% after 1 and 1.25 ug/ml mitomycin C). Because this finding did not satisfy the pre-established criteria of statistically significant increases at 2 consecutive concentrations, with at least one response exceeding the historical control range (0-5% with S9, 0-6.3% without S9), it was not considered to be biologically significant.

Fosphenytoin was tested in the presence of S9 in 3 separate trials. In the first trial, the positive control (cyclophosphamide) did not significantly increase SCA at either concentration, so the trial was considered invalid (data not submitted). In the second trial (**Table V.1**), with concentrations ranging from 1000-4000 ug/ml, the percentage of cells with aberrations and the mean number of aberrations per cell were both significantly increased at all concentrations and at both harvest times (18 & 24 hr). In many cases, these values were higher than those in the positive control groups, which were also significantly increased. In a third trial (**Table V.2**), with lower concentrations of fosphenytoin (125-2000 ug/ml), no significant increase in chromosomal aberrations was observed at any dose or harvest time. However, the positive control significantly increased SCA only at the highest concentration and only at 1 of the 2 harvest times (18 hr) in this trial (met sponsors minimum criteria for valid assay).

The sponsor postulated that the clastogenic effect was due to the generation of formaldehyde in vitro. Phenytoin was reportedly not clastogenic in previous studies with CHO cells (literature references), while formaldehyde has been reported to induce chromosomal aberrations in vitro in CHO cells at concentrations as low as 5 ug/ml (literature reference). However, attempts to measure formaldehyde in cultures in the present study were unsuccessful. Addition of formaldehyde dehydrogenase to the S9 would have been an alternate approach. The degradation product diphenylhydantoic acid, which was said to be present at 1.5 to 2% of total drug in these studies (prior to metabolic activation), was considered unlikely to be involved, but this possibility was not investigated.

Drug lot: CM 344120

D) MOUSE MICRONUCLEUS (RR 745-01898)

Micronucleus formation in bone marrow polychromatic erythrocytes (PCEs) was determined in groups of male and female mice (5/sex/group/time) after administration of single iv doses of fosphenytoin (50, 100, or 200 mg/kg) The doses were chosen on the basis of a previous acute iv infusion study showing 50 mg/kg to be a no-effect dose and 234 mg/kg to be the combined sex LD50. In the present study, clinical signs were seen at the MD and HD, but no deaths occurred. Significant decreases in PCE/total erythrocyte ratios were seen in HD groups, indicating bone marrow toxicity. Small, but statistically significant (by trend but not pair-wise analysis) increases in micronucleated PCEs (MNPCEs) were observed at 24 and 48 hr sacrifice times in HD animals when sexes were combined. The elevation in MNPCE frequency was less than twice the placebo control rate and was within the historical control range. No significant differences were detected in the analysis of individual sex MNPCE data. The positive control (cyclophosphamide) produced a significant increase (about 12X) in mean MNPCE values at 12 hr compared to vehicle (saline) and placebo (Tris buffer) controls.

Table V.1 Summary of CI-982 In Vitro Chromosome Aberrations With Metabolic Activation (-S9+, Trial 2)

Fixation Time	Conc'n (ug/mL)	Total Gaps	Chromatid Breaks	Chromatid Exchanges	Chromosome Breaks	Chromosome Exchanges	Total Abs (-G)	Abs/ Cell (-G)	% Cells w/Abs (-G)
18-HOUR									
VEHICLE	0	0	1	2	3	0	6	0.0300	3.00
EMEM	0	3	2	0	3	0	5	0.0250	2.00
CI-982	1000	16	13	2	13	1	29	0.1450	12.50
	2000	19	11	2	5	0	18	0.0900	8.00
	3000	32	15	5	20	0	40	0.2000	16.50
	3500	35	15	5	17	1	38	0.1900	15.50
	4000	27	9	6	11	0	26	0.1300	11.00
CP	4	13	7	2	22	0	31	0.1550	12.50
	8	29	19	1	27	0	47	0.2350	18.00
24-HOUR									
VEHICLE	0	4	4	0	0	0	4	0.0200	2.00
EMEM	0	2	1	0	2	0	3	0.0150	1.50
CI-982	1000	9	8	1	2	1	12	0.0600	6.00
	2000	14	6	1	11	0	18	0.0900	7.00
	3000	13	12	9	6	2	31	0.1550	13.50
	3500	22	13	10	6	3	32	0.1600	12.50
	4000	29	19	6	20	2	47	0.2350	18.00
CP	4	13	2	1	11	0	14	0.0700	6.50
	8	9	3	2	17	0	22	0.1100	9.50

CP = Cyclophosphamide
-G = Without Gaps
Abs = Aberrations
N = 200 cells
EMEM = Eagle's minimum essential medium (untreated control)

Table V.2 Summary of CI-982 In Vitro Chromosome Aberrations With Metabolic Activation (S9+, Trial 3)

Fixation Time	Conc'n (ug/mL)	Total Gaps	Chromatid Breaks	Chromatid Exchanges	Chromosome Breaks	Chromosome Exchanges	Total Abs (-G)	Abs/ Cell (-G)	% Cells w/Abs (-G)
18-HOUR									
VEHICLE	0	4	2	1	0	0	3	0.0150	1.50
EMEM	0	3	4	1	4	0	9	0.0450	3.50
CI-982	125	4	2	0	0	0	2	0.0100	0.50
	250	3	4	0	0	0	4	0.0200	2.00
	500	7	8	0	3	0	11	0.0550	3.00
	750	7	3	0	2	0	5	0.0250	2.00
	1000	22	1	0	2	0	3	0.0150	1.50
	1500	6	3	0	6	0	9	0.0450	4.00
	2000	11	6	0	0	0	6	0.0300	3.00
CP	4	11	8	0	1	0	9	0.0450	4.50
	8	30	18	4	7	0	29	0.1450	11.00
24-HOUR									
VEHICLE	0	8	6	0	0	1	7	0.0350	3.50
EMEM	0	7	1	0	1	0	2	0.0100	1.00
CI-982	125	4	0	0	0	0	0	0.0000	0.00
	250	4	4	0	2	0	6	0.0300	2.50
	500	3	3	0	0	0	3	0.0150	1.50
	750	4	0	0	0	0	0	0.0000	0.00
	1000	1	1	0	1	1	3	0.0150	1.50
	1500	4	2	0	0	0	2	0.0100	1.00
	2000	5	5	0	2	0	7	0.0350	3.50
CP	4	2	5	0	0	0	5	0.0250	2.50
	8	5	6	0	5	0	11	0.0550	5.00

CP = Cyclophosphamide
-G = Without Gaps
Abs = Aberrations
N = 200 cells
EMEM = Eagle's minimum essential medium (untreated control)

VI) REPRODUCTIVE TOXICITY

A) SEGMENT I STUDY IN MALE RATS (RR 745-02042, Vol. 1.21)

1. Treatment

Male rats (40/grp) were dosed with 0, 25, 75, or 150 mg/kg, im, for 75 days prior to mating and throughout mating with untreated females (1:1 cohabitation, 10 day maximum), then sacrificed. An additional group remained untreated. Females were either sacrificed on Day 21 of gestation (½) or allowed to deliver and wean their offspring.

Strain: Sprague Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 344120

2. Fo Data

a) Treatment-related clinical signs included injection site skin lesions and salivation in MD and HD males, and chromodacryorrhea, corneal opacity, ataxia, hypoactivity, and prostration in HD males. Convulsions were seen in 1 HD animal on the first day of treatment. Mechanical injuries, ie, damaged incisors, damage or swollen nose, palatine lesion, occurred only in HD rats, and were thus considered indirectly T-R.

b) Two HD animals died during treatment, on Days 11 and 12. In addition, 2 HD males were sacrificed after sustaining mechanical injuries.

c) T-R decreases in BW (10 and 30% in MD and HD, respectively), BW gain (26 and 92% in MD and HD, respectively), and food consumption were observed in MD and HD groups during the premating period.

d) Mean plasma phenytoin concentrations on Day 0 were 4.7, 18.5, and 37.3 ug/ml in LD, MD, and HD males, respectively. On Day 73, levels were 6.6, 20.9, and 44.9 ug/ml in the same respective groups.

f) All groups had lower than expected fertility indices, but there were no apparent relationship to treatment.

g) Histopathologic evaluation of the right testis on Day 91 revealed no drug-induced testicular changes. There were no significant group differences in testicular or accessory organ weights, epididymal sperm count or spermatid head count, percent motile sperm, or percent normal sperm morphology. Hemorrhage at the injection site was increased in all treatment groups relative to controls.

3. Term Sacrifice Parameters

a) A small increase in preimplantation loss was seen in HD group litters. The mean value (12.5%) was within the historical control range, however.

b) The incidence of stunted fetuses was increased in HD group litters. There were 7 fetuses (6 male) weighing <4 g in 4 HD litters vs 1 stunted fetus in both controls. The HD incidence of stunted fetuses was said to be within the historical control range, and group mean BWs were not different. In addition, 4 of the HD stunted fetuses were in 1 litter with 8 resorptions.

c) A statistically significant difference in fetal sex ratio occurred at the MD and HD compared to VC, and was outside the historical control range. However, the VC ratio was outside the range in the other direction. The ratio of males to females was 47:53, 56:44, 53:48, 43:57, and 44:56 for UC, VC, LD, MD, and HD groups, respectively. There were no other group differences in fetal developmental parameters.

4. Delivery and Offspring Developmental Parameters

a) There were no treatment-related effects on reproductive parameters in dams allowed to deliver (gestation length, uterine implants on Day 21 of lactation, viable pups). There were no group differences in offspring sex ratios at birth.

b) Offspring BWs during the lactation period were comparable among groups. Maturation (PN Weeks 3-13) BW was slightly decreased in HD group male offspring.

c) There were no other group differences in various measures of offspring development, including acquisition of developmental landmarks, rotorod performance, locomotor activity, emotionality, acoustic startle response, and shuttle box avoidance behavior.

B) SEGMENT I STUDY IN FEMALE RATS (RR 745-02092, Vol. 1.23)

1. Treatment

Female rats (40/grp) were dosed with 0 (vehicle), 25, 75, or 150 mg/kg, im, for 15 days prior to mating with untreated males, and throughout mating, gestation and lactation. Half of females underwent C-section on Day 21 of gestation, while the remainder were allowed to deliver and wean their offspring.

Strain: Sprague-Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 344120

2. F_0 Data

a) T-R clinical signs included hypoactivity, ataxia, prostration, salivation, chewing, alopecia, swelling of paw or nose, chromodacryorrhea, hypothermia, dyspnea, and eye changes, seen primarily in MD and HD animals. All HD animals exhibited signs of neurotoxicity.

b) Two HD females died and 3 were sacrificed moribund during the premating treatment period. One MD female was sacrificed moribund on Day 23 of gestation with treatment related dystocia.

c) BW and BW gain during the premating period were decreased in MD and HD females. Statistically significant weight loss of 15.5 g occurred in the HD rats compared to a mean gain of 12.6 g in VC. Most of the weight loss in both MD and HD animals occurred during the first 6 days of treatment. During the gestation period, BW gain was significantly decreased by 7 and 45% in the MD and HD groups, respectively. During lactation, weight gain in the HD females was 48% greater than in VC animals (NS).

d) Plasma phenytoin concentrations on Day 7 of gestation are shown in **Table VI.1**.

e) There was a D-R increase in the number of females with prolonged diestrus in the MD and HD groups, and an increase in the number of females with prolonged estrus (>2 consecutive days) at the HD. Five HD females were in constant diestrus during the treatment period and 13 were in diestrus on 15 of 16 days of treatment. All HD females had abnormal estrous cycles consisting of prolonged estrus, prolonged diestrus, or an estrous cycle length of 7 days. There was also a D-R decrease in the number of estrous cycles completed in MD and HD groups.

f) There were no effects of treatment on mating or fertility indices, but number of days to mating was increased (statistically significant) in the HD group (**Table VI.2**).

g) There was an increase in gross pathology findings of small thymus, injection site lesions, alopecia, and ocular abnormalities (chromodacryorrhea, enlargement, opacity, and/or lens prolapse) in F0 females at necropsy.

Table VI.1. Plasma Phenytoin Concentrations

Fosphenytoin Dose (mg/kg)	Cmax (ug/ml)	tmax (hr)	AUC (0-6) (ug*hr/ml)
25	5.80	1.0	17.8
75	18.7	1.0	84.5
150	38.0	1.0	189

Table VI.2. Fertility Data

	Female Fosphenytoin Dose (mg/kg)				
	0 (untreated)	0 (vehicle)	25	75	150
Mating Index (%)[1]	95.0	90.0	95.0	92.5	94.3
Fertility Index (%)[2]	94.7	88.9	92.1	91.9	90.9
No. days to mating	2.2 ± 0.18	2.4 ± 0.23	2.3 ± 0.22	2.6 ± 0.23	3.5 ± 0.37

[1] Mating Index = $\frac{\text{Number Copulated}}{\text{Total Cohabited}} \times 100$

[2] Fertility Index = $\frac{\text{Number Pregnant}}{\text{Number Copulated}} \times 100$

3. C-Section Data

a) Corpora lutea, implants, litter size, and live fetuses were decreased and % pre- and postimplantation loss were increased in the HD group (all but corpora lutea and preimplantation loss statistically significant compared to VC; **Table VI.3**). Fetal BWs were significantly decreased in MD (7% below VC) and HD (50% below VC) litters.

b) The overall malformation incidence and incidences of external/visceral malformations, external/visceral variations, and skeletal variations were increased in HD fetuses (**Tables VI.4a and VI.4b**). The percent of fetuses per litter and percent of litters with external/visceral malformations was 5-10 times those of concurrent and historical controls. These malformations included brain (missing occipital lobe and missing portion of temporal lobe, histologically decreased cerebral cortex size), cardiovascular, limb (ectrodactyly), and reproductive tract (hermaphrodite) defects. One LD fetus also had a brain malformation (microcephaly with dilated fourth ventricle and missing telencephalon). The effect on external/visceral variations was due to an increase in stunted fetuses; 100% of HD fetuses were stunted (BW <4.0 g). The number of stunted fetuses was also increased at the MD. Increased incidences rudimentary ribs and of hypoplastic and unossified bones in the skull, pelvis, and vertebral column were seen in HD

litters. In addition, misshapen, bifid, and dumbbell-shaped centra occurred more frequently in the MD and HD groups. Significantly decreased ossification was seen in MD and HD fetuses.

4. Delivery Data

a) Parturition was significantly delayed in the HD group. Five HD females delivered live litters on Day 24 of gestation and a sixth delivered 1 cannibalized pup on Day 24. Three HD and 1 VC females were sacrificed after failing to deliver by Day 24, and live pups were found in utero. One additional HD dam sacrificed on Day 24 had total litter resorption. One MD dam was sacrificed moribund during parturition, and 1 LD dam had retained placenta and fetuses at necropsy on Day 4 of lactation.

b) Implants, litter size, and number of live pups were significantly decreased and postimplantation loss significantly increased at the HD (**Table VI.5**).

c) Pup birth weights were decreased in HD litters. Postnatal BW gain through week 4 was decreased in MD and HD offspring.

d) Postnatal survival was decreased in HD offspring, especially in the neonatal period (survival 63% vs 96% in controls).

e) Clinical observations of chromodacryorrhea (9 pups in 5 litters) and circling (1 pup) were made only in HD offspring. Eye opening was significantly delayed in HD offspring. There were no group differences in external or visceral malformations among F1 neonates.

Table VI.3. Caesarean Secti . Data (group mean ± SE)

	Fosphenytoin Dose (mg/kg)				
	0 (untreated)	0 (vehicle)	25	75	150
Number of Litters	17	16	17	17	16
Corpora Lutea (no.)	16.6 ± 0.47	15.8 ± 0.46	16.1 ± 0.44	16.8 ± 0.62	14.8 ± 0.73
Uterine Implants	14.8 ± 0.88	14.6 ± 0.83	15.6 ± 0.43	15.4 ± 0.60	12.8 ± 0.79
Live Fetuses	13.7 ± 0.91	13.6 ± 0.88	14.6 ± 0.48	14.0 ± 0.76	10.0 ± 1.12
Resorption	1.1 ± 0.21	0.9 ± 0.27	1.0 ± 0.23	1.4 ± 0.41	2.8 ± 0.71
Litter Size	13.7 ± 0.91	13.6 ± 0.88	14.6 ± 0.48	14.0 ± 0.76	10.0 ± 1.12
Preimplantation Loss (%)	5.6 ± 1.58	8.8 ± 4.02	3.2 ± 1.12	8.2 ± 2.63	13.7 ± 3.58
Postimplantation Loss	12.1 ± 5.34	6.8 ± 2.14	6.5 ± 1.49	9.5 ± 2.84	23.5 ± 6.05
Fetal Body Weight (g)					
Male	5.1 ± 0.06	5.1 ± 0.08	5.1 ± 0.09	4.8 ± 0.11	2.6 ± 0.21
Female	4.8 ± 0.06	4.9 ± 0.08	4.9 ± 0.07	4.5 ± 0.12	2.4 ± 0.22

Table VI.4a. External and Visceral Findings in F1 Fetuses

	Dose (mg/kg)				
	untreated	vehicle	25	75	150
No. of fetuses examined	247	218	248	243	155
No. of litters examined	17	16	17	17	16
Malformed fetuses (litters)	1 (1)	1 (1)	3 (3)	0 (0)	6 (5)
Malformations					
Anophthalmia	1 (1)	-	-	-	-
Brain - malformed	-	-	1 (1)	-	1 (1)
Aortic arch - stenosis	-	-	1 (1)	-	-
- interrupted	-	-	-	-	1 (1)
- retroesophageal	-	-	-	-	1 (1)
Interventricular septal defect	-	-	-	-	1 (1)
Ectrodactyly	-	-	-	-	2 (1)
Hermaphrodite	-	-	-	-	1 (1)
Situs inversus	-	1 (1)	-	-	-
Tail - thread-like	-	-	1 (1)	-	-
Variations					
Brain - dilated ventricles, slight	1 (1)	-	-	-	-
Hematoma - ventral aspect	1 (1)	-	-	-	-
Kidney - dilated pelvis	2 (2)	2 (2)	11 (5)	5 (3)	-
- reduced papilla & dilated pelvis	1 (1)	7 (3)	4 (2)	2 (1)	1 (1)
Liver - lobulated lobe	-	1 (1)	-	-	-
Stunted (<4.0 g)	7 (6)	2 (2)	5 (3)	25 (6)	155 (16)
Ureter - dilated	5 (5)	8 (4)	19 (7)	7 (3)	4 (3)

Table VI.4b. Skeletal Findings in F1 Fetuses

	Dose (mg/kg)				
	untreated	vehicle	25	75	150
No. of fetuses examined	171	149	173	152	105
No. of litters examined	17	16	17	16	15
Malformed fetuses (litters)	3 (2)	0 (0)	1 (1)	1 (1)	3 (2)
Malformations					
Digits					
- ectrodactyly	-	-	-	-	2 (1)
Ribs					
- malformed	-	-	-	1 (1)	-
- agenesis	-	-	-	-	1 (1)
Vertebral column					
- 1 less presacral vertebrae	3 (2)	-	1 (1)	-	2 (2)
- agenesis	-	-	1 (1)	-	-
- malformed	-	-	1 (1)	-	-
Variations					
Limbs					
- calcaneus ossified	7 (4)	2 (1)	6 (3)	-	-
Pelvic girdle					
- unossified	-	-	-	-	20 (7)
- hypoplastic	-	-	-	-	9 (4)
Ribs					
- wavy	-	1 (1)	-	-	-
- short last	3 (2)	4 (4)	5 (2)	8 (4)	5 (4)
- extra rudimentary	3 (1)	2 (1)	6 (3)	3 (3)	12 (5)
- extra cervical	2 (2)	3 (3)	5 (2)	1 (1)	1 (1)
Skull					
- hypoplastic	-	2 (1)	1 (1)	-	24 (7)
- unossified	2 (2)	-	-	-	10 (5)
Sternum					
- asymmetric	-	1 (1)	1 (1)	-	-
Vertebral column					
- extra presacral vertebrae	1 (1)	-	-	1 (1)	1 (1)
- misshapen centra	2 (2)	3 (2)	3 (3)	13 (9)	8 (4)
- bifid centra	2 (2)	2 (2)	2 (1)	8 (4)	12 (8)
- hypoplastic arches	-	-	-	-	20 (6)
- figure 8-shaped centra	-	2 (2)	1 (1)	4 (3)	4 (4)
- unossified ventral tubercle	29 (12)	22 (10)	16 (8)	25 (8)	63 (14)
- caudal/sacral vertebrae unossified	-	-	-	-	27 (7)

Table VI.5: F0 Dam Delivery[a]: Maternal and Litter Parameters[a]

Treatment	Untreated	Vehicle	Fosphenytoin (mg/kg)		
Dose	—	0	25	75	150
Gestation duration (days)	22.2 ± 0.10	22.1 ± 0.07	22.1 ± 0.06	22.3 ± 0.11	23.6 ± 0.22
No. females in subgroup	20	20	20	20	18
No. gravid	18	16	18	17	14
No. nongravid	2	4	2	3	4
No. w/ total resorption	0	0	0	0	1
No. sacrificed GD 24	0	1	0	0	3
No. sacrificed moribund	0	0	0	1	0
No. w/ viable litters	18	15	17[b]	16	10
Liveborn	14.4 ± 0.54	14.1 ± 0.67	14.0 ± 0.36	12.8 ± 0.92	8.9 ± 1.51
Stillborn/dead Day 0	0.4 ± 0.14	0.3 ± 0.15	0.2 ± 0.13	0.4 ± 0.18	0.5 ± 0.27
Litter size	14.8 ± 0.51	14.4 ± 0.67	14.2 ± 0.38	14.1 ± 0.97	9.4 ± 1.51
Implant sites	16.3 ± 0.57	15.0 ± 0.73	15.6 ± 0.29	15.0 ± 0.98	11.9 ± 1.35
Postimplantation loss (%)	11.3 ± 2.77	5.3 ± 1.82	9.5 ± 1.85	7.8 ± 1.65	28.6 ± 9.22

[a] Group mean ± SE, where applicable.
[b] Excludes 1 animal that delivered live pups and retained fetuses in utero.

C) INTRAVENOUS TERATOLOGY STUDY OF FOSPHENYTOIN IN RATS (RR 745-01973, Vols. 1.25-26).

1. Treatment

Pregnant rats (40/group) were treated with 0 (vehicle), 10, 50, or 100 mg/kg, iv, on gestation Days 7 through 17. An untreated control group (N=40) was evaluated concurrently. C-sections were performed on 25/group on Day 21; the remaining 15/group were allowed to deliver and rear offspring. At weaning, 1/sex//litter were retained for behavioral evaluation, and 1/sex/litter were retained for evaluation of reproductive performance.

Strain: Sprague Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 344120

2. F0 Effects:

a) T-R clinical signs, including salivation, chewing motions, hypoactivity, ataxia, and limb rigidity, were noted in HD dams. Salivation was also seen in MD dams.
b) Four HD dams died during treatment (2 dosing accidents, 2 possibly T-R) and another was euthanized due to broken limbs.
c) Gestational BW gain was decreased during (38%) and following (18%) treatment in the HD group.

3. Maternal plasma levels

Mean plasma phenytoin concentrations measured 1 hr postdose (ie, not peak) on gestation Day 17 increased approximately dose-proportionally (**Table VI.6**). One sample from a vehicle control had measurable phenytoin levels, for unknown reasons.

Table VI.6: Maternal Plasma Drug Levels

Treatment	Vehicle	Fosphenytoin		
Dose (mg/kg)	0	10	50	100
No. Dams	5	5	4	5
Phenytoin concentration (ug/ml)*	0.25 ± 0.55	4.10 ± 0.56	24.0 ± 1.62	43.3 ± 6.27

*Mean ± SE; samples taken about 1 hr postdose on gestation Day 17

4. C-Section Data

Term fetuses were examined for external and palatine abnormalities. All fetuses were then examined by fresh dissection for visceral abnormalities, and skeletal examinations were performed on 2/3 of the fetuses from each litter. The heads of the other 1/3 were fixed and examined for abnormalities.

a) Postimplantation loss was increased about 2-fold in HD dams compared to concurrent and historical controls.
b) Mean fetal BW was decreased (30% below VC) in the HD group.
c) Increased incidences of skeletal malformations (slight; primarily hemicentra), external/visceral variations, and skeletal variations were seen in HD litters (**Table VI.7**). The increase in variations was due to a marked increase in growth retarded fetuses in HD litters; 60% of HD fetuses were stunted (BW <4 g).

5. Delivery Data

a) The duration of gestation was significantly increased in the HD group.
b) Postimplantation loss was slightly increased at the MD and HD (**Table VI.8**).
c) Birth weights were significantly decreased (10%) in HD males and females. Weight gain was comparable among groups during lactation, but weight gain from week 3 through 13 and mean weights at week 13 were decreased in all treated male offspring (5, 6, and 15% less than VC, all statistically significant) and in HD female offspring (7%, NS).
d) Vaginal opening was delayed in MD and HD female pups.
e) Two littermates in the HD group exhibited abnormal circling behavior, and 27 pups from 8 HD litters and 1 MD pup had chromodacryorrhea. Both have previously been associated with prenatal phenytoin exposure. One of the HD circlers later died (P 23).
f) Locomotor activity was increased in HD males on P 42; however, this was due to the increased activity of a single HD pup. No group differences were found in acoustic startle parameters on P 43 or in shuttle avoidance parameters during week 9.
g) Reproductive parameters were comparable among F1 groups.

Table VI.7: Incidence of Fetal Malformations and Variations

Treatment	Untreated	Vehicle	Fosphenytoin		
Dose (mg/kg)	—	0	10	50	100
No. fetuses/litters examined	326/24	298/23	323/25	337/24	244/20
No. fetuses/litters with malformations	2/2	2/2	1/1	3/3	6/5
Percent fetuses per litter with:[a]					
Ext/visc malformations	0.6 ± 0.43	0.6 ± 0.40	0.3 ± 0.31	0.3 ± 0.30	0.7 ± 0.50
Skeletal malformations	0.9 ± 0.61	0.9 ± 0.60	0	0.8 ± 0.55	2.9 ± 1.39
Ext/visc variations	6.3 ± 1.85	10.7 ± 3.13	5.4 ± 1.74	3.7 ± 1.18	68.8 ± 7.79
Skeletal variations	29.0 ± 5.86	21.0 ± 4.02	24.5 ± 3.44	24.0 ± 4.28	54.2 ± 7.25
Percent litters with:[b]					
Ext/visc malformations	8.3	8.7	4.0	4.2	10.0
Skeletal malformations	8.3	8.7	0	8.3	20.0
Ext/visc variations	41.7	52.2	44.0	37.5	90.0
Skeletal variations	70.8	69.6	88.0	91.7	95.0

[a] Mean ± SE
[b] Group mean

Table VI.8: F0 Dam Delivery - Maternal and Litter Parameters[a]

Treatment	Untreated	Vehicle	Fosphenytoin		
Dose	---	0	10	50	100
No. delivered:					
Day 20	0	1	0	0	0
Day 21	2	0	2	0	0
Day 22	12	12	12	13	8
Day 23	0	0	0	1	6
Gestation duration	21.9 ± 0.10	21.8 ± 0.15	21.9 ± 0.10	22.1 ± 0.07	22.4±0.14
No. females in subgroup	15	15	15	15	15
No. gravid	14	15	15	14	15[b]
No. nongravid	1	0	0	1	0
No. w/ implants only	0	1	1	0	0
No. w/ viable litters	14	13[c]	14	14[d]	14[d]
Liveborn	13.8 ± 0.35	13.4 ± 0.21	13.9 ± 0.42	12.1 ± 0.94	12.4±0.68
Stillborn/dead Day 0	0.1 ± 0.07	0.2 ± 0.12	0.4 ± 0.14	0.6 ± 0.29	0.5±0.23
Litter size	13.9 ± 0.35	13.6 ± 0.27	14.3 ± 0.45	12.7 ± 0.93	12.9±0.70
Implant sites	15.1 ± 0.32	13.9 ± 0.97	14.2 ± 1.03	14.4 ± 0.98	14.1±0.69
Postimplantation loss (%)	8.4 ± 1.89	9.0 ± 1.51	8.3 ± 1.56	13.8 ± 4.50	13.0±2.50

[a] Mean ± SE, where applicable
[b] Includes 1 animal that died during treatment
[c] Excludes 1 dam unable to deliver, sacrificed on Day 24; 1 fetus in uterus
[d] Includes 1 dam with litter size <8; excluded from group mean calculations

D) INTRAVENOUS TERATOLOGY STUDY IN RABBITS (RR 745-01931, Vol. 1.27).

1. Treatment

Pregnant rabbits (20/group) were treated with 0 (vehicle), 10, 25, or 50 mg/kg, iv, on gestation Days 6 through 18. An untreated control group (N=20) was evaluated concurrently. C-sections were performed on Day 30 of gestation.

Strain: New Zealand White
Drug lot #: CM 345120

2. F0 Effects:

a) Chewing signs during or after dosing were observed in MD and HD animals. Additional signs that occurred daily during treatment in 1 or 2 HD does included ataxia, limb rigidity, and shallow rapid breathing.
b) None of the treated or control animals died during the study.
c) D-R suppression of food consumption and BW gain was evident during the treatment period in MD and HD does (statistically significant at HD). BW gain was significantly increased in HD does during the postdosing period.
d) Mean plasma phenytoin concentrations measured 1 hr postdose on gestation day 18 increased approximately dose-proportionally (**Table VI.9**). HD levels were 1.5-3.5 times the generally accepted range of therapeutic concentrations (10-20 ug/ml).

Table VI.9: Maternal Plasma Drug Levels

Treatment	Vehicle	Fosphenytoin		
Dose (mg/kg)	0	10	25	50
No. pregnant animals	5	5	4	4
Phenytoin concentration (ug/ml)*	0	7.1 ± 1.3	17.5 ± 1.3	35.0 ± 1.5
No. nonpregnant	0	0	1	1
Phenytoin concentration (ug/ml)	0	0	22.1	39.2

* Mean ± SE; samples taken about 1 hr postdose on gestation Day 18

3. Reproductive and Fetal Parameters

a) None of the animals aborted, delivered early, or had total resorption.
b) The numbers of corpora lutea, implantation sites, live, dead, and resorbed fetuses were comparable across groups. Pre- and postimplantation loss were not affected by treatment.
c) Fetal weights were slightly decreased at the HD.

4. Fetal Evaluation

There were no group differences for external, visceral, and skeletal malformations or variations.

E) PERINATAL-POSTNATAL STUDY IN RATS (RR 745-02071, Vol. 1.28).

1. Treatment

Female rats (25/group) were treated with 0 (vehicle), 25, 50, or 100 mg/kg, iv, from Day 15 of pregnancy through Day 20 postpartum. An untreated control group was also included. The dams were allowed to deliver and rear offspring. F1 offspring were evaluated for survival, clinical appearance, growth, behavior, and reproductive performance.

Strain: Sprague Dawley (Crl:CD BR VAF/Plus)
Drug lot #: CM 345120

2. F0 Effects:

a) Clinical signs observed with increased frequency in treated females (primarily at HD) included excessive chewing motion, salivation, hypoactivity, ataxia, and prostration
b) One MD and 9 HD dams died or were sacrificed moribund during dosing, all apparently as a result of treatment. One VC dam died of unknown causes.
c) Maternal BW gain during the gestational treatment period was significantly decreased (-19%) by the HD. Weight gain during the first 2 weeks of lactation was also suppressed at the HD (-20-30%), but overall lactational weight gain was comparable among groups. Food consumption was decreased during the entire treatment period in HD dams.
d) Mean plasma phenytoin concentration determined 1 hr after dosing on the last day of treatment (PND 20) were 6.67, 12.7, and 29.2 ug/ml in LD, MD, and HD groups, respectively.

3. Parturition (**Table VI.10**)

a) One MD and 5 HD dams died around the time of parturition (GD 22-23). All were found to have fetuses in utero, and all dead HD dams had resorptions.
b) A statistically significant increase in the duration of gestation was seen in the MD and HD groups compared to vehicle controls.
c) The number of stillborn pups or pups that died on postnatal Day 0 and the percent postimplantation loss were increased in all treatment groups relative to VC; the increase in stillbirth was statistically significant at the HD. At the LD, this finding was due to 1 litter with 17 dead pups.

Table VI.10: F0 Dam Delivery - Maternal and Litter Parameters[a]

Treatment	Untreated	Vehicle	Fosphenytoin		
Dose	—	0	10	50	100
No. delivered:					
Day 21	2	0	1	0	0
Day 22	15	21	15	12	3
Day 23	5	1	6	10	15
Day 24	0	0	0	0	1
Gestation duration[a]	22.1 ± 0.12	22.0 ± 0.05	22.2 ± 0.11	22.5 ± 0.11	22.9 ± 0.11
No. mated females	25	25	25	25	25
No. gravid	22	24	22	23	24
No. nongravid	3	1	3	2	1
No. dying/sacrificed prior to delivery	0	1	0	1	5
No. dying postpartum	0	0	0	0	4
No. of viable litters	22	22	22	22	19
No. with total dead litters	0	0	1	0	0
No. with total resorption	0	1	1	0	0
Liveborn[a]	14.2 ± 0.65	15.3 ± 0.41	13.6 ± 0.87	14.6 ± 0.62	13.8 ± 0.92
Stillborn/dead Day 0	0.2 ± 0.15	0.2 ± 0.08	1.0 ± 0.78	1.0 ± 0.48	1.4 ± 0.72
Litter size	14.5 ± 0.65	15.5 ± 0.41	14.5 ± 0.59	15.5 ± 0.43	15.2 ± 0.59
Implant sites	15.6 ± 0.70	16.7 ± 0.38	15.6 ± 0.56	17.2 ± 0.28	16.4 ± 0.62
Postimplantation loss (%)	8.6 ± 1.55	9.0 ± 1.62	12.6 ± 4.55	14.3 ± 3.38	15.8 ± 4.55

[a] Mean ± SE

4 F1 Neonatal and Weanling Parameters

a) Survival at birth was decreased in all treatment groups, and was statistically significant at the HD. Subsequent survival was not affected by treatment.

b) Offspring BW at birth and postnatal weight gain through weaning were decreased (10% compared to VC; statistically significant) in HD males and females. This effect on pup BW at the HD persisted into the maturation period (below).

c) Several developmental landmarks (pinnae detachment, lower incisor eruption, and testes descent) appeared significantly earlier in treatment groups than in controls. This can be attributed to their increased time of in utero development. There were no group differences for eye opening and vaginal opening. All pups responded positively to the visual placement test on PND 21.

d) In external and visceral examinations performed on stillborn, dead, and pups sacrificed at weaning, malformation were found in 1 untreated control pup (patent ductus arteriosus) and 2 HD pups (unilateral forepaw brachydactyly; microphthalmia, microstomia, short tail, and malformed nose).

e) Structural variations of the ureter and kidney were increased in MD and HD litters compared to C. At the MD, almost all observations came from 1 litter. In the HD group, findings were primarily from 2 litters. All kidney/ureter variations were observed in pups from dams that died during late gestation.

5. F1 Offspring Behavior

a) Rotorod performance was comparable among groups.

b) Treated male offspring were different (NS) from controls on several measures of activity on PND 42: total distance traveled during minute 2 was increased by 13% in LD and MD males and by 41% in HD males and was elevated by 21%, 27%, and 32% during minute 3 in the LD, MD, and HD groups, respectively; average speed was elevated 14-20% at the HD for minutes 2-4, relative to VC; vertical movements during minute 3 were increased 29, 19, and 40% in LD, MD, and HD males, respectively; vertical time was increased 33 and 70% during minute 2 in MD and HD males, respectively, and during minute 3 was elevated 41, 39, and 52% in LD, MD, and HD males, respectively; and the amount of time spent in the center of the open field was 38% less in HD males. Increased activity has been reported previously in rats prenatally exposed to phenytoin.

c) Results of acoustic startle testing on PND 43 indicated no T-R differences in startle response.

d) Increases (NS) in shuttle box avoidance responding, recall testing, and number of crossing were observed in MD and HD males relative to VC during postnatal Week 9, presumably secondary to hyperactivity.

6. F1 Offspring Maturation Parameters

a) Weight gain over PN weeks 3-13 and BW at 13 weeks were decreased (5-10%) in HD males (significant) and females (NS).

b) Reproductive performance of F1 animals was comparable among groups. Although corpora lutea were slightly decreased in HD females at term, the value was within the historical control range. An increased incidence of stunted fetuses was found in litters born to HD group F1 females at term sacrifice, but the number of affected litters was the same as in the control group.

VII. SUMMARY

PHARMACODYNAMICS

In the initial pharmacological evaluation by NINDS, fosphenytoin showed good anticonvulsant activity in the MES test but, as expected, was not active in the scMET test. Activity against MES-induced seizures was equivalent to that of phenytoin after ip and oral administration (**Table I.1**). Fosphenytoin displayed slightly greater toxicity (Rotorod TD50) after ip administration, possibly due to more rapid absorption. The anticonvulsant potency of fosphenytoin against MES-induced seizures in mice was not significantly different than that of phenytoin either 10 or 30 minutes after iv dosing, and the time courses of anticonvulsant action were comparable for the two drugs (**Tables I.1 and I.2**).

The ability of fosphenytoin to reverse cardiac glycoside-induced arrhythmias in intact dogs was similar to that of phenytoin when the two drugs were administered intravenously, although phenytoin restored normal rhythm marginally faster. In an *in vitro* preparation, it was determined that the prodrug had no inherent antiarrhythmic effect.

In a study comparing the hemodynamic effects of iv infusion of equimolar amounts of fosphenytoin or phenytoin to anesthetized dogs, both drugs produced marked reductions in blood pressure, heart rate, and left ventricular contractility. When equimolar doses of the two drugs were rapidly infused (40 mg/kg PE over 2 min), changes in CV parameters were similar but somewhat more pronounced after fosphenytoin than after phenytoin. The onset of action was slightly delayed by fosphenytoin administration, and CV effects appeared to correlate with plasma phenytoin levels (**Figures I.1-3**). When lower equimolar doses (21 mg/kg PE) of fosphenytoin or phenytoin were infused over 15-30 min, the maximum effects (reductions in diastolic BP and contractility) were comparable and were observed at similar plasma levels of phenytoin (**Figures I.4-6**). The maximum effects of fosphenytoin appeared to be primarily determined by the total dose rather than the rate of administration. At times when plasma levels of both fosphenytoin and phenytoin (formed from fosphenytoin) were high, effects were not greater than those seen at comparable levels of phenytoin alone; therefore, it did not appear that fosphenytoin had any significant hemodynamic effects of its own *in vivo* under the conditions of this study. However, under *in vitro* conditions in which less than 1% of phenytoin was present, fosphenytoin (EC50=43 ug/ml) had a cardiac depressant effect similar to that of phenytoin (EC50=27 ug/ml) in guinea pig left atrial preparations (**Figure I.7**). No such intrinsic activity of fosphenytoin was seen in guinea pig right atria.

Fosphenytoin was shown to reduce brain damage in several models of ischemic stroke, but did not protect against NMDA-induced brain damage.

ADME

Absorption and Pharmacokinetics

Single-dose studies were performed in rats and dogs to compare fosphenytoin and phenytoin pharmacokinetics following im and iv administration. Peak blood levels of phenytoin were greater (5-fold) following im administration of fosphenytoin (115-500 mg/kg) to rats than after im administration of phenytoin (equimolar), indicating that prodrug administration significantly enhanced phenytoin bioavailability.

After an iv dose of 14.8 mg/kg of fosphenytoin (equivalent to 10 mg/kg of phenytoin) to dogs, fosphenytoin t1/2, Vd, and AUC values averaged 2.6 min, 150 ml/kg, and 255 ug·min/ml, respectively. The Cl of 40.2 ml/min/kg approximated hepatic blood flow, which would be consistent with metabolism to phenytoin by phosphatases in kidney and liver. Fosphenytoin was not detected in blood at 30 min postdose. Peak phenytoin levels (mean 6.98 ug/ml) were reached at 3.3 min, with the formation t1/2 averaging 0.42 min. During the first 30 min after administration of phenytoin, phenytoin levels were higher than after administration of fosphenytoin, but thereafter, levels were similar. The elimination t1/2, Cl, Vd, and AUC of phenytoin were not significantly different after iv administration of fosphenytoin or phenytoin sodium (**Table II.1**). The bioavailability of phenytoin after iv fosphenytoin administration averaged 97%. The metabolic elimination pattern was not

different after iv prodrug, with the m-HPPH glucuronide constituting the major urinary metabolite and accounting for approximately the same % of the dose (55%) after administration of either drug.

After im administration of fosphenytoin (14.8 mg/kg), fosphenytoin levels reached a mean peak of 20.4 ug/ml at 10 min (**Table II.3**), then rapidly decreased such that fosphenytoin was not detectable in plasma after 120 min. The absorption and elimination t1/2 values averaged 3.2 and 17.4 min, respectively. The appearance of phenytoin in the plasma was fairly rapid after im administration of fosphenytoin. The formation t1/2, Cmax, and tmax for were 24.7 min, 6.8 ug/ml, and 76.9 min, respectively (**Table II.2**). The corresponding values after im administration of an equimolar dose of phenytoin were 17.4 min, 2.16 ug/ml, and 68.1 min for the absorption t1/2, Cmax, and tmax, respectively. The elimination t1/2 and apparent volume of distribution of phenytoin after fosphenytoin administration averaged 164 min and 1058 ml/kg, respectively, which were significantly different than corresponding values of 369 min and 4086 ml/kg, respectively, obtained after im phenytoin. These results are consistent with precipitation of phenytoin at the injection site, with slow release into the circulation. The AUC values obtained after administration of phenytoin were substantially lower than phenytoin AUCs after fosphenytoin, indicating that the bioavailability of phenytoin administered as fosphenytoin was increased compared to phenytoin sodium after im administration. Fosphenytoin was completely absorbed after im administration of a dose of 14.8 mg/kg (10 mg/kg PE) to dogs (**Table II.3**).

The exposure to phenytoin following im administration of fosphenytoin (14.8 mg/kg) to dogs was essentially the same as that after iv administration of the prodrug (**Table II.4**). Although the rate of conversion to phenytoin was slower after im than iv fosphenytoin, and time to peak plasma phenytoin level was longer, other phenytoin parameters (Cmax, elimination t1/2, Vd, Cl, and AUC) were equivalent.

Protein Binding

In vitro binding of [14C]-fosphenytoin to dog and human plasma proteins was assessed by ultrafiltration. Binding of 20 ug/ml to dog and human plasma proteins averaged 91.3% and 95.7%, respectively. Albumin accounted for 88% of the fosphenytoin binding to human plasma proteins. Phenytoin binding decreased with increasing fosphenytoin concentrations. At a DPH concentration of 5 ug/ml, the free fraction of phenytoin increased from 4 to 18% when the fosphenytoin concentrations increased from 7.5 to 500 ug/ml. These results indicate that at high concentrations, fosphenytoin may enhance the pharmacological or toxicological effects of phenytoin by displacing DPH from its binding sites.

Drugs highly bound to albumin, such as phenylbutazone, sulfisoxazole, or warfarin, can displace fosphenytoin from binding sites on albumin. When toxic concentrations of AEDs such as PHB, DPH, or VPA were added to plasma, the drugs significantly increased (5-20%) the free fraction of fosphenytoin. Diazepam, phenytoin, and carbamazepine at a concentration of <10 ug/ml did not change the free fraction of fosphenytoin. Since fosphenytoin has little intrinsic pharmacological effect, the changes in free fraction should have no clinical significance. Addition of fosphenytoin at equimolar concentrations to carbamazepine, phenobarbital, or VPA resulted in small but significant displacement of these drugs from its plasma binding sites. The degree of displacement of diazepam or carbamazepine was not enhanced by increasing the concentration of fosphenytoin 30-80-fold. The slight increase in free fraction of these drugs caused by fosphenytoin is unlikely to have clinical significance.

In Vitro Hydrolysis

The *in vitro* hydrolysis of fosphenytoin to phenytoin was examined in tissues and whole blood from rats and dogs and in human whole blood. Rat whole blood and tissue hydrolyzed fosphenytoin rapidly, with kidneys, small intestine, and liver exhibiting the highest phosphatase activity. Dog and human whole blood hydrolyzed the drug much more slowly. Mean *in vitro* half-lives of fosphenytoin in rat, dog, and human whole blood were 5.89, 321, and 189 minutes, respectively. Faster prodrug conversion was observed in dog tissue homogenates, with the small intestine, kidney, and liver again the most active in mediating hydrolysis of the prodrug. Studies with partially purified enzymes revealed that fosphenytoin was a better substrate for alkaline phosphatase than for acid phosphatase. Despite the presence of alkaline phosphatase activity in plasma, in

vitro hydrolysis of fosphenytoin was slow in dog and human blood compared to in vivo conversion. There was no explanation for the discrepancy between *in vitro* and *in vivo* fosphenytoin conversion times.

IM Injection Site Accumulation

Potential accumulation of phenytoin in dog hindlimb muscles was assessed following single- and multiple-dose (BID) im administration of 14C-fosphenytoin (10 mg/kg) and 3H-phenytoin (10 mg/kg). At 8 hr following simultaneous single-dose administration, phenytoin concentrations at the injection site were 150-fold greater in the hindlimb injected with phenytoin compared to the limb injected with fosphenytoin. The difference increased to 2500-fold following repeated administration, indicating increased accumulation of precipitated phenytoin at the injection site. Although im phenytoin consistently resulted in edematous swelling at the injection site, im fosphenytoin did not precipitate or cause tissue damage following single or multiple-dose administration.

Distribution, Metabolism, and Elimination

Following iv bolus administration of 14C-fosphenytoin (10 mg/kg; label on hydantoin ring), both tissue distribution and elimination were rapid. Highest levels of radioactivity in blood, heart, kidneys, liver, lung, and spleen were measured within 5 min postdose. Highest brain levels (0.2% of dose) occurred at 10-60 min. Three radioactive peaks were identified as p-HPPH glucuronide, p-HPPH, and phenytoin. Elimination t1/2's for phenytoin ranged from 50-90 min in blood and various tissues. At 48 hr postdose, >98% of the administered radioactivity was eliminated, demonstrating that fosphenytoin and/or its metabolites were not retained.

After administration of 14C-fosphenytoin to rats, recovery of radioactivity from urine and feces over 72 hr averaged 52 and 48%, respectively. Mean cumulative urinary and fecal recovery was 99%. p-HPPH glucuronide accounted for >40% of dose recovered from urine and feces over the 0- to 24-hr collection interval.

Urine and feces (rat only) were collected for metabolite profiling following administration of 14C-fosphenytoin to rats and unlabeled fosphenytoin and phenytoin to dogs. Phenytoin, p-HPPH, and p-HPPH glucuronide were urinary metabolites common to both species. p-HPPH glucuronide (33.9%) was the major metabolite in rat urine, whereas m-HPPH glucuronide (51-58%) was the major metabolite in dog urine. Rodent fecal samples contained only p-HPPH (21.6%), p-HPPH glucuronide (8.3%), and an unidentified metabolite (10.2%). The metabolism and excretion profiles of fosphenytoin and phenytoin were the same following iv administration to dogs.

Toxicokinetics

Toxicokinetic studies in rats showed that the rate of phenytoin appearance in plasma was decreased following im administration relative to iv administration of a single 150 mg/kg dose of fosphenytoin (tmax values 10-15X greater), peak phenytoin levels were reduced (50-60%) after im administration, there was a sex differences in phenytoin clearance (elimination t1/2 4-7.5-fold longer in females), and total phenytoin exposure (AUC) was similar within sex following im or iv administration of the same dose (**Table II.5**). Fosphenytoin levels were not determined.

Phenytoin kinetics determined after single im or iv doses of 50 mg/kg fosphenytoin to dogs (**Table II.6**) were fairly comparable. Although tmax values following im fosphenytoin were longer than those following iv fosphenytoin (1.2 hr for im versus 0.6 hr for iv), Cmax values (21.3 ug/ml for im versus 26.8 for iv) and plasma phenytoin concentration-time profiles (im and iv AUC values of 159 and 163 ug hr/ml, respectively) were similar for both routes. Mean elimination t1/2 values were essentially the same following im (2.8 hr) and iv (3 hr) administration. There was no sex difference in pharmacokinetics in dogs. Fosphenytoin levels were not determined.

Thus, rate of phenytoin appearance in plasma was decreased following im fosphenytoin administration relative to iv administration, but total phenytoin exposures as determined by AUC data were similar in rats and dogs following im and iv fosphenytoin. Relative fosphenytoin exposures were not determined.

TOXICOLOGY

Acute toxicity

Acute iv toxicity studies were conducted in mice, rats, rabbits, and dogs (**Table III.1**). The median lethal doses of fosphenytoin and phenytoin in mice and rats were essentially equivalent when both drugs were administered by iv infusion, with values ranging from approximately 150-350 mg/kg. Phenytoin was more potent than fosphenytoin when the drugs were administered as an iv bolus, probably due to a more gradual rise in peak phenytoin levels with the prodrug. Similar CNS-related signs were observed after iv injection of fosphenytoin or phenytoin in both rodents and non-rodents and included ataxia, hypoactivity, prostration, and convulsions. In addition, salivation and vomiting were seen in dogs, and tremors and dyspnea occurred in rodents. The MLD's of iv fosphenytoin and phenytoin in weanling rats were the same as in adults; however, neonatal rats were more sensitive to the toxic effects of both drugs than weanling rats following ip administration. After im administration, fosphenytoin induced clinical signs, convulsions, and/or deaths in rats and dogs at lower doses than phenytoin due to increased absorption and higher blood concentrations achieved by this route (**Table III.2**). Gross pathologic changes were not observed in acute studies with fosphenytoin, while tissue necrosis at im injection sites in rats and dogs was observed with phenytoin.

Multidose toxicity

Rat

A 4-week rat study (10/sex/group main study, 5/sex/group recovery, 3/sex/group PK) was conduced with iv (bolus) doses of 0 (vehicle), 30, 60, and 150 mg/kg of fosphenytoin. T-R clinical signs were seen primarily in MD and HD animals and consisted of ataxia, hypoactivity, salivation, and dyspnea. BW gain during the dosing period was decreased (32%) in HD males compared to controls. Erythrocyte parameters (RBC, HGB, HCT) were slightly decreased and MCHC was increased in HD females compared to controls. ALT and ALP were increased by about 50% in HD males and females at week 4. Liver weights were increased in females at all doses, and periportal vacuolization was observed microscopically in HD males and females. Liver changes were not seen following a 4 week recovery period. The increased liver weights and enzyme activities presumably reflected the induction of hepatic microsomal drug metabolizing enzymes, which is a well recognized effect of phenytoin in animals and humans. The increased periportal vacuolization in HD rats was shown by EM to be mainly due to the presence of larger areas of glycogen deposition than in controls. Reversible injection site irritation was seen at all doses (D-R). Plasma phenytoin levels 15 min after dosing during week 2 were proportional to dose and similar in males and females; mean concentrations ranged from 9.1 at the LD to 52.8 ug/ml in the HD group (**Table III.3**).

A 13 week rat study (10/sex/group main study, 5/sex/group PK) was conducted with im doses of 0 (saline), 30, 60, or 150 mg/kg of fosphenytoin. A group receiving phenytoin (100 mg/kg, equimolar to HD) served as a positive control (PC). Hypoactivity, ataxia, and salivation were observed in both the HD and PC groups. In addition, autocanibalism of the hindlimbs was seen in phenytoin-treated rats. T-R deaths occurred only in the HD (2/15 M, 1/15 F) and PC groups (8/15 M, 10/15 F). There were no hematologic effects related to fosphenytoin treatment. AST, ALT, and ALP levels were elevated in HD males and females, while only slight increases in ALP were seen in the PC group. Increased plasma glucose levels (2 hr after dosing) and glucosuria were observed in the HD and PC groups. Liver weights were increased in the MD (females) and HD groups, and thymus weights were decreased in HD animals. Injection site lesions were observed in fosphenytoin- and phenytoin-treated animals (D-R in fosphenytoin groups). Intracytoplasmic hepatocyte vacuolization was seen in the HD group (8/10 M, 9/10 F) and single cell hepatocyte necrosis was observed in PC animals (3/10 M, 3/10 F). Decreases in thymus weights in HD animals correlated with histologic evidence of lymphoid depletion. Plasma phenytoin levels were 3-4 times higher following HD fosphenytoin

administration than after phenytoin injection by the im route; concentrations ranged from 46.7 to 48.9 ug/ml after the HD of fosphenytoin and from 15.2 to 23.8 ug/ml after an equimolar dose of phenytoin (**Table III.4**).

Dogs

Four groups of dogs (3/sex/group main study, 1/sex/group recovery) were given iv bolus doses of fosphenytoin at 0 (vehicle), 15, 30, or 50 mg/kg for 4 weeks. Clinical signs were observed with a D-R incidence in treated dogs and consisted of emesis, diarrhea, salivation, erythema of the gums, hypoactivity, ataxia, mydriasis, and tremors (HD only). No deaths occurred. There were no significant T-R effects on weight gain or food consumption. Hematological parameters were comparable among groups. Serum ALP was elevated about 2-fold in HD dogs compared to C at 4 weeks and after a 4-week recovery period. Increased salivary gland weights and hypertrophy of mandibular and parotid salivary gland acini were noted in HD dogs. There was a trend toward increased liver weights in MD and HD animals, but no apparent histological correlate. Small (10%) increases in absolute and relative heart weights were seen in MD and HD males, but no pathology was seen upon microscopic examination. No differences in the incidence or severity of injection site alterations were noted between vehicle controls and treated groups. Plasma phenytoin levels 30 after dosing during week 2 increased approximately dose-proportionately and were similar between sexes; mean concentrations ranged from 6.6 at the LD to 23.7 ug/ml in the HD group (**Table III.5**).

Fosphenytoin was administered im to 5 groups of dogs (4/sex/group) at dose levels of 15, 30, and 60 mg/kg/day for 13 weeks. A negative control group was administered saline, and a positive control group received phenytoin sodium (40 mg/kg, equimolar to HD). Ataxia, decreased activity, and mucoid diarrhea were observed in the HD group, and emesis and ptyalism were seen in all fosphenytoin-treated dogs in a dose-related manner. Ataxia, emesis, and diarrhea were observed in the phenytoin group, with incidences intermediate between that seen in the MD and HD fosphenytoin groups. Both phenytoin and fosphenytoin groups exhibited swelling at the injection sites. All animals survived to termination. BW gain was increased in male fosphenytoin-treated dogs and decreased in phenytoin group males and females compared to saline controls. No changes in hematologic values were noted in the analysis of blood samples. However, one HD fosphenytoin female had an elevated myeloid/erythroid ratio (M/E = 6.1) in the bone marrow smear performed post mortem, indicating depressed erythrogenesis. Alkaline phosphatase and creatine phosphokinase levels were moderately elevated in MD, HD and PC groups. The former was probably related to hepatic enzyme induction and the latter may have been related to muscle tissue injury. A dose-related increase in liver weights occurred in fosphenytoin-treated males (+35% at HD) and females (+28% at HD). Liver weight was also increased in the PC group (+28% M, 14% F). Livers of 1 male and 1 female from the phenytoin group and of all females from the HD fosphenytoin group showed diffuse increases in intracytoplasmic vacuolization of hepatocytes. Injection site changes were observed in dogs from the phenytoin group and from the MD and HD fosphenytoin groups, but were reportedly more extensive and severe in the phenytoin group. Phenytoin levels peaked at approximately 60 min after prodrug administration (**Table III.6**), averaging 25.5, 23.3, and 28 ug/ml on days 1, 42 and 91, respectively, in the HD group (there was no apparent effect of repeated dosing). Peak phenytoin levels in the phenytoin group were consistently about 1/3 times those in the equimolar fosphenytoin group, averaging 8.6, 7.8, and 8.1 ug/ml on days 1, 42, and 91 (also comparable over time). In the phenytoin group, measurable phenytoin levels were still present in samples collected just prior to dosing, indicating slow absorption after im injection. No phenytoin was measured in predose samples from fosphenytoin groups.

SPECIAL TOXICITY

Local irritation

Fosphenytoin produced significantly less venous and perivascular irritation (based on microscopic irritation scores) than phenytoin at equimolar concentrations. Local irritation after im injection of fosphenytoin to rabbits was significantly lower than after im phenytoin. When injected im into the hindlimb of rabbits daily for 5 consecutive days, phenytoin was more irritating than equimolar concentrations of fosphenytoin.

Cardiovascular effects

The cardiovascular effects of equimolar doses of phenytoin (18 mg/kg) and fosphenytoin (27 mg/kg) were comparable following iv bolus (3 sec) injection to anesthetized female dogs (4/group). Intravenous phenytoin resulted in decreases in heart rate (80% of baseline), LvdP/dt (max -55% compared to C), and MAP (-40% compared to C) and significantly increased LVEDP (2-3-fold). Fosphenytoin resulted in more gradual decreases in HR (80% of baseline), LvdP/dt (max -36% compared to C), and MAP (-40% compared to C and baseline). Effects on LVEDP were variable and did not appear to be as pronounced as those produced by phenytoin administration. Effects on CV parameters appeared to correlate with phenytoin blood levels in both cases. The major difference between drugs was in effects on LVEDP. The less pronounced effects seen after fosphenytoin presumably reflect the lower peak blood level of phenytoin resulting from its administration (22 ug/ml vs 49 ug/ml after phenytoin administration). (**Figures IV. 1 & IV.2** and **Table IV.1**).

Formaldehyde formation

The theoretical maximum dose of formaldehyde (assuming complete, instantaneous conversion) after an iv dose of 2100 mg fosphenytoin (30 mg/kg is given as maximum dose in proposed labeling) would be 5.17 mmol or about 0.1 mmol/kg (3 mg/kg) for a 50 kg person. The pharmacokinetics of formaldehyde and its major metabolite, formate, were modeled using data from a published report in which formaldehyde (30 mg/kg) was administered iv to monkeys. Based this model, peak formaldehyde and formate concentrations resulting from first order input of 3 mg/kg formaldehyde (formation half-life = 8 min) were simulated (**Figures IV. 3** and **IV.4**). These simulations were analogous to bolus administration of a fosphenytoin dose of 2100 mg. Peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 min. Maximal formate levels were predicted to be 0.08 mmol/L, which is below the baseline levels measured in 2 monkeys in a published study (0.18 and 0.27 mmol/L). Background levels of formate in humans have been reported in the literature to be 0.07 to 0.4 mmol/L.

Since the theoretical maximum dose of formaldehyde represents only a fraction of the total body burden from normal metabolism (36 g/day in a 50 kg person), and since the PK simulations indicated that formaldehyde concentrations would exceed background levels for a relatively short time, the sponsor considers the potential risks associated with formaldehyde exposure as a result of fosphenytoin administration to be negligible. Plasma formate levels measured in 4 healthy volunteers following administration of 1200 mg of fosphenytoin by iv infusion over 30 min were not significantly different from those observed in a placebo group or from baseline levels (25 mg/L). (The dose and infusion rate used in this study were considerably lower than the maximum values in the proposed dosing recommendations, ie, 30 mg/kg and 225 mg/min, respectively; and the sample was very small.)

GENETIC TOXICITY

No biologically significant effects on revertant frequencies were seen with fosphenytoin in the Ames test. Fosphenytoin was negative for effects on mutation frequency at the HGPRT locus in V79 Chinese hamster lung cells were evaluated after exposure to fosphenytoin concentrations up to 4000 ug/ml in the absence or presence of metabolic activation. Structural chromosome aberration frequency in V79 Chinese hamster lung cells was increased by exposure to fosphenytoin concentrations ≥ 1000 ug/ml in the presence of metabolic activation (**Table V.1 & V.2**). In mice given single iv doses of up to 200 mg/kg (iv LD50 = 234 mg/kg), no biologically significant differences in micronucleus formation were detected.

REPRODUCTIVE TOXICITY

Segment I (male)

Male rats (40/grp) were dosed with 0, 25, 75, or 150 mg/kg, im, for 75 days prior to mating and throughout

mating with untreated females (1:1 cohabitation, 10 day maximum), then sacrificed. Females were either sacrificed on Day 21 of gestation (1/2) or allowed to deliver and wean their offspring. Paternal toxicity, characterized by clinical signs (injection site lesions, neurotoxicity) and suppression of BW gain, occurred at the MD and HD. Two HD males died and 2 were sacrificed moribund. Mean plasma phenytoin concentrations ranged from about 5 (LD) to 45 ug/ml (HD) and did not appear to accumulate during treatment. No T-R effects were apparent for male reproductive parameters, including semen evaluation. F0 fertility indices were decreased compared to historical data, but both control and treated males were affected. No biologically significant effects on female reproductive or fetal parameters were observed at C-section. There was a slight increase in stunted fetuses (<4 g) at the HD, but the value was within the historical control range. In litters from females allowed to deliver, there were no T-R effects on reproductive parameters or on neonatal growth, survival, and acquisition of developmental landmarks. In addition, no group differences were found in several postweaning tests of neurobehavioral function, and there were no treatment effects on F1 reproductive parameters.

Segment I (female)

Female rats (40/grp) were dosed with 0 (vehicle), 25, 75, or 150 mg/kg, im, for 15 days prior to mating with untreated males, and throughout mating, gestation, and lactation. C-sections were performed on 1/2 of the females on Day 21 of gestation; remaining females were allowed to deliver and wean their offspring. A high incidence of neurotoxicity (hypoactivity, ataxia, and prostration) was observed in HD females, which is consistent with the blood levels achieved at this dose (33-38 ug/ml). Similar CNS signs have been reported at plasma phenytoin levels >25-30 ug/ml, in rats and humans. BW gain was decreased in MD and HD females during the premating and gestation periods. Estrous cycles were altered at the MD and HD, but mating and fertility indices were unaffected. Parturition was significantly delayed at the HD, and disturbed at all doses. Fosphenytoin produced developmental toxicity primarily at the HD (decreased growth, increased intrauterine and postnatal death, malformations, functional effects; **Tables VI.3-5**), although there were effects on growth at the MD. The MD and HD produced peak maternal plasma phenytoin concentrations of approximately 20 and 40 ug/ml, respectively (10-20 ug/ml considered therapeutic). Teratogenicity (cardiac, digit, brain anomalies) was significant at the HD; however, the occurrence of a brain malformation in a single LD fetus may have been drug-induced, since brain malformations are rare and have been previously reported after prenatal phenytoin exposure. Chromodacryorrhea and circling were seen in HD offspring; these have been previously reported after prenatal phenytoin exposure.

Segment II (rat)

Pregnant rats (40/group) were treated with 0 (vehicle), 10, 50, or 100 mg/kg, iv, on gestation Days 7 through 17. C-sections were performed on 25/group on Day 21; the remaining 15/group were allowed to deliver and rear offspring. Maternal toxicity occurred primarily in HD dams and consisted of death (4 HD dams), clinical signs (salivation, chewing, ataxia, hypoactivity, and limb rigidity), and suppression of BW gain. Mean maternal plasma phenytoin levels at 1 hr postdosing (approximate Cmax) were 4, 24, and 43 ug/ml in LD, MD, and HD groups, respectively. At C-section, postimplantation loss was increased (2-fold) in HD dams compared to concurrent and historical controls. Mean fetal BW was decreased (30% below VC) in the HD group. Incidences of skeletal malformations, external/visceral variations, and skeletal variations were increased in HD litters (**Table VI.7**). Although classified as malformations, several of the skeletal anomalies (hemicentra) may have reflected retarded ossification. The increase in variations was due to a marked increase in growth retarded fetuses in HD litters; 60% of HD fetuses were stunted (BW <4 g). Among dams allowed to deliver, the duration of gestation was significantly increased at the HD. Postimplantation loss was slightly increased at the MD and HD (**Table VI.9**). Birth weights and postnatal weight gain were decreased in HD males and females (10-15%). Vaginal opening was delayed in MD and HD female pups. Two littermates in the HD group exhibited abnormal circling behavior, and 27 pups from 8 HD litters had chromodacryorrhea. Both have previously been associated with prenatal phenytoin

exposure. One of the HD circlers later died (PND 23). Locomotor activity was increased in HD males on PND 42; however, this was mostly due to increased activity in a single HD pup. No group differences were found in acoustic startle parameters on P 43 or in shuttle avoidance parameters during week 9.

Segment II (rabbit)

Pregnant raboits (20/group) were treated with 0 (vehicle), 10, 25, or 50 mg/kg, iv, on gestation days 6 through 18. C-sections were performed on Day 30 of gestation. Maternal toxicity, characterized by clinical signs (chewing motions, ataxia, limb rigidity, and shallow, rapid breathing) and suppression of BW gain, occurred at the MD and HD. Mean maternal plasma phenytoin levels increased proportionally from about 7 (LD) to 35 ug/ml (HD). No T-R effects on maternal reproductive or fetal developmental parameters were apparent at C-section.

Segment III

Female rats (25/group) were treated with 0 (vehicle), 25, 50, or 100 mg/kg, iv, from Day 15 of pregnancy through Day 20 postpartum. Maternal toxicity, characterized by death, significant reductions in BW gain, and clinical signs (ataxia, hypoactivity, and imbalance), was observed primarily in HD group females. A D-R increase in gestation length was seen in treated dams, and postimplantation loss was dose-dependently increased at all doses (**Table VI.10**). Pup survival and BW at birth were significantly decreased at the HD, but were lower than controls at all doses. The effect on BW persisted into the maturation period in HD group offspring. Increased pup mortality and reduced postnatal growth have previously been reported after oral administration of 100 or 200 mg/kg of phenytoin on Days 7-18 of gestation. There was no increase in malformations among fosphenytoin exposed offspring, but treatment started after the major period of organogenesis. An increased incidence of structural variations in fetuses from dams that died around the time of parturition can be attributed to developmental delay. Hyperactivity was apparent in all treatment group male offspring, but values for activity parameters were outside the control range primarily in HD offspring. Enhanced avoidance responding and apparent memory enhancement were seen in treatment group offspring (MD & HD males, HD females), probably due to exposure-induced hyperactivity. Circling behavior, which has previously been reported following prenatal exposure to phenytoin and was seen in the segment II study, was not observed in this study. No apparent effects on the reproductive performance of F1 offspring were observed.

Table VIII.1 Summary of the Effects of Fosphenytoin and Phenytoin for Prevention of Tonic Extensor Seizures from Maximal Electroshock in Mice (All Fosphenytoin Doses are Expressed as Phenytoin Equivalents). Data Taken From Reference 16

	Dose Route (Time After Dose)	ED_{50} Value mg/kg (95% Confidence)	Rotorod Ataxia ED_{50}, mg/kg (95% Confidence)
Fosphenytoin	IV (10 min)	10.8 (8.4-17.5)	
	IV (30 min)	6.8 (6.1-7.5)	
Phenytoin	IV (10 min)	8.3 (6.1-11.2)	
	IV (30 min)	6.6 (5.1-8.0)	
Fosphenytoin	PO (6 hr)[a]	11.9 (9.7-14.9)	81.7[b] (75.4-88.6)
	IP (60 min)[a]	10.2 (8.57-11.4)	42.2[b] (38.9-45.7)
Phenytoin	PO (2 hr)[a]	9.04 (7.4-10.6)	86.7[b] (80.4-96.1)
	IP (2 hr)[a]	9.50 (8.1-10.4)	65.4[b] (52.5-72.1)

[a] ED_{50} values for each test were determined at the approximate time of peak effect after dosing.
[b] Data are taken from the US National Institutes of Health Antiepileptic Drug Discovery Project.

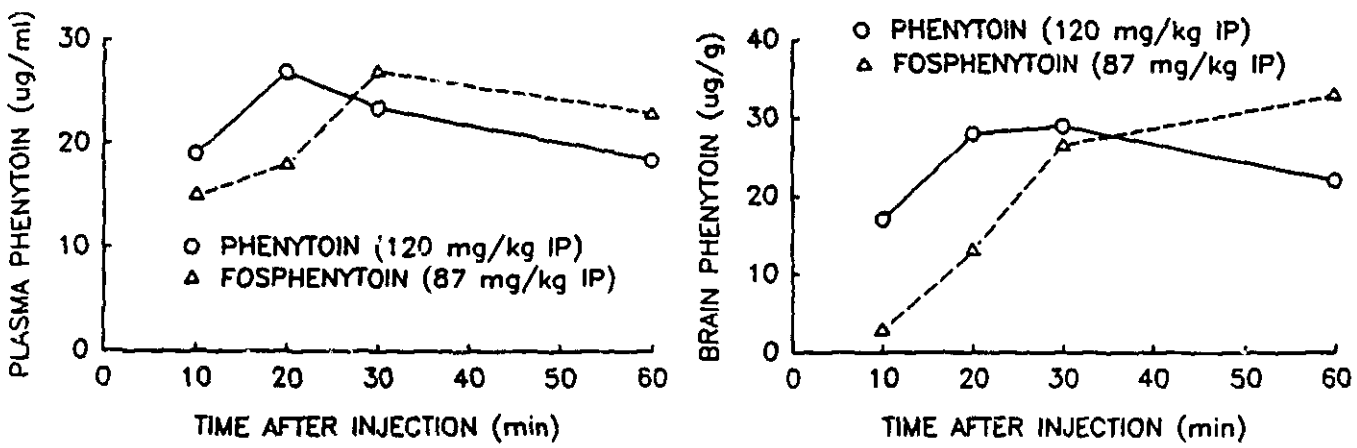


Figure VIII.1 Time Course of Changes in Phenytoin Concentrations in Plasma (above) and Brain (below) in Rats Given Doses of Fosphenytoin and Phenytoin IP in a Study of Action against Status Epilepticus

Rats were given a single intraperitoneal dose of either fosphenytoin (87 mg/kg phenytoin equivalents) or phenytoin (120 mg/kg) and samples of blood plasma or brain tissue were obtained at various times after dosing. Each data point is the mean from 3 individual samples. Data are from Reference 17.

VIII. EVALUATION

Fosphenytoin is a water soluble phosphate ester prodrug of phenytoin, intended as a replacement for parenteral phenytoin (poorly soluble, requires an alkaline organic solvent and precipitates in iv fluids). Fosphenytoin is quantitatively converted to phenytoin *in vivo* by ubiquitous phosphatases, with a conversion half-life of about 8, 3, and <1 min in man, dog, and rat, respectively. Because of the phosphate ester, 150 mg fosphenytoin yields 100 mg phenytoin. The properties of phenytoin are well established; therefore, the primary safety issues with fosphenytoin relate to possible differences in the pharmacological/toxicological profile of phenytoin resulting from administration of the prodrug. These differences could involve intrinsic effects of fosphenytoin, changes in phenytoin disposition, or effects of breakdown products, as discussed below.

Fosphenytoin and phenytoin were equipotent against MES-induced seizures in mice after oral, ip, or iv administration (**Table VIII.1**). Although time courses of anticonvulsant action were comparable when the two drugs were given iv, there was some indication of a delayed onset after fosphenytoin administration. This delay could be important in the treatment of status epilepticus. A published study by Walton and Treiman (Epilepsy Res 5:165-8,'90) indicated that fosphenytoin was less effective than phenytoin in a rat model of status epilepticus. Although similar final plasma and brain phenytoin concentrations were reached after ip administration of the two drugs, a slower rise in brain phenytoin levels following fosphenytoin administration was thought to reduce its anticonvulsant efficacy in this animal model (**Figure VIII.1**). Thus, the time required for conversion of fosphenytoin to phenytoin could have a negative impact on the effectiveness of treatment.

However, clinical iv PK studies have shown that free phenytoin concentration-time profiles similar to those seen with parenteral phenytoin can be obtained by increasing the fosphenytoin infusion rate. This is partly due to altered protein binding of phenytoin in the presence of fosphenytoin. *In vitro* studies and clinical PK data indicate that fosphenytoin displaces phenytoin from plasma binding sites, ie, the phenytoin free fraction increased with increasing fosphenytoin concentrations. In human volunteers, the extent of phenytoin displacement for a given dose, and therefore the Cmax and AUC values for free phenytoin, increased with the infusion rate. Following infusion of fosphenytoin (1200 mg PE - phenytoin equivalents) at 100 and 150 mg PE/min, increases in free fraction resulted in free phenytoin concentrations and tmax values similar to those seen after administration of an equimolar dose of phenytoin at the maximum recommended rate of 50 mg/min. Such infusion rates of fosphenytoin are reportedly well tolerated. At steady-state, administration of fosphenytoin could enhance the pharmacological or toxicological effects of phenytoin by displacing it from its binding sites, although the increase in free fraction would be transient. The potential for such displacement effects was not addressed in the preclinical studies; free phenytoin levels were not determined in any of the *in vivo* animal studies.

Phenytoin has been shown to produce significant reductions in blood pressure when infused iv in both animals and man. Phenytoin-induced hypotension appears to be dependent on both total dose and rate of infusion. The maximum recommended adult human infusion rate is 40-50 mg/min and the total dose is usually limited to 1250-1500 mg. In a study comparing the hemodynamic effects of phenytoin and fosphenytoin in dogs, qualitatively and quantitatively similar changes in CV parameters were seen: both drugs produced comparable decreases in blood pressure, heart rate, and contractility. When the CV effects of fosphenytoin (21 mg/kg PE) infusion over 15-30 min were compared with those seen after infusion of an equimolar dose of phenytoin over 30 min, the maximum effects were nearly identical and were observed at comparable plasma levels of phenytoin (**Figures I.4-6**). The rapidity of fosphenytoin infusion (within the range tested) appeared to affect the onset but not the maximum response. At times when plasma levels of both fosphenytoin and phenytoin (formed from fosphenytoin) were high, effects were not greater than those seen at comparable levels of phenytoin alone; therefore, it did not appear that fosphenytoin had any significant hemodynamic effects of its own. When higher equimolar doses (40 mg/kg PE) were rapidly infused (over 2 min), the magnitude of the changes in CV parameters produced by fosphenytoin appeared to be somewhat greater than those seen with phenytoin (**Figures I.1-3**). However, 3 of the phenytoin-treated animals (ie, the most sensitive to CV effects) died within 4 min of infusion onset following marked reductions in MAP and HR, while all 6 fosphenytoin dogs recovered; so the means depicted in the figures may be misleading. Although the CV changes produced by fosphenytoin seemed to correlate with plasma levels of phenytoin, and similar peak total phenytoin concentrations were achieved after phenytoin or fosphenytoin administration, it is possible that the

displacement effect described in the preceding paragraph resulted in higher maximal free phenytoin levels following rapid fosphenytoin infusion, which might have contributed to any increased response observed. In addition, formaldehyde formation could have added to the CV effects seen after rapid infusion of fosphenytoin. Formaldehyde has been shown to decrease the rate and contractility of isolated rat atria *in vitro*, and cardiodepression has been reported in rats infused with 0.12 mmol/kg/min formaldehyde (Strubelt et al, J Toxicol Clin Toxicol 28:221-33,'90). The rate of fosphenytoin infusion in the dog study was 0.08 mmol/kg/min. However, the theoretical maximal rate of exposure to formaldehyde clinically, based on the proposed maximal rate of fosphenytoin administration (225 mg/min), would be 0.01 mmol/kg/min (50 kg BW). Fosphenytoin exhibited intrinsic activity only in one *in vitro* assay: the prodrug inhibited developed tension in a guinea pig left atrial preparation with a potency equivalent to that of phenytoin. Fosphenytoin was inactive in isolated right guinea pig atria, however. This *in vitro* effect is unexplained but unlikely to be of any clinical importance.

The toxicological profile of fosphenytoin was essentially the same as that of phenytoin. The acute toxicity of fosphenytoin was equivalent to that of phenytoin when the two drugs were administered by iv infusion (30 min) to mice, rats, rabbits, and dogs (**Table III.1**). However, phenytoin was more toxic than fosphenytoin after single iv bolus administration to rats, probably due to a more gradual rise in phenytoin levels when fosphenytoin was given. When compared on an equimolar basis, im fosphenytoin produced more acute systemic toxicity than phenytoin in rats and dogs, presumably due to better absorption by this route (**Table III.2**). Fosphenytoin produced less injection site irritation than phenytoin by both the iv and im routes. Unfortunately, the only multiple dose toxicity studies that included a phenytoin positive control were the 3 month im rat and dog toxicity studies. Because of its lower bioavailability by the im route, phenytoin was less toxic than an equimolar dose of fosphenytoin, except with regard to injection site irritation. Toxicokinetic studies indicated that equivalent phenytoin exposures (AUCs) were achieved after iv or im administration of fosphenytoin to rats and dogs (**Tables II.5 and II.6**). Peak phenytoin levels following im administration were about the same as those seen with iv administration in dogs and were about 1/2 iv peak levels in rats. Fosphenytoin was not measured in these high dose toxicokinetic studies. At a lower dose (10 mg/kg PE), fosphenytoin exposures were equivalent following iv and im administration to dogs, but peak fosphenytoin levels were about 10-fold higher after iv administration (**Table II.3**). Therefore, possible intrinsic effects of fosphenytoin or effects related to systemic formaldehyde may not have been adequately assessed in im toxicity studies. Effects on serum hepatic enzymes and liver weights observed in multidose studies in rats and dogs are known effects of phenytoin in animals and are consistent with microsomal enzyme induction. Microscopic changes in the liver were attributed to increased cellular glycogen content secondary to phenytoin-induced hyperglycemia. Phenytoin causes hyperglycemia in animals and humans by inhibiting the insulin response to glucose stimulation.

The *in vivo* hydrolysis of fosphenytoin produces 1 mole each of formaldehyde and phosphate for each mole of prodrug. No attempt to measure blood formaldehyde levels was made in any of the preclinical studies, but the pharmacokinetics of formaldehyde and its major metabolite formate were modeled using data from a published report in which formaldehyde was administered iv to monkeys, and formaldehyde and formate concentrations resulting from first order input of 0.1 mmol/kg of formaldehyde were simulated (**Figures IV. 3 & IV.4**). This was considered to be the theoretical maximum human dose of formaldehyde, based on the complete conversion of an iv (bolus) fosphenytoin dose of 2100 mg (5.17 mmol or 0.1 mmol/kg using 50 kg BW). (The proposed MHD of fosphenytoin is 30 mg/kg at 225 mg/min.) Peak formaldehyde levels were predicted to be approximately 0.18 mmol/L, with concentrations declining to background levels (0.027-0.068 mmol/L) within 20 min (formaldehyde is rapidly eliminated, with a t1/2 of 1.5 min in monkeys). Qualitative and quantitative similarities in formaldehyde metabolism between monkeys and humans suggest that these findings could be extrapolated to humans, but the actual data on which the PK model was based are very limited, ie, blood levels measured in 1 monkey. The toxicity of formaldehyde has been extensively examined, but inhalation has been the route of exposure in most studies. Effects were generally confined to the nasal and gastric epithelia after inhalation and oral administration of formaldehyde. Following a single iv injection, the median lethal dose of formaldehyde in rats was reported to be 87 mg/kg. The chronic toxicity of iv formaldehyde has apparently not been investigated. Formaldehyde is genotoxic in a variety of systems, and both chronic and subchronic inhalation exposures to high formaldehyde concentrations (15 ppm 6 h/d) have resulted in the induction of squamous cell carcinomas in the nasal cavity of rats. However, despite the widespread exposure of humans to formaldehyde, epidemiological studies have not demonstrated that it

represents a significant cancer risk to man (Heck et al, Critical Reviews in Toxicology 20:397-426,'90). OSHA (Third Annual Report on Carcinogens, USDHHS Public Health Service,'83) has set permissible formaldehyde exposure levels at 3 ppm as an 8 hr time weighted average and 10 ppm as a maximum peak concentration for 30 min in an 8 hr period, but there are no good estimates of acceptable plasma formaldehyde levels. It has been reported (J Piotrowski, Exposure Tests for Organic Compounds in Industrial Toxicology,'77) that workers exposed to formaldehyde at a concentration of 5.4 ppm (presumably 8-h TWA, but not stated) developed maximal blood levels of 0.13 mmol/L (ie, similar to predicted peak levels after fosphenytoin). However, occupational exposure patterns may be very different from the pattern of formaldehyde exposure in fosphenytoin-treated patients. Formaldehyde is generated during normal intermediary metabolism - the body turns over up to 50 g/day - and there are many sources of environmental exposure. Assuming that the simulations used by the sponsor are reasonably accurate, the formaldehyde formed from fosphenytoin would not be expected to overwhelm the body's detoxification capacity, and any elevation in blood levels would likely be transient; however, clinical data are needed to verify the model (see original IND review of this issue). Intravenous administration of high concentrations of phosphate can result in toxicity due to reduction of Ca^{2+} in the circulation and precipitation of calcium phosphate in tissues. This potential risk was not addressed by the sponsor. Although it is unlikely that the amount of phosphate which would be contributed by fosphenytoin administration (max ~5 mmol) would raise serum concentrations to the levels which are associated with such effects (3.2 mmol/L), transient or local effects are possible. No findings obviously attributable to increased formaldehyde or phosphate exposure were observed in the fosphenytoin acute studies or in the 4-week toxicity studies at iv bolus doses up to 5 (rats) and 1.5 (dogs) times the maximum human dose (mg/kg basis).

The major pathway for metabolism of formaldehyde involves oxidation to formate and incorporation into biological macromolecules via tetrahydrofolate-dependent one-carbon synthetic pathways. Since formate accumulation is thought to be responsible for the known toxic effects of high dose methanol exposure (ie, severe metabolic acidosis and ocular toxicity), formate toxicity also represents a potential concern with fosphenytoin administration and may be more relevant to short-term use. Hepatic alcohol dehydrogenase and catalase metabolize methanol to formaldehyde, then a glutathione-mediated pathway involving formaldehyde dehydrogenase rapidly metabolizes formaldehyde to formic acid. The accumulation of methanol-derived formate to toxic levels is primarily influenced by the rate of formate metabolism, which depends on the activity of formyltetrahydrofolate synthetase, methenyltetrahydrofolate dehydrogenase, and the cosubstrate tetrahydrofolate. Following MeOH administration, formate has been shown to accumulate in the blood of primates but not of rodents or other nonprimates, and this is thought to account for a species difference in susceptibility to MeOH poisoning. Tissue folate levels are thought to be key determinants of susceptibility to neuro-ocular toxicity following exposure to methanol. Primates have lower total liver folate concentrations, slower formate metabolism, and are thus more sensitive to methanol-induced toxicity compared to resistant species such as rodents. This interaction of formate and folate may be especially important in view of the fact that phenytoin and other AEDs have been shown to interfere with folate-dependent one-carbon metabolism. Folate depletion due to chronic AED therapy or other causes could increase formate levels during fosphenytoin administration. Furthermore, because of species differences in formate metabolism, the preclinical toxicity studies of fosphenytoin in rats and dogs are probably not appropriate for evaluating possible toxic effects related to the metabolism of the prodrug to formate. However, neuro-ocular toxicity in methanol- and formate-poisoned monkeys (Martin-Amat et al, Arch Ophthalmol 95:1847-1850,'77; Martin-Amat et al, TAP 45:201-208,'78) and in methanol-poisoned humans (Mahieu et al, Human Toxicol 8:135-137,'89; McMartin et al, Am J Med 68:414-418,'80) is reportedly associated with marked elevations in blood formate concentrations (>7-10 mM) for prolonged periods of time (often > 24 hr). In a folate-reduced rat model of methanol toxicity (Murray et al, Arch Ophthalmol 109:1012-1016,'91), exposure to blood formate concentrations of 8-12 mmol/L for more than 12 hr was required to produce changes in ERG and ultrastructural damage to the retina and optic nerve following administration of methanol (4 g/kg ip followed by 2 g/kg every 12 hr for 60 hr); formate levels up to 3 mmol/L were not toxic in this model (Louis-Ferdinand, personal communication). Formate has also been shown to be embryotoxic and dysmorphogenic to developing mouse and rat embryos *in vitro* at concentrations >10 mM (Dorman et al, Teratology 52:30-40,'95). In the PK simulations described above, maximal formate levels after administration of a 2100 mg dose of fosphenytoin were not predicted to exceed the range of background concentrations (0.1-0.56 mM). Based on these projected levels, formate formed from fosphenytoin should not constitute a significant hazard. However, while plasma formate levels were measured in 4 volunteers following administration of fosphenytoin and did

not increase significantly above those observed in a placebo group or baseline levels (all ~0.5 mmol/L), the dose and infusion rate used in this study (1200 mg over 30 min) were well below the maximum values in the proposed dosing recommendations (30 mg/kg at 225 mg/min); therefore, additional human data are needed. *Note to clinical reviewer*: Because the safety data related to formaldehyde and phosphate are so limited, a request that the sponsor measure blood levels of formaldehyde and/or formate and assess any changes in calcium concentration or acid-base equilibrium following administration of fosphenytoin to humans at the maximum recommended dose should be considered.

Developmental toxicity seen in rats given fosphenytoin is consistent with that previously reported with phenytoin; however, no direct comparisons were made in the current reproductive toxicology studies. Segment I studies were conducted using im administration. As noted above, toxicokinetic studies indicated that similar phenytoin exposures (AUCs) were achieved after iv or im administration of fosphenytoin, but the question of im fosphenytoin bioavailability has not been adequately addressed. In the female Segment I study, maternal and reproductive toxicity were evidenced at 75 and 150 mg/kg by decreased maternal body weight gain, altered estrous cycles, and delayed parturition. Developmental toxicity, including teratogenic and functional effects (decreased growth, increased intrauterine and postnatal death, cardiac and digit anomalies, chromodacryorrhea, and circling), occurred primarily at 150 mg/kg, although 1 brain malformation seen at the LD (16.6 mg/kg) may have been treatment-induced and there were effects on growth at the MD. In a rat iv teratology study, developmental toxicity (growth retardation, chromodacryorrhea, increased locomotor activity, circling) was seen at 100 mg/kg along with overt maternal toxicity (neurotoxicity, decreased weight gain, dystocia). In an iv Segment III study, decreased pup survival and growth and offspring behavioral changes (hyperactivity) were observed at doses as low as 50 mg/kg, with maternal toxicity over the same dose range. The developmental effects of fosphenytoin were very similar to those reported in the literature following administration of phenytoin to rats, and they occurred at maternal plasma phenytoin levels comparable to those associated with developmentally toxic doses of phenytoin (ie, therapeutic levels or greater). The appearance of neurotoxicity (lethargy, ataxia, and imbalance) has previously been reported at plasma phenytoin concentrations ≥30 ug/ml, which is consistent with the levels observed in the present study following neurotoxic doses of fosphenytoin. Embryolethality, IUGR, and defects encompassing the cardiovascular, urogenital, craniofacial, and skeletal systems have been variably demonstrated in mice, rats, and rabbits exposed to phenytoin *in utero*. Cardiac malformations similar to those seen in HD fetuses in the rat Segment I study with fosphenytoin are typical of the fetal hydantoin syndrome in humans as well as those previously reported in phenytoin-exposed rat fetuses. The incidence of ectrodactyly was also increased in HD fosphenytoin treated fetuses in this study, and digit malformations such as adactyly and digital phalangeal hypoplasia have been reported in rodents and humans following prenatal exposure to phenytoin. Decreased postnatal viability and growth, chromodacryorrhea, increased locomotor activity, and circling behavior have also been reported in rats after prenatal phenytoin exposure (Vorhees, Teratology 35:287-303,'87). Thus, studies examining the reproductive and developmental effects of fosphenytoin confirm previous findings with phenytoin, but do not indicate any additional toxicity resulting from administration of the prodrug.

Fosphenytoin was clastogenic in V79 Chinese hamster lung cells *in vitro* but negative in *in vitro* mutagenicity assays and in the mouse micronucleus test *in vivo*. The sponsor postulated that the clastogenic effect was due to the generation of formaldehyde *in vitro*, since the effect was seen in the metabolic activation assay only. Phenytoin was reportedly not clastogenic in previous studies with CHO cells, while formaldehyde has been reported to induce chromosomal aberrations *in vitro* in CHO cells at concentrations as low as 5 ug/ml. As mentioned above, formaldehyde is genotoxic in a variety of *in vitro* assays, eg, increased mutation frequencies in Chinese hamster V79 cells were induced by formaldehyde at 0.3-1 mM concentrations; but no *in vivo* mutagenicity has been reported. Attempts to measure formaldehyde in cultures treated with fosphenytoin were unsuccessful. Addition of formaldehyde dehydrogenase to the S9 is a possible approach to addressing this question. Although one could assume that conversion to phenytoin would take place in the presence of S9, the extent of fosphenytoin hydrolysis *in vitro* was not measured in any of the genotoxicity assays. It seems likely that the clastogenicity of fosphenytoin is due to formaldehyde formation, but this has not been supported by data and could not be stated in the labeling without additional work.

Labeling

The Carcinogenicity and Pregnancy sections of the labeling are inaccurate and/or inadequate. Despite the findings in Chinese hamster lung cells, the statement is made that fosphenytoin was neither mutagenic nor clastogenic. The pregnancy category should be D, based on the known - or at least strongly suspected - human developmental toxicity of phenytoin; and since phenytoin has a pregnancy warning, fosphenytoin warrants the same. The warning needs to be updated or rewritten by the sponsor so that the information reflects the current scientific consensus regarding the effects of phenytoin on human development. Where adequate data are available, risk estimates and factors affecting risk should be included. The fosphenytoin animal findings, which are given 1 sentence in the proposed labeling, should be described in more detail. There are also some minor errors in the Mechanism of Action section. Suggested changes are as follows:

Mechanism of Action

In the second paragraph, replace the first three sentences with the following (in italics; sponsor's reference numbers retained):

After intravenous (IV) administration to mice, fosphenytoin *blocked the tonic phase of maximal electroshock seizures* at doses that are equivalent (on a molar basis) to those effective for phenytoin. *In addition to its ability to suppress maximal electroshock seizures in mice and rats[4], phenytoin exhibits anticonvulsant activity against kindled focal and secondarily generalized seizures in rats[3], audiogenic tonic-clonic seizures in mice[5], and generalized seizures produced by electrical stimulation of the brainstem in rats[6].* The cellular mechanisms of phenytoin ...

Carcinogenesis, Mutagenesis, Impairment of Fertility

Replace the second sentence in proposed text with the following:

The carcinogenic potential of fosphenytoin is not known. *Structural chromosome aberration frequency in cultured V79 Chinese hamster lung cells was increased by exposure to fosphenytoin concentrations ≥ 1000 ug/ml in the presence of metabolic activation. No evidence of mutagenicity was observed in bacteria or Chinese hamster lung cells in vitro, and no increase in micronucleus formation occurred after administration to mice in vivo.*

Add the following dosage information to the last sentence:

.... following administration of fosphenytoin during mating, gestation, and lactation *at doses of 75 and 150 mg/kg/day, or approximately 40% and 80%, respectively, of the maximum human daily dose (MHDD; 30 mg/kg) on a mg/m2 basis.*

Pregnancy - *Category D; see Warnings.*

Add the following sentence at the beginning of the first paragraph of the current, or updated, Dilantin Usage in Pregnancy warning:

Although there are no studies of fosphenytoin in pregnant women, epidemiological data indicate that prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly, and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and the neonate after birth.

Add the following paragraph after the human pregnancy information (sponsor's reference number):

Fosphenytoin demonstrated developmental toxicity, including structural and behavioral teratogenicity, in rats. When fosphenytoin was administered to female rats prior to and during mating, pregnancy, and lactation (25, 75, or 150 mg/kg/day), increased frequencies of malformation, death, and functional impairment were observed among the offspring of dams receiving 150 mg/kg/day, or approximately 80% of the maximum human daily dose (MHDD; 30 mg/kg) on a mg/m2 basis. This dose produced peak maternal plasma phenytoin concentrations approximately 2-4 times human therapeutic levels (10-20 ug/ml). Offspring growth was reduced by doses of 75 mg/kg/day (40% of MHDD on a mg/m2 basis) or greater, and maternal toxicity was evident over the same dose range. When pregnant rats were given fosphenytoin (10, 50, or 100 mg/kg/day) during the period of embryonic organogenesis, growth retardation and abnormal postnatal function were observed in offspring exposed to 100 mg/kg/day (50% of MHDD on a mg/m2 basis). Overt maternal toxicity was also associated with this dose. When female rats received fosphenytoin during the last third of pregnancy and throughout lactation (25, 50, or 100 mg/kg/day), decreased offspring viability and growth and alterations in offspring behavior were observed at doses of 50 mg/kg/day (30% of MHDD on a mg/m2 basis) or greater. Maternal toxicity was noted over the same dose range. The developmental effects of fosphenytoin in rats were similar to those which have been reported following administration of phenytoin to rats[2].

IX. RECOMMENDATIONS

The NDA is approvable with respect to the pharmacology/toxicology portion. Recommendations concerning the proposed labeling are made in the Evaluation section of the review.

cc:
NDA (20-450)
Div File
HFD-120/GFitzgerald/EFisher/RNighswander

YGF 1/30/96

E. Fisher, Ph.D.

Review and Evaluation of
Pharmacology and Toxicology
Continuation of Review # 1

Drug: 9653-010

Category:

Anticonvulsant; prodrug for phenytoin.

Summary:

It was noted out in our team meeting for this new drug that the in vivo hydrolysis of 9653 occurs in 2 steps, producing one mole of formaldehyde for each mole of prodrug. In the initial clinical Phase I trial, the top dose of 2250 mg would produce 5.5 mmoles of HCHO. The possible hazard from this burden will be discussed from several different veiwpoints below. All calculations are gross approximations, based on available information.

1. OSHA has adopted a permissible exposure level for toxic effects of formaldehyde other than cancer of 3 ppm as an 8 hour time weighted average, and 10 ppm maximum peak concentration for 30 minutes in an 8 hour period (Third Annual Report on Carcinogens, USDHHS Public Health Service, September, 1983, page 73). It has been reported that workers exposed to formaldehyde at a concentration of 7 mg/m^3 developed blood levels of 0.6 - 4.0 mg/l. The duration of exposure was not given (J.Piotrowski, Exposure Tests for Organic Compaounds in Industrial Toxicology, Gant Printing Office, DC, 1977, p.122). [1m^3 = 1000 l; wt. of air = 1.293 gms/l at 0°C + 760 mm Hg; therefore 7 mg/m^3 = 7 mg/1.293 kg = 5.4 mg/kg = 5.4 ppm in air]

   Since 5.4 ppm of HCHO → a maximum of 4 mg/l in blood, the 10 ppm maximum allowed by OSHA would → approximately 7.4 mg HCHO/liter or 0.25 meq HCHO/l in blood. This figure should more or less represent the maximal allowable blood level of HCHO according to OSHA. If we then assume that the 5.5 mmoles of HCHO that are split from the prodrug all appear in the circulation (ave. volume 5 liters) the concentration would be 33 mg/l or 1.1 meq/l, or approximately 4 fold higher than the OSHA level allowed. However, this is a very crude estimate since the data are not readily available for taking the time factor allowed under the OSHA limit into consideration.

2. There is a great deal of information in the literature that suggests that it is formic acid that is repsonsible for the ocular toxicity and acidosis seen following acute methanol poisoning (methanol → formaldehyde → formate). This toxicity would be of greater concern when dealing with a drug to be used acutely than would potential carcinogenicity. Although a role for HCHO has not been clearly ruled out, experiments in monkeys suggest that the resultant formate levels are of more concern.

In a model in rhesus monkeys for methanol ocular toxicity and metabolic acidosis, formate blood and CSF levels of 7 to 34 meq/l were associated with optic disc edema, morphological alterations in optic nerve and swelling of oligodendroglial cytoplasm (Martin - Amat, Hayreh, Baumtach et al, Arch Ophthalmol., 95, 1847-50, 1851-58, 1859-61; Martin-Amat, et.al., TAP, 45, 201-208, 1978). Pretreatment with folate increased the metabolism of formate and decreased the toxicity (McMartin et al, JPET, 201, 564-572, 1977). In the proposed clinical trial, if we assume the 5.5 meq of HCHO goes to 5.5 meq of formate, with a blood concentration of 1.1 meq/l, there is a minimum of a 7-fold safety factor before ocular toxicity occurred in the monkey (which is thought to metabolize HCHO like the human).

3. It has been reported that the mechanism for ocular toxicity caused by methanol is the inhibition of cytochrome oxidase by formate (Nicholls, BBRC, 67, 610-616, 1975). Since cytochrome oxidase activity is low in white matter, it has been suggested that its activity may be critical in that tissue. The Ki values determined for formate inhibition of cytachrome oxidase are between 5 and 30 m M (above reference plus Martin-Amat, Arch Ophthol., 95, 1847-50, 1977). Based on this data, blood levels of formate of 1.1 m M would be somewhat lower then those expected to produce toxicity.

4. In dogs and cats administered 35 mg/kg (1.2 meq/kg) of formaldehyde by i.v. infusion, a blood HCHO concentration of 25 mg/l (0.83 meq/l) was produced which declined to about 1 mg/l by 1 hour after the infusion. (4 x as much HCHO was in erythrocytes as in plasma). The peak plasma concentration of formate, however, was 144 mg/l (3.1 meq/l) at the end of the infusion, which declined with a $T_{1/2}$ of 1.5 hours. Toxicity was not addressed (G. Malorney et al, Naunyn - Schmiedebergs A.E.P.P., 250, 419-436, 1965). These data would suggest that peak levels of the possibly more toxic metabolite, formate, might be approximated as follows for top dose in the clinical trial:

   5.5 meq of HCHO (155 mg) = 3 mg/kg in a 50 kg person. If 35 mg/kg of i.v. HCHO → 144 mg/l of formate, 3 mg/kg or HCHO may result in peak blood levels of formate of 12 mg or 0.26 meq/l. (This is assuming comparable relative blood levles to body weight in humans and animals. Actually, dogs may have slightly larger blood volume/kg of body weight than humans, so the estimate for humans is possibly on the low side. The assumption for comparable metabolism is also made).

This figure is considerably lower than the Ki for formate inhibition of cytochrome oxidase and it is about 25-30 fold lower than the lowest levels of formate associated with ocular toxicity in monkeys (see numbers 2 and 3 above). If instead, we examine the blood HCHO concentration using these data, an i.v. dose of prodrug that yields 5.5 mmoles of HCHO (0.11 mmoles/kg) would be expected to result in a peak blood concentration of HCHO of 0.08 mmoles/liter, or 1/3 of the maximal allowable HCHO exposure according to OSHA.

Evaluation and Recommendations:

The above approximations are extremely crude, but they do provide some data for evaluating the risk involved from a drug which will be used acutely that is metabolized to produce a mole of formaldehyde for every mole of drug.

Based on OSHA limits for exposure to formaldehyde, the guestimate is that the top dose of prodrug planned in the rising dose trial (2250 mg) would result in anywhere from 1/3 of 7 times the maximal allowable blood level of formaldehyde. If we assume that formate is responsible for the expected acute toxicty (occular and acidosis), there may be anywhere between a 7 fold and a 30 fold safety factor, based on toxicity observed in monkeys and blood levels of formate measured after i.v. administration of HCHO to dogs. If we believe that formate toxicity occurs through cytochrome oxidase inhibition, there is at least a small margin of safety based on the Ki.

In any case, it is a close call, and there are a couple of precautions that might be considered. Monitoring of blood formic acid, blood pH, bicarbonate and pCO_2 is recommended. Since folinic acid pretreatment hastens the elimination rate, a supplement of 2 mg, p.o., might be given the day before the trial. However, if it is considered that this is an appropriate time to determine whether or not formate levels in blood are detectable (since in practice there would not be time to give folinic acid) I would recommend careful monitoring for formate levels at all doses before proceeding to the next higher dose. SRD is May 4, so sponsor should be phoned.

Glenna G. Fitzgerald

Glenna G. Fitzgerald PhD

cc: Orig.IND
HFN-120
HFN-120/JContrera/5/2/86
/GFitzgerald
rd/pjd/5/15/86:ft/5/16/86
doc 0471f

Review and Evaluation of Pharmacology and Toxicology

Memo to File

NDA: 20-450

Sponsor: Parke-Davis Pharmaceutical Research
Ann Arbor, MI 48105

Drug: Cerebyx (fosphenytoin sodium)

Category: Parenteral antiepileptic; prodrug of phenytoin for use in status epilepticus and neurosurgery

Related IND(s):

Submission: Response to NDA approvable letter (received 7/15/96)

Contents for Pharm/Tox review: Sponsor's final labeling (Tab 3)

Evaluation and Recommendations:

The sponsor's changes are acceptable, but the following corrections/additions need to be made.

Usage in Pregnancy,
B. *Risks to Fetus* - p 12, last sentence of first paragraph

Change contribution to contributions.

Preclinical - pp 12 and 13

Make wording of dose comparisons and plasma level data consistent (changes in italics):

paragraph 1, sentence 2: ... (*approximately* 30% of the maximum human loading dose or higher on a mg/m2 basis), which produced peak maternal plasma phenytoin concentrations *of approximately 20 ug/ml or greater.*

paragraph 1, sentence 4: ... (approximately *10%* of the maximum human loading dose on a mg/m2 basis) ...

paragraph 2, sentence 1: .. (*approximately* 50%...

paragraph 2, sentence 2: ...(*approximately* 120%..

Carcinogenesis, Mutagenesis, Impairment of Fertility - p 18, last sentence of second paragraph

Add the following (in italics): Maternal toxicity and altered estrous cycles, delayed mating, prolonged gestation length, and developmental toxicity were observed following administration of fosphenytoin during mating, gestation, and lactation at doses *of 50 mg PE/kg or higher (*approximately 40% of the maximum human loading dose or higher on a mg/m2 basis*).*

cc:
NDA (20-450)
Div File
HFD-120/GFitzgerald/EFisher/RNighswander

JE 1/25/96

JE. Fisher, Ph.D.
July 24, 1996

DEC 2 1 1995

Clinical Pharmacology and Biopharmaceutics Review
NDA 20-450 -- Fosphenytoin Sodium Injection

Sponsor:	Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road, P.O. Box 1047 Ann Arbor, MI 48106-1047
Submission dates:	February 27, 1995 October 19, 1995 November 3, 1995 November 20, 1995
Reviewers:	Robert Harris, Ph.D. Raymond Miller, Ph.D. Gene Williams, Ph.D. Raman Baweja, Ph.D. (team leader)

TABLE OF CONTENTS

IMPORTANT NOTE

A previous Division of Biopharmaceutics reviewer requested that the Human Pharmacokinetics and Bioavailability portion of the NDA be written with fosphenytoin doses and administration rates expressed in phenytoin equivalents. Since the molecular weight of fosphenytoin is 1.5X the molecular weight of phenytoin, phenytoin equivalents were calculated by multiplying the dose or adminstration rate of fosphenytoin by 0.67.

Not all of the NDA has fosphenytoin doses and rates expressed in terms of phenytoin equivalents. Fosphenytoin was initially developed by and Parke-Davis did not convert studies to express fosphenytoin doses and rates in phenytoin equivalents.

The studies conducted after Parke-Davis' acquisition of fosphenytoin are the most critical in evaluating the application. Thus, they constitute the majority of the Synopsis and Summary. In order to provide consistency between photocopied portions of the NDA and portions of the review constructed *de novo* by the reviewer, doses and rates of fosphenytoin will be expressed in phenytoin equivalents in all portions of this review prior to the individual study reports. The convention used in the individual study reports (Appendix 2) varies according to that used in the NDA and is detailed below.

The following studies were conducted by doses and rates are expressed **WITHOUT** conversion to phenytoin equivalents: 98201, 98202, 98205, 98206, 98207, 98210, and 98211. Studies 98213, 98214, 98215, 98216, 98218, 98220, and 98224 have doses and rates of fosphenytoin expressed as phenytoin equivalents.

During site visits by the Division of Scientific Investigations, it was determined that plasma concentration measurements of fosphenytoin from studies conducted by Parke-Davis were inaccurate due to an error in the weighing of standards. This error did not affect dosing of fosphenytoin. Parke-Davis has since determined that the accuracy of plasma concentration measurements of fosphenytoin from studies is uncertain. A description of these inaccuracies is given in the "Response to EIRs identified in 483 Forms" section of this review (p.20). The errors in fosphenytoin concentrations have **NOT been documented** in the individual study reports (Appendix 2). The values have little bearing on the interpretation of studies -- the specie of clinical interest is generally plasma phenytoin, not plasma fosphenytoin. The errors are accounted for in all portions of this review prior to the individual study reports (Appendix 2).

Synopsis

Fosphenytoin is a phosphate ester prodrug of phenytoin developed as an alternative for parenteral phenytoin. Only one fosphenytoin formulation (the to-be-marketed formulation) was studied clinically. Since fosphenytoin is a phenytoin prodrug and no new therapeutic claims beyond those approved for parenteral phenytoin are being made, proof-of efficacy studies were not conducted. Rather, the development program hopes to establish that fosphenytoin and phenytoin are bioequivalent sources of phenytoin.

Study 98224 demonstrates that using the 90% confidence interval approach and the log 80 - 125% C. I. criteria, 1200 mg of IV fosphenytoin at 150 mg/min is bioequivalent to 1200 mg IV phenytoin at 50 mg/min in terms of maximal free phenytoin concentration observed (Cmax) and area under the free concentration/time curve from t = 0 to the least quantifiable concentration (AUC_{0-TLDC}). A desired indication for fosphenytoin is treatment of acute status epilepticus. Because rapid attainment of sufficient phenytoin plasma concentration is critical in treatment of status epilepticus, analyses were performed to compare cumulative AUC over time. Using the forementioned confidence interval approach, cumulative $AUC_{free\ pht}$ following administration of 1200 mg of fosphenytoin at 150 mg/min is bioequivalent to the cumulative $AUC_{free\ pht}$ following 1200 mg of phenytoin at 50 mg/min from 30 minutes onward. At doses of 1200 mg and rates of 50 and 100 mg/min, fosphenytoin is equivalent to 1200 mg phenytoin dosed at 50 mg/min in terms of total $AUC_{free\ pht}$ but not $Cmax_{free\ pht}$.

Fosphenytoin exhibits non-linear pharmacokinetics: as dose and rate of administration are increased, clearance increases. Fosphenytoin is highly protein bound, and its non-linear clearance is hypothesized to result from protein binding considerations: as dose and rate of administration increase, protein binding saturates and greater concentrations of free drug are available to be cleared. Independent of dose and rate of administration fosphenytoin is a short-lived specie; terminal elimination half-life of the drug is approximately 15 min and, regardless of dose or rate of administration, fosphenytoin is rarely quantifiable 5 hrs post-dosing. The conversion of fosphenytoin to phenytoin is consistent and essentially complete.

Unlike phenytoin, fosphenytoin is readily absorbed when administered IM. Average bioavailability of phenytoin from 250 mg of IM fosphenytoin is 101%.

Study 98207 examined the disposition of fosphenytoin in renal failure and hepatically compromised patients. Fosphenytoin clearance is more than 2-fold as great in cirrhosis patients and about 1.8-fold as great in renal failure patients as in healthy volunteers. This is consistent with decreases in plasma protein concentrations in these patients reducing fosphenytoin binding and increasing the concentration of fosphenytoin available to be cleared.

Because treatment of status epilepticus often includes concomitant administration of phenytoin and diazepam, a drug interaction study of fosphenytoin with diazepam was performed. Neither drug affected the pharmacokinetics of the other. However, submaximal doses of fosphenytoin and diazepam were used in the study.

The analytical methodology presented throughout the NDA was a validated assay. However, commercially available fluoresence immunoassays for phenytoin are routinely used to monitor phenytoin plasma concentrations. Cross-reactivity of these assays to fosphenytoin occurs.

Differences in fosphenytoin disposition between age, gender, race or any other sub-group were not observed and there is no evidence of atypical phenytoin pharmacokinetics due to differences in fosphenytoin disposition between individuals.

Recommendation:

The Human Pharmacokinetics and Bioavailability portion of New Drug Application 20-450 meets the requirements of the Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology and Biopharmaceutics. Our labeling revisions have been included in the comprehensive copy of labeling provided as Appendix 1 of this review. Please note the **"Comments to the Medical Officer"** below.

Comments to the Medical Officer:

1. Study 98207, Conversion Of CI-982 To Phenytoin In Patients With Renal Or Hepatic Disease - A Pilot Study, was performed at low dose and low rate of fosphenytoin (250 mg at 8.3 mg / min), and did not measure free phenytoin. The use of low dose and low rate fosphenytoin is not optimal because the conditions with greatest potential for maximal deviation from the norm are high dose and high rate. Failure to measure free phenytoin is problematic because it is free phenytoin which would be best correlated with efficacy and toxicity. Although the results obtained do allow the sponsor to label that fosphenytoin clearance is enhanced in patients with renal or hepatic disease, they are of little value in advising a clinician on how to administer high dose and high rate fosphenytoin (as would be recommended in status epilepticus) to individuals who are hepatically or renally compromised.
This study does demonstrate that neither renal nor hepatic disease have marked effects on the extent of conversion of fosphenytoin to phenytoin.

2. Study 98211, Evaluation Of The Pharmacokinetic Interaction Between Diazepam and CI-982 In Healthy Male Volunteers, was performed at submaximal dose and rate of fosphenytoin (750 mg at 50 mg / min) and submaximal dose of diazepam (10 mg at 5 mg / min). Diazepam, in status epilepticus, can be administered at doses up to 30 mg / 30 min. Although a drug interaction was not observed in this study, the conditions with greatest potential for maximal deviation from the norm (maximal dose and rate) were not studied.

List of Studies

Dose Ranging and Tolerance
- 98201 -- IV fosphenytoin

Bioavailability
- 98202 -- IV fosphenytoin and IV phenytoin
- 98210 -- IV fosphenytoin and IV phenytoin
- 98206 -- IM fosphenytoin and IV phenytoin

Bioequivalence
- 98220 -- IV fosphenytoin and IV phenytoin
- 98224 -- IV fosphenytoin and IV phenytoin

Dose Proportionality
- 98218 -- IV fosphenytoin

Clinical
- 98205 -- IM and IV fosphenytoin substituted for PO phenytoin in epileptic patients
- 98213 -- IM fosphenytoin substituted for PO phenytoin in epileptic patients
- 98214 -- IM fosphenytoin for seizure prophylaxis in neurosurgery patients
- 98215 -- IV fosphenytoin or IV phenytoin for seizure prophylaxis in neurosurgery patients
- 98216 -- IV fosphenytoin in status epilepticus patients

Special Populations
- 98207 -- IV fosphenytoin in hepatically compromised and renal failure patients

Drug Interaction
- 98211 -- IV fosphenytoin and IV diazepam

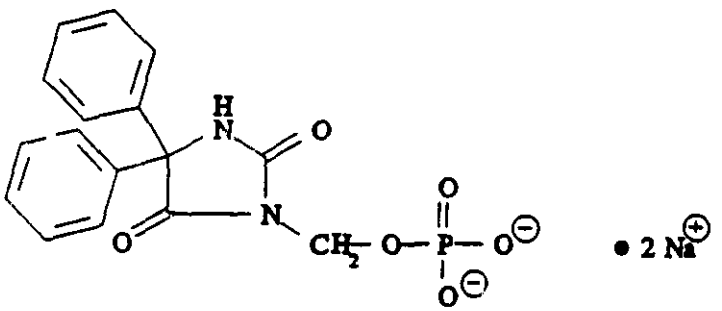
Research Reports
- RR 764-02124 -- protein binding of fosphenytoin and phenytoin
- RR-X 764-02114 -- pharmacokinetic meta-anlysis of fosphenytoin clinical trials
- RR 764-02074 -- cross-reactivity of fosphenytoin in phenytoin immunoassays
- RR 764-02073 -- stability of fosphenytoin in blood and plasma containing heparin or EDTA

Introduction

The following (pp. 7 - 9) are excerpted from the NDA and provide a suitable introduction to the pharmacology and chemistry of fosphenytoin. Statements regarding BA/PK/PD within this Introduction are the sponsor's contentions and not necessarily the reviewer's conclusions.

The nomenclature for fosphenytoin is as follows:

Structural Formula



Molecular Formula	$C_{16}H_{13}N_2O_6PNa_2$
Molecular Weight	406.24
Chemical Name	5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
Code Designations	CI-982 disodium salt PD 135711-15B 9653
USAN	Fosphenytoin sodium
CAS Registry Number	92134-98-0
Other Name	Cerebyx®

Fosphenytoin sodium (hereafter referred to as fosphenytoin) is a prodrug of the anticonvulsant phenytoin, intended for parenteral administration. Fosphenytoin is rapidly and completely converted to phenytoin in vivo. The pharmacological effects of phenytoin derived from fosphenytoin are essentially the same as those of parenteral phenytoin. The anticonvulsant effects of phenytoin have not been observed with fosphenytoin prior to conversion to phenytoin.

2.3.2. Scientific Rationale

Parenteral phenytoin is used for the acute treatment and control of seizures in patients with status epilepticus, for the treatment or prophylaxis of seizures in patients with epilepsy or in neurosurgical patients, and as a substitute for oral phenytoin when oral administration is not feasible. The current parenteral formulation is prepared in a vehicle of 40% propylene glycol and 10% ethanol adjusted to pH 12 with sodium hydroxide, and can be administered either intravenously or intramuscularly. Intravenous administration of phenytoin often produces local pain and burning and has also been associated with hypotension, cardiac rhythm disturbances, and severe tissue necrosis following extravasation. Intramuscular administration of phenytoin is not widely used because its absorption is erratic and unreliable, it crystallizes at the injection site, and it also produces local reactions.

Unlike phenytoin, fosphenytoin is freely soluble in aqueous solutions and is formulated in TRIS buffer at a pH of 8.6 to 9.0. Fosphenytoin is rapidly and completely converted to phenytoin in vivo. Parke-Davis developed fosphenytoin as an alternative to parenteral phenytoin based on the assumption that its formulation without organic solvents at a lower pH would result in better injection- or infusion-site tolerance and fewer of the complications associated with parenteral phenytoin administration. The development program focused on demonstrating bioequivalence between fosphenytoin and phenytoin and the safety of fosphenytoin. Since fosphenytoin is a phenytoin prodrug and no new therapeutic claims are being made beyond those already approved for parenteral phenytoin, proof-of-efficacy studies were not conducted.

2.3.3. Potential Clinical Benefits

Fosphenytoin is rapidly and completely converted to phenytoin. With IV administratior of equimolar loading doses at the proper rate, fosphenytoin produces plasma concentrations of unbound phenytoin that are equivalent to those of IV Dilantin. Fosphenytoin administered IM is readily absorbed and is fully bioavailable. Fosphenytoin achieves therapeutic plasma phenytoin concentrations with the following clinical benefits:

- Fosphenytoin is significantly better tolerated at the injection or infusion site than parenteral Dilantin.

- Intravenous administration of fosphenytoin has fewer complications than parenteral Dilantin, including decreases in infusion rate because of local irritation or hypotension, changes in the IV site, and complications from infiltration.

- Fosphenytoin can be mixed with normal saline or 5% dextrose in water and administered without an in-line filter.

- Fosphenytoin offers IM administration as a viable alternative route.

2.3.4. Intended Use

This New Drug Application (NDA) supports the short-term (up to 14 days) use of fosphenytoin for the acute treatment and control of seizures in patients with status epilepticus, for the treatment or prophylaxis of seizures in patients with epilepsy or in neurosurgical patients, and as a substitute for oral phenytoin when oral administration is not feasible.

Bioequivalence

It is imperative to read IMPORTANT NOTE on p. 3 before reading the following.

As stated in the Introduction, the sponsor did not perform proof-of-efficacy studies with fosphenytoin, and desires that the drug be approved on the basis of bioequivalence with phenytoin.

Because phenytoin is highly (≈ 90%) protein bound in vivo, free phenytoin is the specie of clinical importance. Studies 98220 and 98224 are crossover studies comparing plasma free phenytoin concentrations following IV administration of fosphenytoin and Dilantin.

Study No. and Description	No. Entered	Demography	Drug Administration						
			Drug, Route	Dose (mg)	Dose (mgPE)	Regimen	Rate (mg PE/min)	No. of Participants	Duration of Dosing
982-020	Total	Age Range	FOS, IV	1800	1200	Single dose	50	12	Single dose
	12	18-49	DIL, IV	1200	1200	Single dose	50	12	Single dose
Double-blind, randomized, placebo-controlled, 3-way crossover, single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects			PBO, IV[a]	NA	NA	Single dose	NA	12	Single dose
	Treatment	Gender							
	12 PBO	12 Males							
	12 FOS	0 Females							
	12 DIL								
	Analyzed[c]	Race							
	12 FOS	10 White							
	12 DIL	1 Black							
		1 Other							
982-024	Total	Age Range							
	12	20-42	FOS, IV	1800	1200	Single dose	100	12	Single dose
			FOS, IV	1800	1200	Single dose	150	12	Single dose
Nonblind, randomized, 3-way crossover, single-dose, single-center, safety, tolerance, and pharmacokinetic study of IV fosphenytoin and Dilantin in healthy subjects	Treatment	Gender	DIL, IV	1200	1200	Single dose	50	12	Single dose
	12 FOS	12 Males							
	12 DIL	0 Females							
	Analyzed[c]	Race							
	12 FOS	10 White							
	12 DIL	2 Other							

The results from these studies are excerpted on the following page.

TABLE 3. Comparison of Mean Free Phenytoin Pharmacokinetic Parameter Values Following IV Administration of 1200 mg Fosphenytoin and Dilantin (N = 12): Studies 982-20 and -24

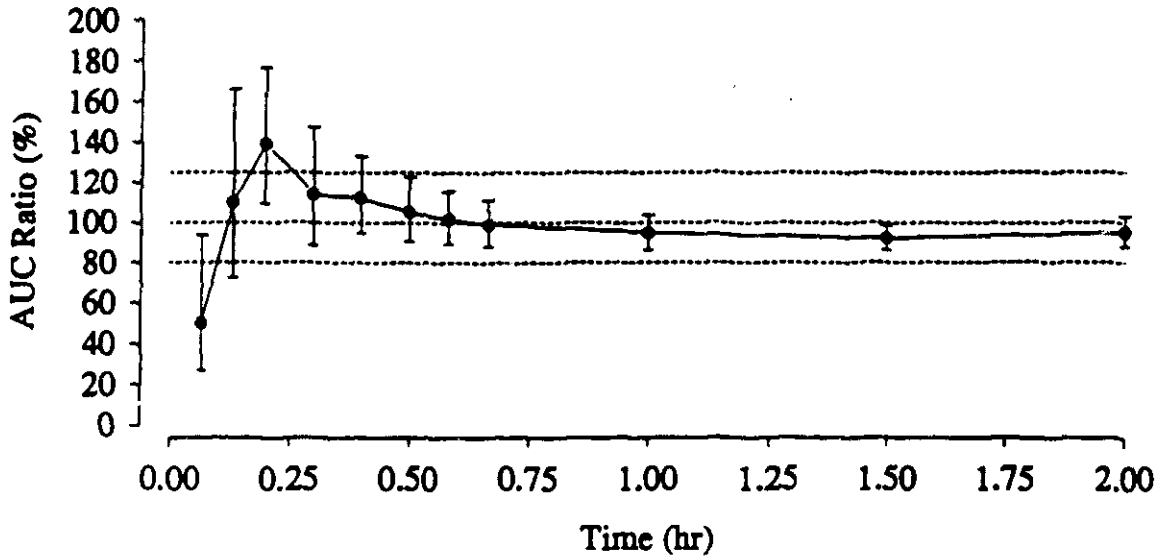
Parameter	Fosphenytoin		Dilantin		Ratio	90% Confidence[a] Interval
	Mean	%RSD	Mean	%RSD		
	50 mg/min		50 mg/min			
Cmax, µg/mL	2.58	20.4	4.04	33.2	64.6[b]	53.8 - 77.8[b]
tmax, hr	0.49	35.2	0.46	22.2	108.2	94.7 - 121.7
AUC(0-tldc), µg·hr/ml	66.1	30.9	74.1	24.8	87.2[b]	83.0 - 91.7[b]
	100 mg/min		50 mg/min			
Cmax, µg/mL	2.78	21.8	3.30	25.6	84.7[b]	72.7 - 98.8[b]
tmax, hr	0.52	37.0	0.53	17.3	99.5	69.7 - 129.2
AUC(0-tldc), µg·hr/mL	79.5	14.1	87.1	22.0	92.2[b]	88.4 - 96.2[b]
	150 mg/min		50 mg/min			
Cmax, µg/mL	3.18	28.3	3.30	25.6	95.8[b]	82.1 - 111.7[b]
tmax, hr	0.57	58.5	0.53	17.3	109.5	79.8 - 139.3
AUC(0-tldc), µg·hr/mL	85.5	16.6	87.1	22.0	98.9[b]	94.8 - 103.2[b]

Mean = Arithmetic mean of untransformed data.
%RSD = Relative standard deviation (% of mean value).
Ratio = Ratio of treatment least-squares mean values (Fosphenytoin/Dilantin) expressed as a percentage.

[a] 90% Confidence Interval is the 90% confidence estimate for ratio of treatment least-squares mean values.

[b] These values are based on antilogs of treatment least-squares mean values.

Study 98224 demonstrates that, using standard bioequivalence criteria on free phenytoin data, 1200 mg IV fosphenytoin at 150 mg / min is bioequivalent to 1200 mg IV Dilantin at 50 mg / min based on AUC and Cmax. Dissimilarly, at the 100 mg/min rate and using free phenytoin data, fosphenytoin and Dilantin are equivalent for AUC but not equivalent for Cmax.



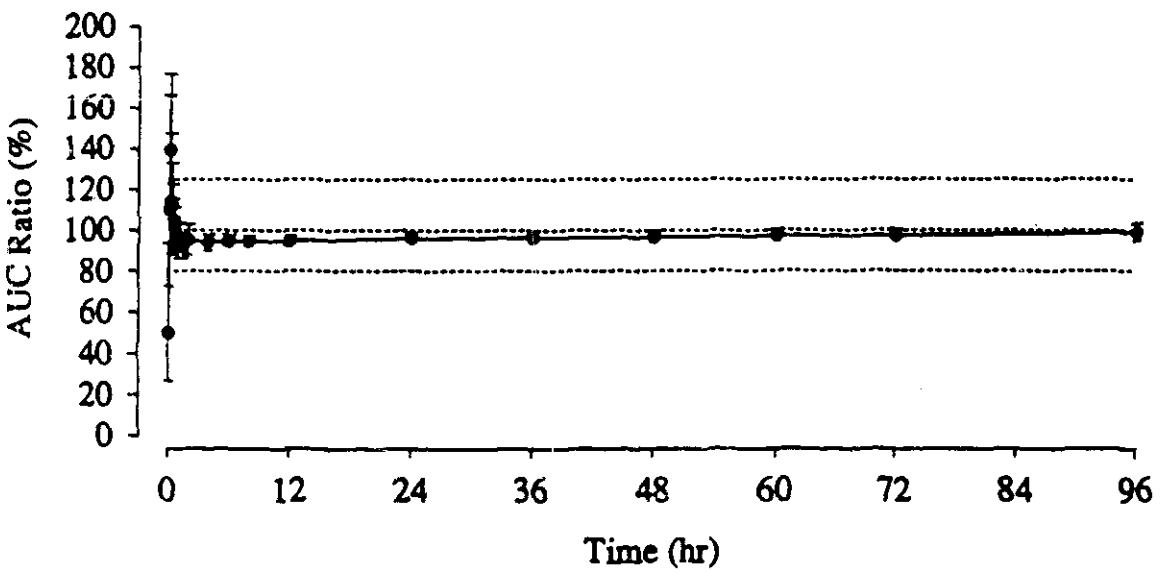


FIGURE 13. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 150 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

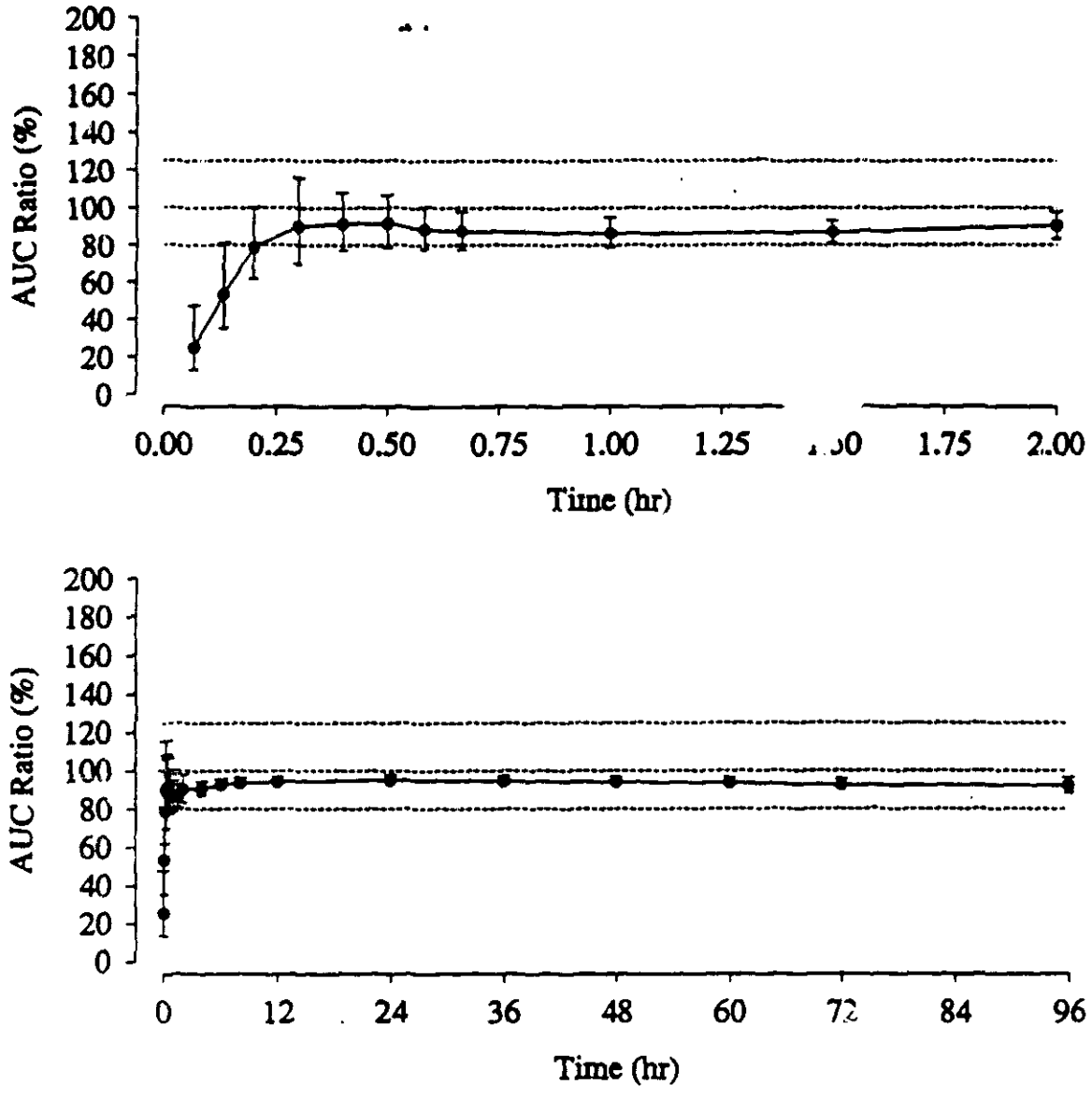


FIGURE 14. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 100 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

One of the desired indictions for fosphenytoin is acute status epilipticus. Efficacy in this disorder is presumably due to rapid attainment of high concentrations of plasma free phenytoin. Therefore, free phenytoin $AUC_{(0-TLDC)}$ may not be a measure of relevant exposure, and the sponsor was requested to calculate, across the first 2 hours post-initiation of dosing, the ratio of cumulative free phenytoin AUC from fosphenytoin administration to that from phenytoin administration. At both the 100 and 150 mg/min infusion rates, the 90% confidence interval for Cumulative AUC falls within the 80 - 125% range from about 30 minutes onward.

Studies 98220 and 98224 are the only investigations which attempt to show bioequivalence of free phenytoin from fosphenytoin and Dilantin. They provide a scientific basis for dosing recommendations when maximal dose / infusion rate is desired (eg. status epilepticus).

Fosphenytoin Pharmacokinetics

Plasma fosphenytoin concentrations increase with increasing dose and infusion rate and then decline with a terminal $t_{1/2}$ of approximately 0.25 hr independent of dose and infusion rate.

Fosphenytoin clearance is dependent upon both dose and infusion rate. Fosphenytoin is highly bound to plasma albumin (approximately 95 % bound at Cmax following high dose / high rate administration), and the changes in clearance are hypothesized to be a result of nonlinear protein binding: as dose and infusion rate increase, higher plasma fosphenytoin concentrations are attained, protein binding saturates, more free fosphenytoin is available to be metabolized, and fosphenytoin clearance is enhanced. The figure below illustrates the changes in clearance observed with changes in dosing regimen.

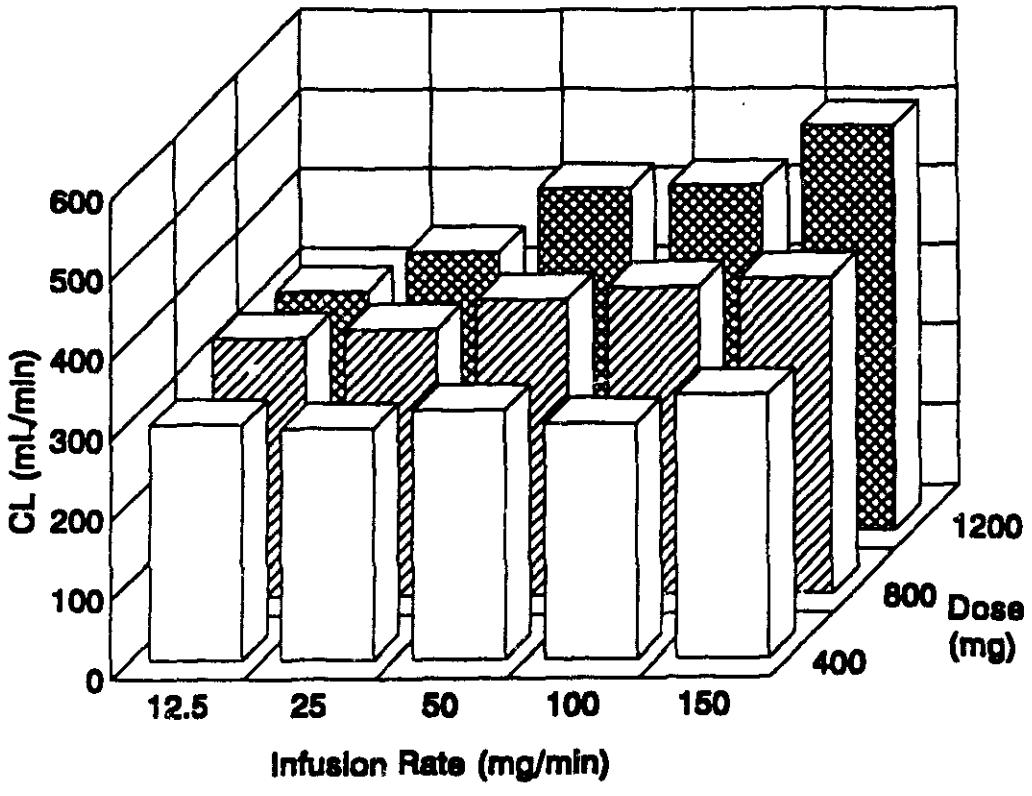


FIGURE 1. Relationship Between Mean Fosphenytoin Clearance Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects

The effect of the above mentioned changes in clearance on the concentration-time profile are not easily summarized. No structure exists which allows for the change in clearance to be used to describe changes occuring "early" in the concentration-time profile. What is meant by "early" is prior to the terminal linear phase of elimination. The sponsor has shown that concentration-dependent changes in clearance are accompanied by proportional changes in fosphenytoin volume of distribution during the terminal linear phase of metabolism (Vd_{area} varies from 4.3L when 100 mg is infused at 3.3 mg / min to 10.8 L when 1200 mg is infused at 150 mg / min). These Vd changes are consistent with a protein binding interaction model: as concentration increases free fraction increases and drug leaves plasma. The combination of increased clearance with increased Vd_{area} result in a constant elimination $t_{1/2}$.

Independent of dose, route or rate of administration, fosphenyotin is a short lived specie. The total number of individuals receiving serial sampling in studies 98213, 14, 15,

16, 18, 20 and 24 was 124. Of these 124 only 7 (< 6%) had detectable fosphenytoin plasma concentrations at 5 or more hours post-initiation of administration.

Based upon equal AUC of total phenytoin from IV phenytoin and from fosphenytoin, it appears that conversion of fosphenytoin is essentially complete.

Special Populations

A study with renal failure patients and hepatically compromised patients was performed. Before examining the first table below (Table 3.), please note that the values listed for Cmax, AUC, Cl and Vd require adjustment -- the values for Cmax and AUC can be determined by multiplying the table values by 0.753. The values for Cl and Vd can be determined by dividing the table values by 0.753. The values for Tmax, lambda$_z$ and $t_{1/2}$ do not require adjustment. The second table below (Table 7.) is for phenytoin and no correction factor is required.

TABLE 3. ACC-9653 PHARMACOKINETIC PARAMETERS
(MEAN ± SD)

note: portions of this table require correction -- see text above

Parameter (Units)	Volunteer Group Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (µg/mL)	35.6 ± 13.2[a]	25.9 ± 10.5	43.4 ± 6.9
T_{max} (min)	30.1 ± 8.1[a]	28.7 ± 5.9	31.8 ± 1.4
λ_z (hr^{-1})	5.59 ± 2.20	10.42 ± 3.85[c]	4.71 ± 1.61
$t_{1/2}$ (min)	8.56 ± 3.91[b]	4.36 ± 1.77[b]	9.51 ± 2.71[b]
AUC_{0-T} (µg*hr/mL)	17.8 ± 8.6	12.9 ± 5.7	25.5 ± 6.2
$AUC_{0-\infty}$ (µg*hr/mL)	17.9 ± 7.9	13.0 ± 5.7	25.5 ± 6.2
Cl (L/hr)	21.3 ± 8.4	29.3 ± 11.7	13.7 ± 3.7
Cl (L/hr/kg)	0.291 ± 0.142	0.337 ± 0.147	0.158 ± 0.047
V_d (L)	4.04 ± 1.50	2.80 ± 0.57	2.97 ± 0.43
V_d (L/kg)	0.0528 ± 0.0193	0.0327 ± 0.0108	0.0344 ± 0.0077

(a) - N=3

(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 7.44 ± 2.93, 3.99 ± 1.88, and 8.83 ± 3.36 minutes for the renal, hepatic, and healthy volunteer groups, respectively.

(c) - Significant difference from healthy subjects ($p < 0.05$). (Hepatic ≠ Healthy)

TABLE 7. PHENYTOIN PHARMACOKINETIC PARAMETERS
(MEAN ± SD)

Parameter (Units)	Volunteer Group		
	Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (μg/mL)	4.59 ± 1.28[a]	4.41 ± 1.33	4.28 ± 0.62
T_{max} (hr)	0.79 ± 0.39[a]	0.71 ± 0.22	1.3[a] ± 0.51
λ_n (hr^{-1})	0.0421 ± 0.0132	0.0293 ± 0.0108	0.0338 ± 0.0077
$t_{1/2}$ (hr)	17.8 ± 5.8[b]	26.5 ± 11.2[b]	21.3 ± 4.8[b]
$AUC_{0-\tau}$ (μg•hr/mL)	59.9 ± 17.4	58.4 ± 11.1	62.2 ± 9.4
$AUC_{0-\infty}$ (μg•hr/mL)	97.4 ± 40.9	104.7 ± 27.2	112.1 ± 26.6

(a) - N=3.
(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 16.5 ± 5.6, 23.7 ± 7.9, and 20.5 ± 4.8 hours for the renal, hepatic, and healthy volunteer groups, respectively.
No statistically significant differences were observed between volunteer groups ($p > 0.05$).

Using the corrected values, fosphenytoin clearance is more than 2-fold as great in cirrhosis patients and about 1.8-fold as great in renal failure patients than in healthy volunteers; however, it should be noted than the number of patients in each group of this study is small. Based on these data plasma concentration monitoring for patients with renal and hepatic disease is recommended in labeling.

Visual inspection of fosphenytoin concentration-time profiles does not show differences across age, gender, race or any other sub-group. This is consistent with the fact that phosphatase activity is extensive and differences between individuals are likely to result in little or no difference in the conversion of fosphenytoin to phenytoin.

The conversion of fosphenytoin to phenytoin is consistent and essentially complete. There is no evidence of atypical phenytoin pharmacokinetics due to differences in fosphenytoin disposition between individuals.

Drug interactions

Standard treatment for status epilepticus at many institutions includes concomitant administration of IV diazepam and IV phenytoin. Therefore, the sponsor performed a drug interaction study examining the effect of concomitant administration of fosphenytoin and diazepam on the pharmacokinetic profiles of fosphenytoin, diazepam and phenytoin derived from fosphenytoin. No differences in the kinetics of fosphenytoin, phenytoin or diazepam occurred. However, the doses of fosphenytoin and diazepam used in the study were submaximal: 750 mg of fosphenytoin was administered, labeling is for up to 20 mg/kg (1400 mg in a 70 kg individual). Ten mg of diazepam was administered, labeling is for doses up to 30 mg. Thus, conditions likely to show an interaction (maximium dose of both agents) were not examined.

The metabolism of fosphenytoin to phenytoin is accomplished by phosphatases. Since phosphatases are generally not responsible for xenobiotic drug metabolism, pharmacokinetic drug interactions between fosphenytoin and agents which are not phosphate pro-drugs are unlikely. Given the abundance and wide distribution of phosphatases, it is unlikely that drug interactions between fosphenytoin and other phosphatase-converted pro-drugs would be significant.

IM administration

Because phenytoin is not usually administered IM, fosphenytoin IM was compared to phenytoin PO and phenytoin IV.

Average absolute bioavailability of phenytoin derived from a maintenance dose (250 mg) of IM fosphenytoin administered to healthy volunteers is 101% (Study 98206).

In epilepsy patients being maintained on PO Dilantin, substitution of equimolar IM fosphenytoin for PO Dilantin results in an increase in $Cmax_{free\ phenytoin}$ (38%), $AUC_{free\ phenytoin}$ (24%), and $trough_{free\ phenytoin}$ (16%) (study 98213). This observed increase in Cmax may be due to differences in dosing frequency: PO Dilantin was administered QID while IM fosphenytoin was given QD.

Formulation

Only one fosphenytoin formulation (the to-be-marketed formulation) was studied clinically.

Analytical methods

Page
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Response to EIRs identified in 483 Forms

Following site inspections for the 98214, 98218 and 98224 studies, the Division of Scientific Investigations issued multiple Form 483 to Parke-Davis. A review of the EIRs detailed in these 483 is provided as Appendix 5. We find that two of the EIRs need be addressed. The first is identified as 1. in Appendix 5 and is reproduced below.

1. Reported fosphenytoin concentrations were in error since the water content of the fosphenytoin reference standard was not taken into account in calculations.

The water content of the fosphenytoin sodium reference material was reported to be 22.5%. The salt form represented only 77.5% of the weight of the undried powder. The firm did not dry the powder on the grounds that the material was unstable with respect to heat. Therefore, the reported concentrations of fosphenytoin in plasma are in error, and need to be corrected. Similarly, some of the derived pharmacokinetic parameters for fosphenytoin (Cmax, AUC, CL, Vd) require correction.

In response to the identification of this deficiency, Parke-Davis audited the NDA to determine if errors in the calculation of fosphenytoin concentrations occured in studies other than 98214, 98218 and 98224. A portion of their conclusions is presented on the following page.

Parke Davis-generated studies

As noted in the October 19, 1995, submission, fosphenytoin concentrations and estimates of fosphenytoin Cmax, AUC, CL and Vd in clinical trials conducted by Parke-Davis may be corrected by applying a correction factor of 0.753. Fosphenytoin free fraction, tmax, elimination rate and half life estimates are unaffected as their estimation does not depend on the absolute value of concentrations used in their derivation. Therefore, parameters documenting the rate of fosphenytoin conversion to phenytoin are not affected. Further, phenytoin and free phenytoin concentrations, whether derived from Dilantin or fosphenytoin, are unaffected and thus the bioequivalency of fosphenytoin and phenytoin as presented in the pending NDA are not affected.

generated studies

Our submission of October 19, 1995, indicated that we were attempting to determine if the fosphenytoin concentrations reported in the initial studies generated by were also in error. We have since determined that these concentrations in the clinical studies are most likely in error. We have determined the lot number and water content of fosphenytoin reference standard used in Protocols 982-007 (renal and hepatic disease) and 982-011 (diazepam interaction). Our findings indicate that it is likely that fosphenytoin concentrations and parameters in these reports can be corrected by applying the same correction factor used in Parke-Davis studies. Since these reports were prepared by we have not modified the original reports, but have added appropriate information to the cover page. Lot numbers, and thus the water content, of fosphenytoin reference standards used in other studies cannot be unequivocally determined at this time. We have also added information identifying this potential problem to the cover pages of these reports. These early studies document phenytoin pharmacokinetics following low fosphenytoin doses (Studies 982-1,3), the absolute bioavailability of phenytoin following intravenous and intramuscular fosphenytoin dosing (Studies 982-2,5,6,10), the effects of hepatic and renal insufficiency on fosphenytoin conversion to phenytoin (Study 982-7), and a diazepam-phenytoin drug-drug interaction study following fosphenytoin administration (Study 982-11). These studies are intended to address questions of rate and extent of fosphenytoin conversion to phenytoin. Parameters used to reflect these processes (fosphenytoin half-life and phenytoin AUC, Cmax, and tmax) are unaffected. Therefore, the conclusions from these studies are not affected by our inability to accurately modify the fosphenytoin concentrations in these early studies.

The errors in fosphenytoin concentrations have NOT been accounted for in the individual study reports (Appendix 2). The values have little bearing on the interpretation of studies -- the specie of clinical interest is generally plasma phenytoin, not plasma fosphenytoin.

The second EIR of significance is identified as 3. in Appendix 5 and is reproduced below.

3. Failure to use the appropriate matrix to prepare QC samples for validating stability in storage and reliability of the ultrafiltration step (assays of free phenytoin in plasma ultrafiltrate) and for validating stability in frozen urine.

The assay for phenytoin in sample plasma ultrafiltrate included the following stages: frozen storage, thawing, possible refreezing and rethawing, ultrafiltration, dilution, extraction, and chromatography. In the case of the QC samples, used both for validating stability in storage and monitoring daily performance of the assay, the stages of frozen storage, thawing, and freeze/thaw cycles were conducted after ultrafiltration, out of the sequence for study samples. Thus, the possibilities that phenytoin stability was different in PUF vs. plasma, that the binding proteins were unstable, and that the binding equilibria between free and protein-bound phenytoin disproportionated during frozen storage, thawing, or freeze/thaw cycles, were not investigated. The recovery of free phenytoin during the ultrafiltration stage was not established. The within-day and between-day variability of the ultrafiltration stage was not considered. The reproducibility of the ultrafiltration stage was not monitored during the assay of subject samples, because plasma-based QC samples were not ultrafiltered with each run.

QC samples for the assay of phenytoin in PUF should have been prepared in fresh whole plasma. The firm replied that phenytoin stability in whole plasma was demonstrated, and contended that this established stability of phenytoin measured in PUF. The considerations outlined in the previous paragraph (differences in

stability, stability of binding proteins, disproportionation, recovery, ultrafiltration variability) were not addressed.

There is literature evidence that plasma proteins do not degrade with multiple freeze/thaw cycles, and there is also literature evidence that plasma phenytoin can be stored frozen for lengthy periods of time without degradation of phenytoin. The NDA provides evidence that fosphenytoin is stable when stored frozen in plasma. However, because of the improper handling of the standards, we cannot categorically rule out the possibility that differences in stability of fosphenytoin, phenytoin and/or binding proteins, did occur between the samples assayed in studies 98214, 98218 and 98224. We believe that such differences likely did not occur, but this belief is not based upon empirical evidence from the studies themselves.

Sign-off

This review was presented to the Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology and Biopharmaceutics on December 18, 1995. Attendees:

Office of Clinical Pharmacology and Biopharmaceutics: Drs. Lesko, Malinowski, Chen, Gillespie, Baweja, Harris, Miller, Williams

Division of Neuropharmacologic Drug Products: Drs. Leber, Feeney, Fitzgerald, Fisher

FT Robert Z. Harris 12/21/95 Robert Harris, Ph.D.

FT R. Miller 12/21/95 Raymond Miller, Ph.D.

FT Gene Williams 12/21/95 Gene Williams, Ph.D.

FT R. Baweja 12/21/95 Raman Baweja, Ph.D.
Team Leader

cc: NDA 20-450 (orig), HFD 120, HFD 860 (Harris, Miller, Williams, Baweja, Malinowski), HFD 340 (Viswanathan), HFD 019; Drug, Chron, and Reviewer files

APPENDIX 1

28 Pages

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APPENDIX 2

STUDY: A dose ranging tolerance study of CI-982 in healthy volunteers: A single center study

PROTOCOL NUMBER: 982-01 (9653-86-01)

RESEARCH REPORT NUMBER: RR 744-00024

STUDY DESIGN: This was a single blind, dose-ranging study with randomized placebo control. The drug was administered by iv infusions over 30 minutes. The dose administered was: 150 mg (n=5), 300 mg (n=4), 600 mg (n = 4), and 1200 mg (n=3). The maximum infusion rate was 40 mg/min. Blood was sampled up to 72 hours after the initiation of the infusion.

DOSAGE FORM: See Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

SAFETY RESULTS: No adverse experiences were reported at the 300 and 600 mg dose. Minor CNS adverse reactions including lightheadedness, headache and nystagmus were reported at the 600 and 1200 mg doses. None of the subjects prematurely discontinued the study.

PHARMACOKINETIC RESULTS: The pharmacokinetic results are summarized in Table 1 below. Fosphenytoin was rapidly converted to phenytoin with a half-life of approximately 7.7 minutes. Fosphenytoin appeared to display linear kinetics in this concentration range. This result is consistent with later studies because the highest dosage in this study (1200 mg fosphenytoin at a rate of 40 mg/min = 800 mg phenytoin equivalents at a rate of 27 mg/mL) is lower than the dosages at which nonlinearities have been observed. Phenytoin kinetics were consistent with those previously reported. Thus, at the relatively low doses used in this study it does not appear that fosphenytoin has a large effect on phenytoin pharmacokinetics. Subtle changes in phenytoin pharmacokinetics would not have been detected in this type of study.

CONCLUSIONS: In healthy volunteers, fosphenytoin is safely administered at the highest level studied (1200 mg given over 30 minutes). It is rapidly converted to phenytoin.

Table 1. Fosphenytoin and phenytoin pharmacokinetic parameters. Values are mean ± standard deviation.

	FOSPHENYTOIN				PHENYTOIN			
DOSE (mg)	Cmax (μg/mL)	CL (L/hr)	Vc (L)	T1/2 (min)	Cmax (μg/mL)	CL (L/hr)	Vc (L)	T1/2 (hr)
150	19.9 ±2.6	13.3 ±2.0	2.5 ±0.3	7.75 ±0.5	2.2 ±0.4	3.1 ±1.3	48 ±11	10.7 ±2.2
300	36.0 ±4.6	14.2 ±3.2	3.0 ±0.3	8.93 ±1.2	4.1 ±0.4	2.8 ±1.0	48 ±4.9	14.7 ±10.2
600	70.3 ±5.0	14.0 ±2.2	2.4 ±0.3	7.23 ±0.2	6.9 ±0.7	3.2 ±0.4	59 ±6.4	12.5 ±0.4
1200	135 ±13.0	14.2 ±1.8	2.3 ±0.5	6.55 ±7.4	18.8 ±1.3	1.4 ±0.3	41 ±1.5	20.4 ±3.9

STUDY: Absolute bioavailability of phenytoin after intravenous CI-982 administration of healthy male volunteers

PROTOCOL NUMBER: 982-02 (9653-86-02)

RESEARCH REPORT NUMBER: RR 744-00025

STUDY DESIGN: This was a randomized, open-label, two treatment crossover. The 250 mg phenytoin and 375 mg fosphenytoin doses were administered by iv infusions over 30 minutes. Twenty six blood samples were obtained per treatment up to 120 hours after drug infusion. Total drug concentration in the plasma was measured at all time points, total concentration in the blood was measured at six of the collection times points, and unbound concentration in the plasma was measured at two time points (at the end of the infusion and 30 minutes after the end of the infusion). Treatments were separated by two weeks.

SUBJECTS: Healthy male volunteers (n=12).

DOSAGE FORM: See Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study, and the temperature at which ultrafiltration was performed is not clear from the study report.

SAFETY RESULTS: No major adverse reactions were observed in this study. Fosphenytoin injection caused less injection site irritation than did phenytoin injection.

PHARMACOKINETIC RESULTS: The bioavailability of phenytoin after iv fosphenytoin administration compared to after iv phenytoin administration was 99.2% ± 0.031 (because of the low variability the two dosages are actually bioequivalent in terms of AUC; Table 3). The concentration time profiles were similar but not superimposable at early time points (Figure 1). The unbound fraction of phenytoin was highest immediately after the fosphenytoin infusion (Table 1, this result is consistent with fosphenytoin displacing phenytoin from plasma proteins. The effect is quite small because of the relatively small fosphenytoin dose used in this study). The blood to plasma ratio for fosphenytoin was approximately 0.5 for 5 of the six time points measured (Table 2). At the latest time point (3 hr) the ratio increased to approximately 2. This unexpected result is likely due to analytical errors caused by the very low fosphenytoin concentrations at this time point. As described in the analytical section above, the results of this part of the study are in question due to the use of heparin as the anticoagulant.

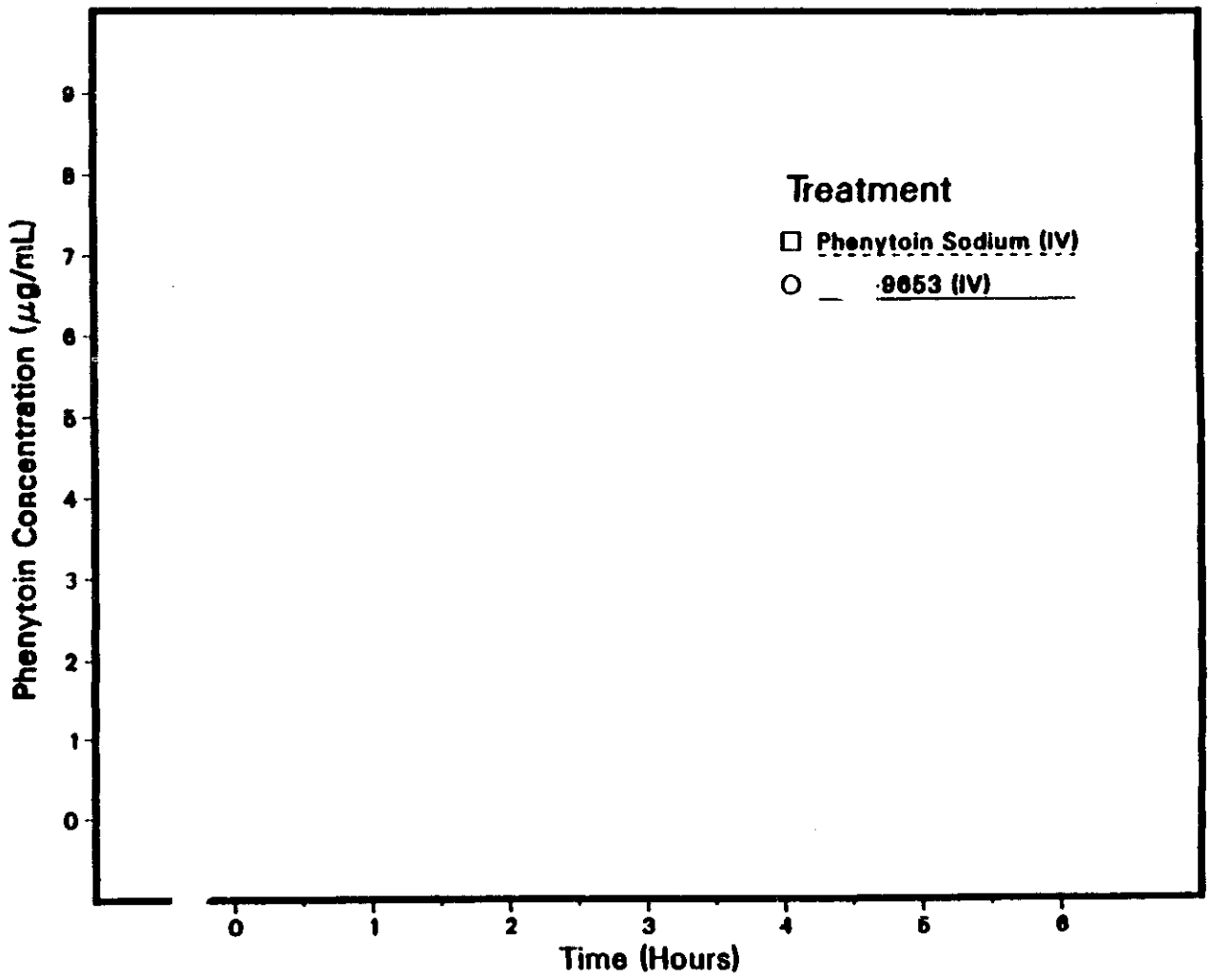
Bioavailability would have been better determined by a comparison of unbound AUCs instead of total AUCs. This is because bioavailability calculations are based on the assumption that clearance does not differ in the two treatments that are being compared. In this case, fosphenytoin can displace phenytoin from plasma proteins thereby increasing fu and total phenytoin clearance. Unbound clearance would not have been affected by this phenomenon and thus unbound AUC comparison would have been a better measure of bioavailability. However, because fosphenytoin is relatively short-lived in the plasma, and because the fu of phenytoin was only increased by approximately 1% due to fosphenytoin this effect should have had only a very

small influence on phenytoin AUC. The fact that the phenytoin concentration/time profiles were very similar for most of the time period also helps support the validity of the bioavailability conclusions made in this study.

CONCLUSIONS: Fosphenytoin is completely converted to phenytoin after intravenous administration. Fosphenytoin does not significantly distribute into red blood cells.

Figure 1
~~Figure 3~~

Mean Phenytoin Plasma Concentration Versus Time



* Significant difference between treatments.

Medical Summary
#9653-86-02

Table 1
~~Table 9~~

Mean Free Fraction of Phenytoin in Plasma -
Analysis of Difference Between Treatments At Each Time Point

Time Since Start	Free Fraction of Phenytoin (%)

* - Significant difference between treatments (P <0.05).

Table 2
~~Table 5~~

Mean Blood Concentration/Plasma Concentration Ratios
c ·9653 as a Function of Time

Time Since Start of Infusion (hr:min)	Ratio		
	N	Mean	(SEM)
0:10			
0:20			
0:30			
0:45			
1:00			
3:00			

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STUDY: Because of similarities, Studies 98205 and 98213 are being reviewed together. Evaluation of Phenytoin Levels After IM and IV ACC-9653 Administration in Epileptic Patients on Chronic Oral Dilantin Monotherapy (Protocol 9653-86-05 or 982-05). A 5-Day, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Clinical Study of Tolerance and Safety of Multiple Doses of Intramuscularly Administered Fosphenytoin Sodium (CI-982) Substituted for Oral Dilantin in Epilepsy or Neurosurgery Patients (Protocol 982-013).

PROTOCOL NUMBER: 982-05 (9653-86-05), 982-013

RESEARCH REPORT NUMBER: RR 720-03273, RR 720-03148

STUDY DESIGN: 98205 -- a 2 arm crossover where a single dose of IM fosphenytoin (150 - 450 mg; n = 38) and a single dose of IV fosphenytoin (150 - 450 mg; n = 40) were substituted for oral Dilantin in 42 epilepsy patients being maintained on oral Dilantin BID. A single trough concentration was taken 12 hrs after PO Dilantin. Serial sampling was performed for 12 hours following IM and IV fosphenytoin

98213 -- 5 doses (200 - 500 mg/day) of IM fosphenytoin (QD) were substituted for oral Dilantin in epilepsy patients being maintained on oral Dilantin QID. Serial sampling was performed prior to receiving fosphenytoin (day -1) and on day 5 following the final dose of fosphenytoin in 11 patients.

SUBJECTS: 98205;

age: 39.1 $\pm$ 12.0 yrs
38 white, 5 black
32 male, 11 female

98213; analyses performed by reviewer on evaluable population (those having free concentrations following both PO Dilantin and IM fosphenytoin):

age: 38.3 $\pm$ 9.2 yrs
6 white males, 3 white females, 1 black male, 1 black female

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in Study 98205. EDTA was used as an anti-coagulant and ultrafiltration performed at 37° C in Study 98213.

SAFETY RESULTS: 98205 -- Parenteral fosphenytoin was well tolerated by the patients. No clinically significant changes in blood pressure, heart rate, respiration, neurological status (except nystagmus), and the electrocardiogram were observed following either IM or IV treatment.

98213 -- There were no clinically significant differences in the type and frequency of adverse events between fosphenytoin and Dilantin treatment groups, and the adverse event profile was similar to that expected with phenytoin therapy.

PHARMACOKINETIC RESULTS: 98205 (single dose fosphenytoin) -- The data are presented on the following 3 pages (Figures 1 and 2; Table 1), and show that, as expected, IV administration produces a steeper rise in the concentration time profile than IM administration.

98213 (multiple dose fosphenytoin) -- The data are presented on pp 62-63 (Figure 3, Table 2). For at least the first 4 hrs post-administration, free concentrations of phenytoin following IM fosphenytoin administration are considerably greater than those following PO Dilantin administration (Figure 3). This is consistent with a protein binding interaction: when fosphenytoin is present phenytoin is displaced and free phenytoin concentrations increase. It is also consistent with the total phenytoin data: total phenytoin is more bioavailable from IM fosphenytoin than from PO Dilantin (Figure 3, Table 2). This increase in total phenytoin concentrations results in the increased free phenytoin concentrations noted.

Quantitatively, $Cmax_{free\ phenytoin}$ is 38% greater, $trough_{free\ phenytoin}$ is 16% greater and $AUC_{free\ phenytoin}$ is 24% greater, following fosphenytoin IM than following Dilantin PO (Table 2).

Figure 8

MEAN PHENYTOIN PLASMA CONCENTRATIONS AS A FUNCTION OF TIME AFTER IV ADMINISTRATION OF -9653

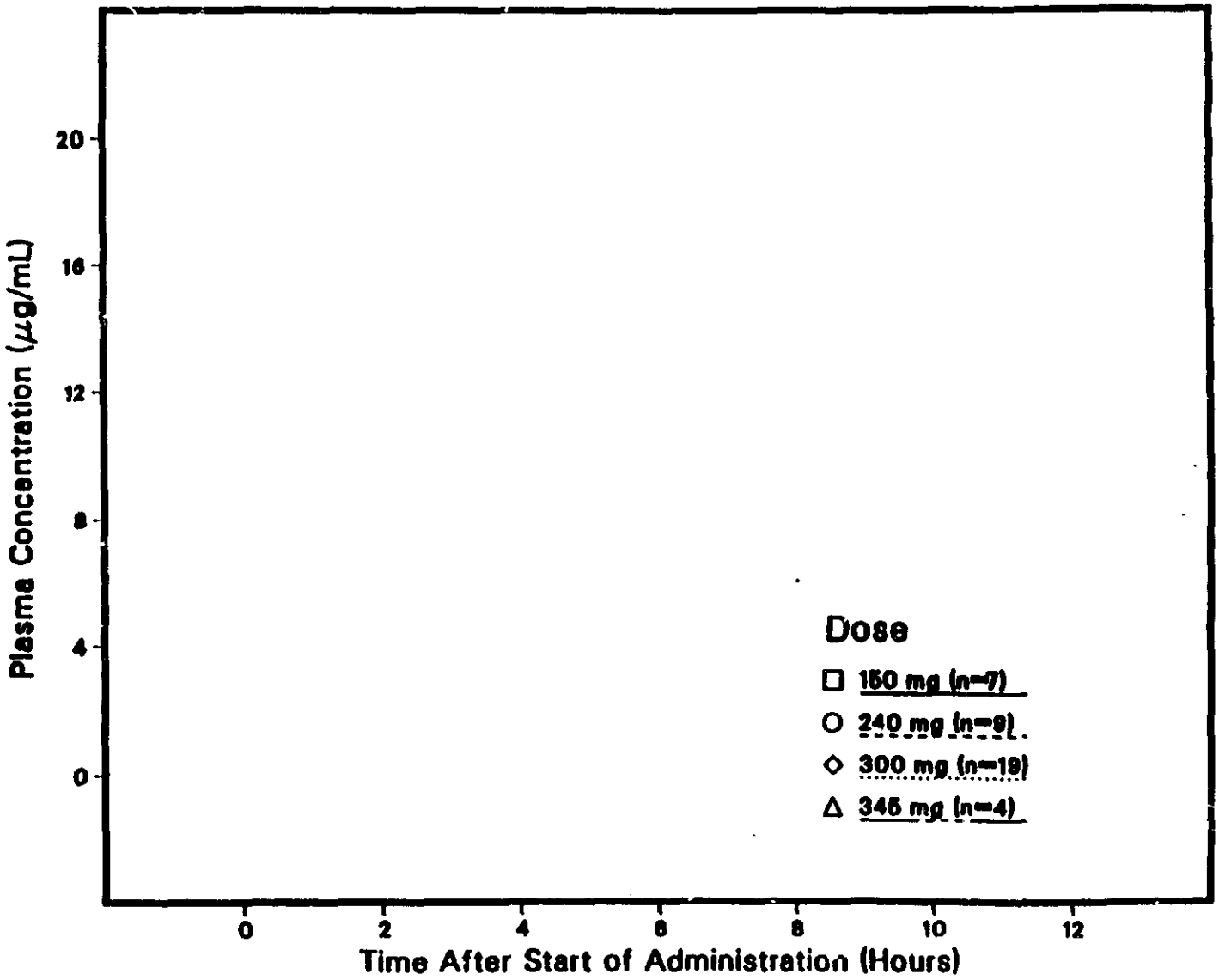


Figure ~~4~~ 2

MEAN PHENYTOIN PLASMA CONCENTRATIONS
AS A FUNCTION OF TIME AFTER IM ADMINISTRATION OF 9653

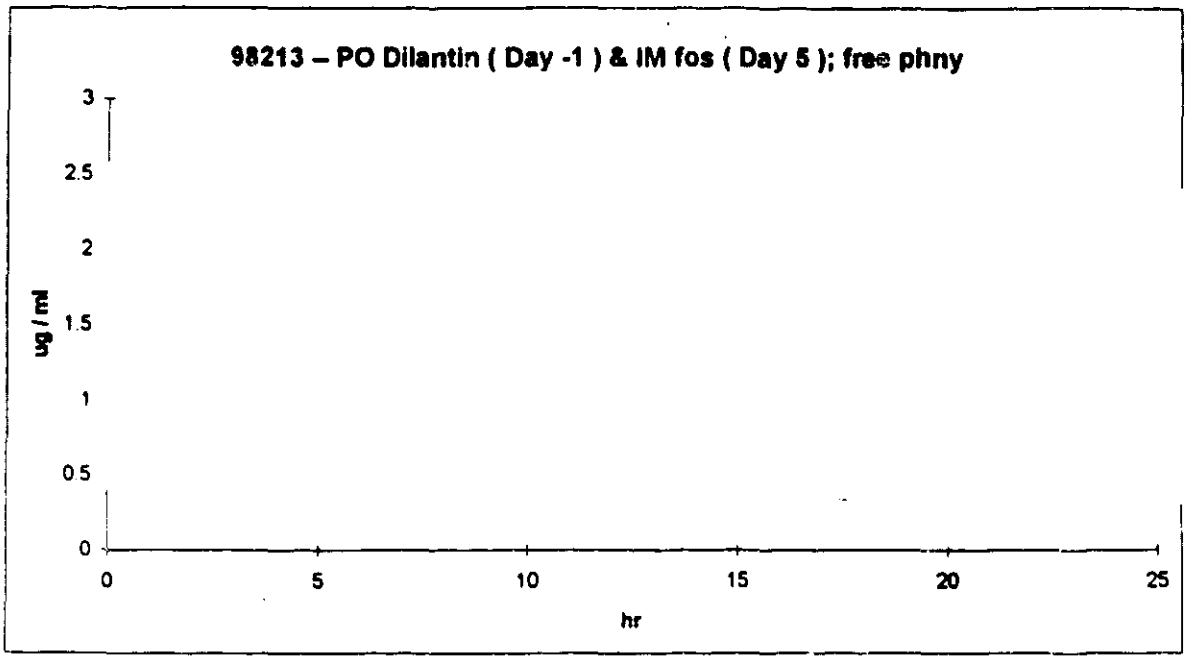
TABLE X

Trough Phenytoin Levels (µg/mL) After IV and IM Administrations of -9653*

Route	Dose (mg)	N	Baseline**	12 Hr Post 9653	Difference	P-Value
IV	150	7	12.0(1.6)	12.0(1.5)	0.0(0.7)	0.946
	195	1	22.8(-)	21.3(-)	-1.5(-)	
	240	9	11.3(1.7)	10.4(1.6)	-1.0(0.6)	0.128
	300	16	13.9(1.9)	14.3(2.0)	0.4(0.5)	0.435
	345	4	12.9(1.8)	16.3(3.3)	3.4(2.6)	0.279
	450	1	7.2(-)	6.0(-)	-1.3(-)	--
IM	150	6	12.7(1.7)	12.1(2.3)	-0.7(0.8)	0.420
	195	1	22.4(-)	21.1(-)	-1.3(-)	--
	240	9	12.0(1.8)	11.3(1.7)	-0.7(0.3)	0.056
	300	16	14.7(2.0)	14.7(2.1)	0.0(0.6)	0.985
	345	4	14.8(1.6)	15.3(1.9)	0.5(1.1)	0.687
	450	2	13.4(9.7)	15.6(10.1)	2.2(0.5)	0.129

* - All data are expressed as mean (SEM).
** - Concentrations were determined 12 hours after the patient's last dose of oral Dilantin®.

Figure 3


98213 – PO Dilantin (Day -1) & IM fos (Day 5); free phny
ug / ml
3
2.5
2
1.5
1
0.5
0
0
5
10
15
20
25
hr

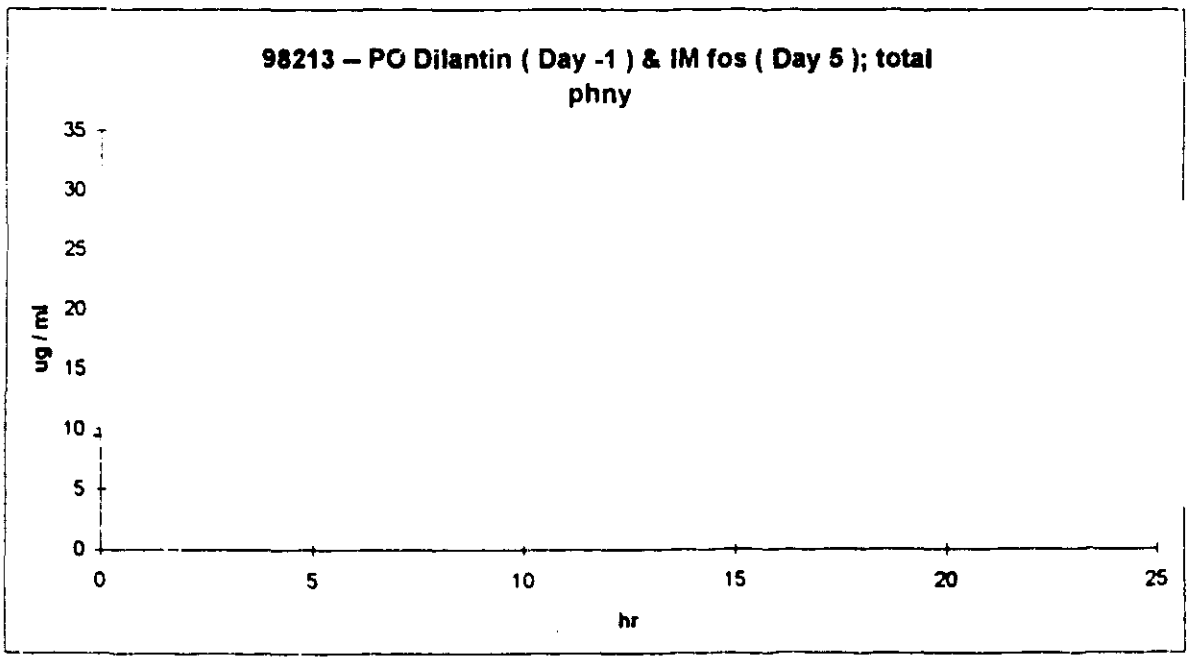

98213 – PO Dilantin (Day -1) & IM fos (Day 5); total phny
ug / ml
35
30
25
20
15
10
5
0
0
5
10
15
20
25
hr

Table 2

Study 98213 -- densely sampled PK data from 1 center ***

free phenytoin

dose (mg / day)	n	Cmax (ug / ml) PO Dilantin	IM fosphenytoin	AUC (ug hr / ml) PO Dilantin	IM fosphenytoin	trough (ug / ml) PO Dilantin	IM fosphenytoin
200	1	2.59	2.17	38.05	39.68	1.40	1.73
300	2	1.19	1.74	24.94	33.57	0.99	1.21
400	5	1.54	1.97	31.61	35.71	1.14	1.19
500	3	1.29	2.45	26.66	39.97	0.95	1.27
200 - 500	11	1.51 ± 0.53	2.08 ± 0.67	29.83 ± 8.44	36.84 ± 12.42	1.09 ± 0.40	1.27 ± 0.61

total phenytoin

dose (mg / day)	n	Cmax (ug / ml) PO Dilantin	IM fosphenytoin	AUC (ug hr / ml) PO Dilantin	IM fosphenytoin	trough (ug / ml) PO Dilantin	IM fosohenytoin
200	1	24.4	36.6	505.9	548.6	17.5	19.1
300	2	13.6	15.7	276.3	283.4	10.3	9.9
400	5	17.9	19.7	368.5	378.1	12.9	[illegible]
500	3	21.9	28.9	459.1	556.8	17.2	
200 - 500	11	18.8 ± 5.4	23.0 ± 7.9	388.1 ± 121.4	425.1 ± 149.0	14.0 ± 5.0	14.9 ± 6.1

*** dataset is the same as in the graphs on the previous page
values are means; values for 200 - 500 are mean ± S.D.
Cmax from inspection of C vs T data, AUC from trapezoids

CONCLUSIONS: Substitution of equimolar IM fosphenytoin for PO Dilantin results in an increase in $Cmax_{free\ phenytoin}$ (38%) and $AUC_{free\ phenytoin}$ (24%) (study 98213). The increase in Cmax may be due to differences in dosing frequency: PO Dilantin was administered QID while IM fosphenytoin was given QD.

The effect of substitution of IV fosphenytoin for PO Dilantin on Cmax of free phenytoin can be inferred. IM administration of fosphenytoin results in higher $Cmax_{phenytoin}$ than PO administration of phenytoin, and IV administration of fosphenytoin results in higher $Cmax_{phenytoin}$ than IM administration of fosphenytoin. Thus, IV administration of fosphenytoin is likely produces an even greater increase in $Cmax_{phenytoin}$ than does IM administration of fosphenytoin. This increase in $Cmax_{phenytoin}$ would be expected to result in an increase in $Cmax_{free\ phenytoin}$. Also, IV administration results in greater $Cmax_{fosphenytoin}$ than does IM administration. Based upon this increased plasma fosphenytoin causing displacement of phenytoin protein binding, $Cmax_{free\ phenytoin}$ should be higher following IV administration of fosphenytoin than following IM administration of fosphenytoin.

STUDY: Absolute bioavailability of phenytoin after intramuscular CI-982 administration to healthy male volunteers

STUDY NUMBER: 982-06 (9653-86-06)

RESEARCH REPORT NUMBER: RR 744-00028

STUDY DESIGN: This was a randomized, open-label, two treatment crossover. Fosphenytoin (250 mg) was injected into the gluteus maximus muscle over approximately 30 seconds. Six volunteers received 2 simultaneous 2.5 mL injections and 6 volunteers received a single 5 mL injection. Phenytoin (250 mg) was administered via an iv infusion over 10 minutes. Twenty six blood samples were obtained per treatment up to 120 hours after drug infusion. Only total fosphenytoin and phenytoin concentrations in the plasma was measured. Treatments were separated by two weeks.

SUBJECTS: Healthy male volunteers (n=12).

DOSAGE FORM: See Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

SAFETY RESULTS: No major adverse reactions were observed in this study. IM fosphenytoin injection caused less injection site irritation than did IV phenytoin injection.

PHARMACOKINETIC RESULTS: The pharmacokinetic results of this study are summarized in Tables 1 - 3. The plasma concentration time curves for phenytoin and fosphenytoin are given in Figures 1 - 3. The elimination half-life for fosphenytoin after IM injection averaged 44 minutes (Table 1), considerably longer that the 15 minute half-life typically observed after IV fosphenytoin injection. This result suggests that flip-flop kinetics are occurring (i.e. terminal rate reflects absorption from muscle tissue). The Cmax was higher and the Tmax was earlier when the dose was administered by 2 IM injections compared to a single IM injection (Table 3).

The bioavailability of phenytoin from IM fosphenytoin (compared to IV phenytoin) was 101.2 ± 1.6% (Table 2). Bioavailability was not affected by whether the drug was given as one or two injections, although the rate of absorption was faster after two injections (Table 3). Not surprisingly, phenytoin Cmax was lower and the Tmax was later after IM fosphenytoin injection compared to IV phenytoin infusion (Table 2, Figure 2).

CONCLUSION: Fosphenytoin is completely converted to phenytoin after intramuscular injection. Fosphenytoin absorption from muscle is fairly smooth and appears to follow simple first order kinetics with a half-life of approximately 0.75 hr. Thus, IM fosphenytoin appears to be a reasonable form of maintenance therapy.

2 Pages

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Table 3

~~Table 5~~

ACC-9853 and Phenytoin Pharmacokinetic Parameters

Analysis of Difference Between Number of 9853 Injections

Compound	Variable	2 IM Injections N	2 IM Injections Mean[$]	2 IM Injections (SEM)	1 IM Injection N	1 IM Injection Mean[$]	1 IM Injection (SEM)	P-Value
9853	C_{max} (mcg/mL)	6	26.02	(2.08)	6	15.40	(1.13)	0.001*
	T_{max} (h)	6	0.38	(0.05)	6	0.83	(0.15)	0.014*
	Terminal Rate Const. (h^{-1})	6	1.23	(0.17)	6	0.85	(0.05)	0.065
	Half-Life (min)	6	37.69	(5.57)	6	50.04	(3.58)	0.091
	AUC (0-120) (mg-h/L)	6	31.92	(2.34)	6	30.15	(1.94)	0.572
	AUC (0-∞) (mg-h/L)	6	32.24	(2.32)	6	30.59	(1.98)	0.601
	% AUC accounted	6	98.99	(0.36)	6	98.67	(0.45)	0.492
	Clearance (L/hr)	6	10.58	(0.68)	6	11.10	(0.72)	0.598
Phenytoin	C_{max} (mcg/mL)	6	6.10	(0.20)	6	5.25	(0.24)	0.021*
	T_{max} (h)	6	2.67	(0.11)	6	3.58	(0.37)	0.040*
	Elim. Rate Const. (h^{-1})	6	0.041	(0.003)	6	0.042	(0.004)	0.915
	Half-Life (h)	6	17.07	(2.03)	6	17.39	(1.73)	0.860
	AUC (0-120) (mg-h/L)	6	173.2	(21.4)	6	141.2	(14.3)	0.243
	AUC (0-∞) (mg-h/L)	5	178.0	(22.7)	6	144.7	(15.1)	0.250
	% AUC accounted	6	97.48	(0.41)	6	97.75	(0.71)	0.751
	Bioavailability	6	1.002	(0.017)	6	1.018	(0.030)	0.646

$ - Means of C_{max}, AUC and clearance are weight adjusted.
* - Significant difference between number of IM injections given ($P < 0.05$).

Figure 1
Mean .9653 Plasma Concentration Versus Time

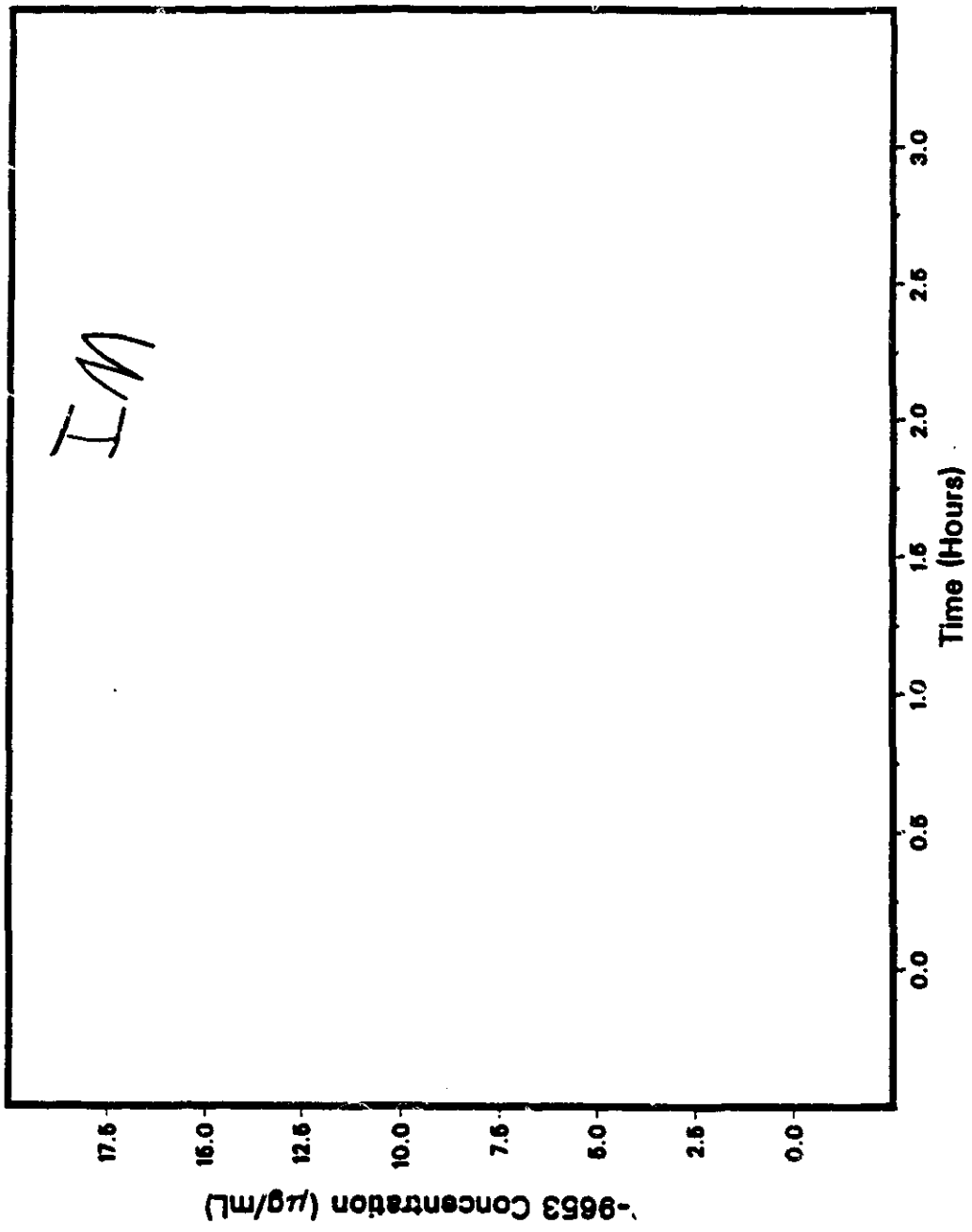
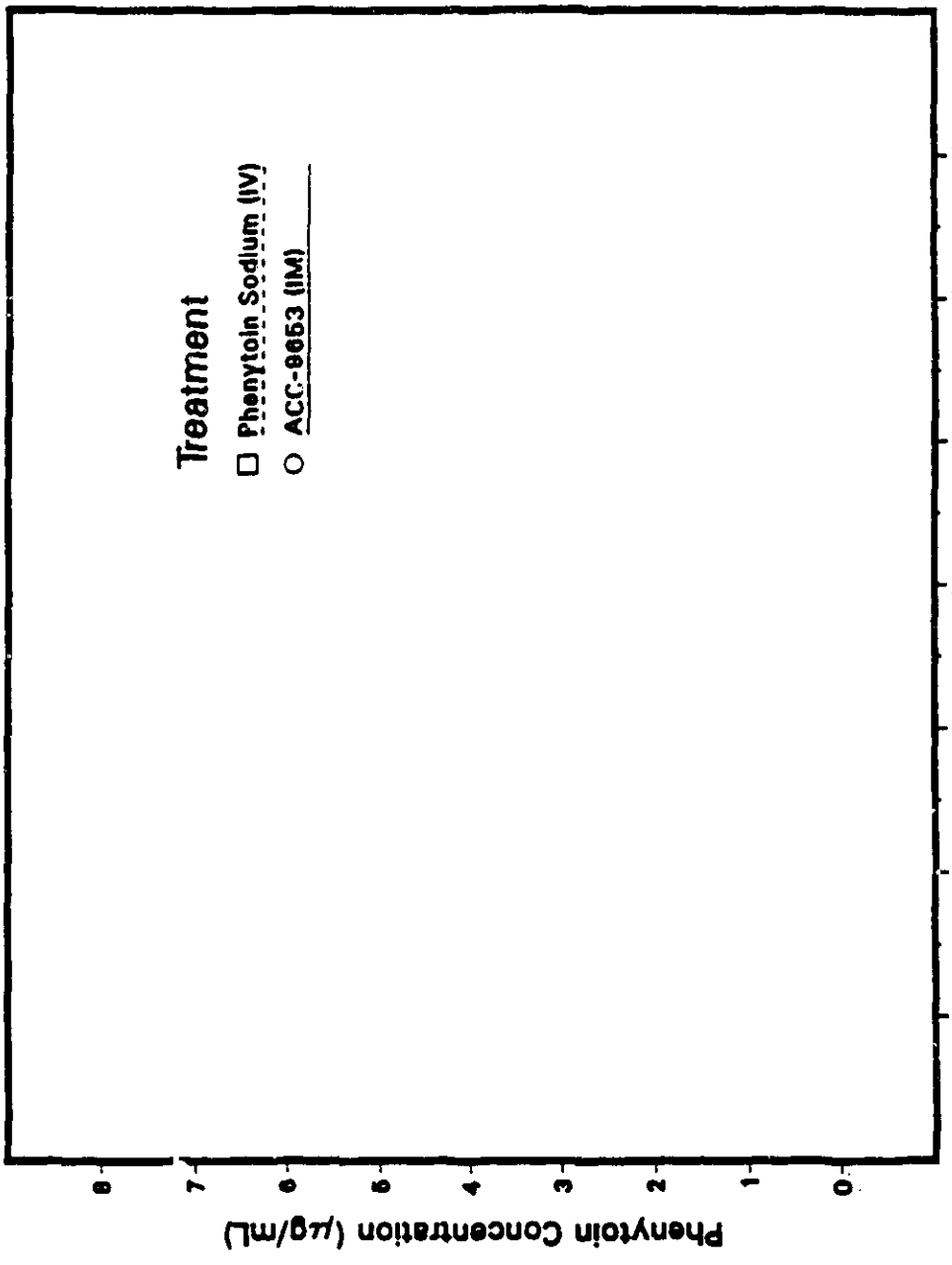
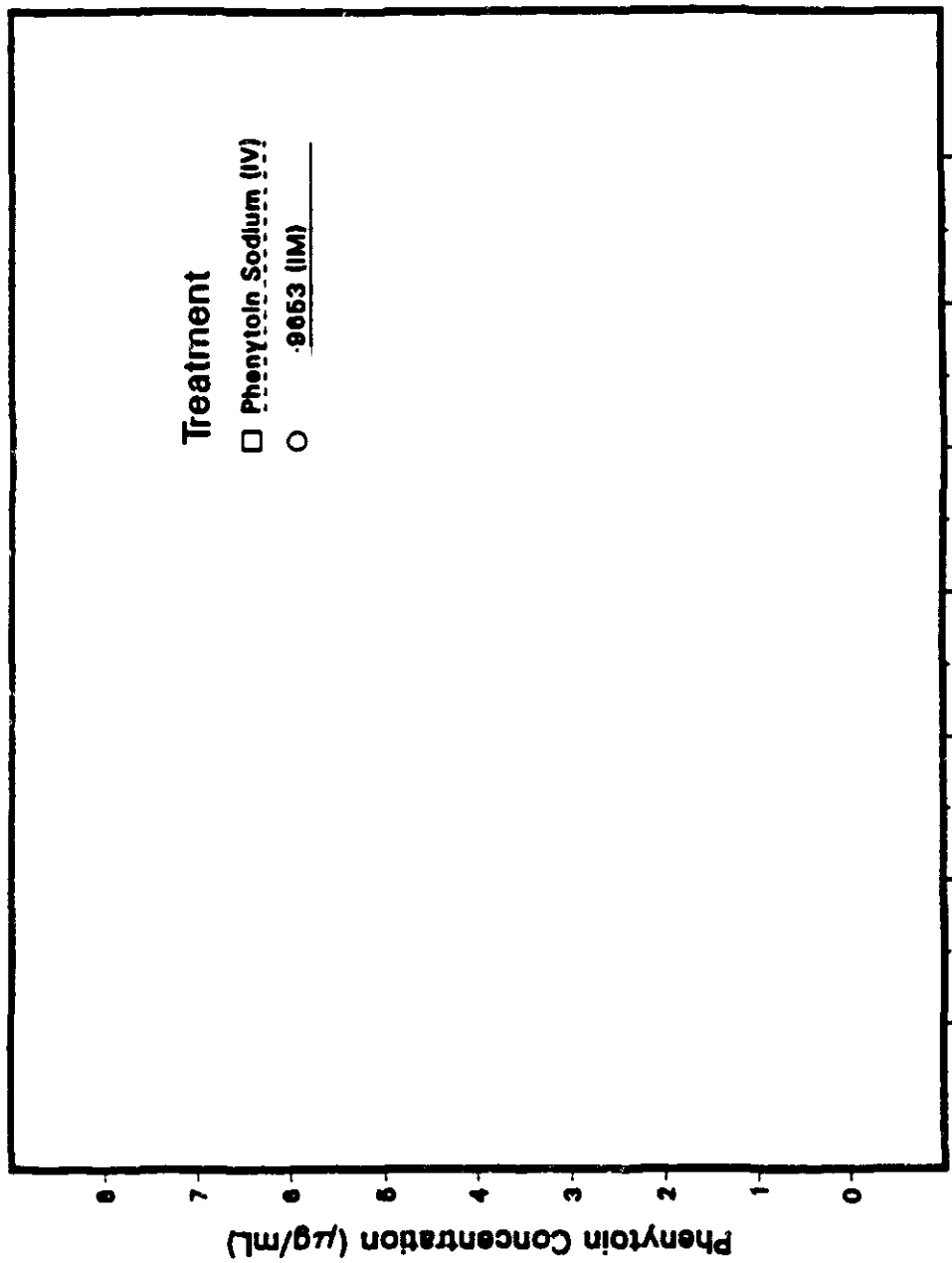


Figure 2
Mean Phenytoin Plasma Concentration Versus Time



* Significant difference between treatments.

Figure 3
Mean Phenytoin Plasma Concentration Versus Time



* Significant difference between treatments.

STUDY: Conversion Of CI-982 To Phenytoin In Patients With Renal Or Hepatic Disease Compared To Healthy Subjects - A Pilot Study

PROTOCOL NUMBER: 982-07 (9653-87-07)

RESEARCH REPORT NUMBER: RR 744-00029

STUDY DESIGN: Single center, open label study with screening, baseline, treatment, and poststudy periods. Each individual received 250 mg phenytoin equivalents of fosphenytoin IV administered over 30 min. It should be noted that the protocol allowed patients to continue ongoing therapy during the trial. Documentation of ongoing therapy was not provided.

SUBJECTS: 15 males were enrolled in the study:

TABLE 1. DEMOGRAPHIC SUMMARY
(MEAN ± SEM)

Parameter (Units)	Volunteer Group		
	Renal (n=5)	Hepatic (n=4)	Healthy (n=6)
Age (years)	54.5 ± 2.8[a]	51.8 ± 5.8[b]	29.2 ± 1.1
Height (cm)	175.3 ± 2.4	179.7 ± 3.5	184.2 ± 2.1
Weight (kg)	77.1 ± 5.3	89.3 ± 9.2	86.8 ± 3.3

Values in the above table are mean ± SEM. Renal failure patients required maintenance hemodialysis, hepatic patients had: 1. liver biopsy evidence of cirrhosis, 2. a total serum bilirubin level less than 4 mg%, 3. a creatinine clearance rate of at least 60 ml / min.

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

PROTOCOL VARIATIONS: Volunteers' #1 (healthy) and #2 (healthy) plasma sample extracts were incorrectly processed and therefore omitted. Volunteer #7 (renal failure) was also omitted due to "Chromatographic interferences". Volunteer #13 received only a 24 minute infusion, and was therefore not included in Cmax or Tmax analyses. Volunteers #4 (hepatic), #12 (renal), #13 (renal), and #14 (renal), received modified, or no, treatment with their ongoing concomitant therapies.

SAFETY RESULTS: No adverse clinical events were reported and no clinically significant changes were observed in the physical examinations, clinical laboratory parameters, clinical observations, or electrocardiograms.

PHARMACOKINETIC AND STATISTICAL METHODS:

Demographic information was summarized for each group (renal, hepatic, and hepatic) separately. Differences among groups were assessed using a one-way ANOVA model for continuous data and Fisher's Exact Text for categorical data.

Maximum plasma concentration (C_{max}) and the time of the maximum plasma concentration (T_{max}) were determined by observation.

The terminal or "apparent" disposition rate constant (λ_n) was calculated as the slope of the terminal portion of the log-linear plasma concentration versus time curve.

The terminal or "apparent" disposition half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \frac{\ln 2}{\lambda_n}$$

Area under the plasma concentration versus time curve ($AUC_{0\to\infty}$) was calculated by the trapezoidal rule up to the last quantifiable concentration ($AUC_{0\to T}$) plus the residual area calculated as the ratio of the final plasma concentration divided by λ_n.

Clearance (CL) of ACC-9653 was calculated by:

$$CL = \frac{Dose}{AUC_{0\to\infty}}$$

Volume of distribution (V_d) of ACC-9653 was calculated by:

$$V_d = \frac{CL}{\lambda_n}$$

CL and V_d values were standardized to each volunteer's weight.

Differences in PK parameters among groups was assessed using a one-way ANOVA model. Statistical analysis and preparation of the summary tables were carried out using SAS. A result was deemed " statistically significant " when the accompanying statistical test yielded a two-tailed probability (p-value) of 0.05 or less.

PHARMACOKINETIC RESULTS:

TABLE 3. 9653 PHARMACOKINETIC PARAMETERS (MEAN ± SD)

Parameter (Units)	Volunteer Group Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (μg/mL)	35.8 ± 13.2[a]	25.9 ± 10.5	43.4 ± 8.9
T_{max} (min)	30.1 ± 8.1[a]	28.7 ± 5.9	31.8 ± 1.4
λ_z (hr^{-1})	5.50 ± 2.20	10.42 ± 3.85[c]	4.71 ± 1.61
$t_{1/2}$ (min)	8.60 ± 3.91[b]	4.38 ± 1.77[b]	9.51 ± 2.71[b]
AUC_{0-T} (μg*hr/mL)	17.8 ± 8.0	12.9 ± 5.7	25.5 ± 8.2
$AUC_{0-\infty}$ (μg*hr/mL)	17.9 ± 7.9	13.0 ± 5.7	25.5 ± 8.2
CL (L/hr)	21.3 ± 8.4	29.3 ± 11.7	13.7 ± 3.7
CL (L/hr/kg)	0.291 ± 0.142	0.337 ± 0.147	0.158 ± 0.047
V_d (L)	4.84 ± 1.50	2.80 ± 0.67	2.97 ± 0.43
V_d (L/kg)	0.0528 ± 0.0193	0.0327 ± 0.0100	0.0344 ± 0.0077

(a) - N=3

(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 7.44 ± 2.83, 3.90 ± 1.00, and 8.83 ± 3.30 minutes for the renal, hepatic, and healthy volunteer groups, respectively.

(c) - Significant difference from healthy subjects ($p < 0.05$). (Hepatic ≠ Healthy)

TABLE 7. PHENYTOIN PHARMACOKINETIC PARAMETERS
(MEAN ± SD)

Parameter (Units)	Volunteer Group: Renal (n=4)	Hepatic (n=4)	Healthy (n=4)
C_{max} (µg/mL)	4.59 ± 1.28[a]	4.41 ± 1.33	4.26 ± 0.62
T_{max} (hr)	0.79 ± 0.39[a]	0.71 ± 0.22	1.38 ± 0.51
λ_n (hr^{-1})	0.0421 ± 0.0132	0.0293 ± 0.0100	0.0336 ± 0.0077
$t_{1/2}$ (hr)	17.0 ± 5.0[b]	26.5 ± 11.2[b]	21.3 ± 4.0[b]
AUC_{0-7} (µg*hr/mL)	59.9 ± 17.4	58.4 ± 11.1	62.2 ± 9.4
$AUC_{0-\infty}$ (µg*hr/mL)	97.4 ± 46.9	194.7 ± 27.2	112.1 ± 26.6

(a) - N=3.
(b) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 18.5 ± 5.6, 23.7 ± 7.9, and 20.5 ± 4.0 hours for the renal, hepatic, and healthy volunteer groups, respectively.
No statistically significant differences were observed between volunteer groups ($p > 0.05$).

TABLE 4. 9653 PROTEIN BINDING SUMMARY
(MEAN ± SD)

Parameter	Volunteer Group: Renal (n=3)	Hepatic (n=3)	Healthy (n=3)
Percent Unbound -9653	12.66 ± 3.37[a]	8.84 ± 0.24	4.97 ± 0.47
Albumin (g/dL)	3.4 ± 0.7[a]	2.9 ± 0.7[b]	4.6 ± 0.3
Protein (g/dL)	6.4 ± 0.7	7.5 ± 0.6	7.8 ± 0.5

(a) - Significant difference from healthy subjects ($p < 0.05$). (Renal ≠ Healthy)
(b) - Significant difference from healthy subjects ($p < 0.05$). (Hepatic ≠ Healthy)

Based on the null hypothesis of no difference between groups, statistical significance ($p < 0.05$) is not reached in nearly all of the comparisons made above. However, the null hypothesis of no difference is inappropriate as differences would be expected based upon the protein binding nature of the drug and decreases in plasma protein which accompany renal and hepatic diseases. The study is insufficiently powered (3 - 4 in each group) to allow for the chosen statistical approach to be utilized, and trends are clearly observable.

CONCLUSIONS: The dose of fosphenytoin administered in this study was 250 mg phenytoin equivalents at 8.33 mg equivalents / min.. The sponsor has labeled the drug for administration at doses as large as 20 mg/kg at 150 mg/min. Clearly, the study fails to encompass the condition where changes in drug disposition are most easily observed and most clinically serious: following high dose and rate of administration. Further, free phenytoin concentrations were not measured in the study. Since free phenytoin is the specie of interest, and serum protein concentrations are altered by renal and hepatic disease (as would be expected these alterations were seen in the current study -- see Table on p.), this severely limits the ability to interpret the effect of renal and hepatic disease on the disposition of free phenytoin from fosphenytoin.

Fosphenytoin clearance is more than 2-fold greater in cirrhosis patients than in healthy volunteers, and over 1.5-fold greater in renal failure patients.

STUDY: Absolute bioavailability of phenytoin from CI-982 in patients with therapeutic serum phenytoin concentrations using stable isotope techniques

PROTOCOL NUMBER: 982-10 (9653-87-10)

RESEARCH REPORT NUMBER: RR 744-00030

STUDY DESIGN: This was a randomized, open-label study in epileptic patients on chronic oral phenytoin monotherapy. At separate injection sites in the same arm, each patient received 128 mg phenytoin equivalents of labelled fosphenytoin and 130 mg phenytoin equivalents of labelled phenytoin simultaneously. Blood was sampled at 25 time points up to 96 hours after drug administration. Urine was collected just prior to the infusions and from 0 - 1, 1 - 24, 24 - 48, 48 - 72 and 72 - 96 hours. Labelled and unlabeled phenytoin and fosphenytoin concentrations were measured in the plasma and urine via satisfactory HPLC and GC/MS methodologies. The phenytoin metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) was also measured in the urine.

SUBJECTS: Epileptic males on chronic oral phenytoin monotherapy (n=6).

DOSAGE FORM: ^{13}C-labelled fosphenytoin disodium (229.4 mg/3.2 mL, Lot #Z88-5-5) and ^{15}N-^{13}C labelled phenytoin sodium (189.9 mg/3.2 mL. Lot #Z88-5-5). see also Formulation Summary: Appendix 3.

ASSAY: See Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study.

SAFETY RESULTS: No major adverse reactions were observed in this study.

PHARMACOKINETIC RESULTS: The pharmacokinetic results of this study are summarized in Tables 1 - 2. The pharmacokinetic parameters determined in these patients are very consistent with what was found in healthy volunteers. The AUC ratio of ^{13}C-phenytoin/^{15}N-^{13}C-phenytoin (i.e. AUC of phenytoin from fosphenytoin injection divided by AUC of phenytoin from phenytoin injection) was 0.96 with a 95% confidence interval for bioequivalence being 0.92 to 1.00. Thus, the bioavailability of fosphenytoin is virtually unity.

No fosphenytoin was detected in the urine. However, slightly more phenytoin was detected in the urine during the first 1 hour after fosphenytoin administration compared to after phenytoin administration (Table 3). This indicates that it is possible that a very small amount of fosphenytoin (approximately 1% of the dose) may be excreted in the urine, where it is subsequently hydrolyzed to phenytoin. The recovery of p-HPPH was higher after phenytoin administration than after fosphenytoin administration (Table 2), but this difference was small and not statistically significant.

CONCLUSION: This was an excellent method for determining bioavailability because intrasubject variability was completely eliminated. An intravenous dose of fosphenytoin was virtually completely converted to phenytoin in patients who were on chronic oral phenytoin therapy.

TABLE 5. PHENYTOIN PHARMACOKINETIC PARAMETERS IN PATIENTS (MEAN ± SD)

Parameter (units)	-9653 Infusion[b]	$^{15}N_2$-$^{13}C_3$-Phenytoin Infusion[b]
C_{max} (µg/mL)	3.25 ± 0.82	4.51 ± 1.07
T_{max} (min)	34.0 ± 30.0	12.7 ± 1.6
λ_z (hrs^{-1})	0.0274 ± 0.0059	0.0285 ± 0.005
$t_{1/2}$ (hrs)	26.4 ± 6.2[a]	25.4 ± 6.0[a]
AUC_{0-T} (µg•hr/mL)	69.2 ± 15.6[b]	73.8 ± 17.9
$AUC_{0-\infty}$ (µg•hr/mL)	75.7 ± 18.5	80.2 ± 20.6
AUC/Dose (µg•hr/mL•mg)	0.591 ± 0.144	0.616 ± 0.160
AUC Ratio (ACC-9653/Phenytoin)	0.963 ± 0.061	

C_{max} - Maximum plasma concentration.
T_{max} - Time of maximum plasma concentration.
λ_z - Terminal elimination rate constant.
$t_{1/2}$ - Terminal elimination half-life.
AUC_{0-T} - Area under the plasma concentration vs time curve from 0 to the time of the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from 0 to infinity.
(a) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 25.3 ± 5.4 and 24.3 ± 5.3 for the $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin infusions, respectively.
(b) - Statistically significant difference between infusions of $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin ($p < 0.05$).
Doses - 128.2 mg from the $^{13}C_3$-ACC-9653 infusion and 130.1 mg from the $^{15}N_2$-$^{13}C_3$-phenytoin infusion in terms of the equivalent amount of unlabelled phenytoin.

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TABLE 3. 9653 PHARMACOKINETIC PARAMETERS IN PATIENTS (MEAN ± SD)

Parameter (units)	-9653 Infusion		
Weight (kg)	85.2	±	13.5
C_{max} (µg/mL)	36.3	±	15.5
T_{max} (min)	13.9	±	1.1
λ_z (hrs^{-1})	6.42	±	2.67
$t_{1/2}$ (min)	6.86	±	7.24(*)
AUC_{0-T} (µg*hr/mL)	11.9	±	3.2
$AUC_{0-\infty}$ (µg*hr/mL)	12.2	±	3.4
CL (L/hr)	16.4	±	6.3
CL (L/hr/kg)	6.197	±	6.078
V_d (L)	3.13	±	1.92
V_d (L/kg)	6.6352	±	6.6157

C_{max} - Maximum plasma concentration.
T_{max} - Time of maximum plasma concentration.
λ_z - Terminal elimination rate constant.
$t_{1/2}$ - Terminal elimination half-life.
AUC_{0-T} - Area under the plasma concentration vs time curve from 0 to the time of the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from 0 to infinity.
CL - Clearance
V_d - Volume of distribution.
(*) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation of half-life was 6.48 ± 2.57 minutes.
Dose - 298 mg $^{13}C_3$-ACC-9653 disodium salt, equivalent to 183.8 mg unlabelled ACC-9653 free acid.

TABLE 6. PHENYTOIN AND P-HPPH CUMULATIVE URINARY EXCRETION FROM PATIENTS (MEAN ± SD)

Elapsed Time (hrs)[a]	Phenytoin Excretion (% Dose) 9653	Phenytoin Excretion (% Dose) $^{15}N_2$-$^{13}C_3$-PHT	p-HPPH Excretion (% Dose) $^{13}C_3$-ACC-9653	p-HPPH Excretion (% Dose) $^{15}N_2$-$^{13}C_3$-PHT	Total Excretion (% Dose) 9653	Total Excretion (% Dose) $^{15}N_2$-$^{13}C_3$-PHT
1	0.98 ± 0.15[b]	0.18 ± 0.06	0.20 ± 0.11[b]	0.37 ± 0.18	1.27 ± 0.[illegible][b]	0.55 ± 0.22
24	3.52 ± 0.81[b]	0.91 ± 0.18	18.81 ± 4.44[b]	21.14 ± 4.96	22.63 ± 4.87[b]	21.94 ± 5.00
48	4.15 ± 0.87[b]	1.18 ± 0.20	33.98 ± 8.50[b]	38.05 ± 9.70	38.11 ± 9.00[b]	39.18 ± 9.94
72	4.24 ± 0.88[b]	1.19 ± 0.30	41.84 ± 10.70[b]	48.54 ± 12.20	46.09 ± 11.35	47.73 ± 12.46
96	4.27 ± 0.85[b]	1.22 ± 0.20	45.45 ± 10.01	50.81 ± 12.11	49.92 ± 11.13[b]	52.03 ± 12.23

Time Interval (hrs)[a]	Phenytoin Excretion Ratio 9653/$^{15}N_2$-$^{13}C_3$-PHT	p-HPPH Excretion Ratio 9653/$^{15}N_2$-$^{13}C_3$-PHT	Total Excretion Ratio 9653/$^{15}N_2$-$^{13}C_3$-PHT
0 - 1	0.81 ± 1.96	0.70 ± 0.11	2.47 ± 0.50
0 - 24	4.07 ± 1.00	0.00 ± 0.02	1.04 ± 0.02
0 - 96	3.62 ± 0.72	0.90 ± 0.02	0.96 ± 0.02

p-HPPH - [5-(4-hydroxyphenyl)-5-phenylhydantoin]
PHT - Phenytoin
Doses - 120.2 mg from the $^{13}C_3$-ACC-9653 infusion and 130.1 mg from the $^{15}N_2$-$^{13}C_3$-phenytoin infusion in terms of the equivalent amount of unlabelled phenytoin.
(a) - Relative to the start of the $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin infusions.
(b) - Statistically significant difference between infusions of $^{13}C_3$-ACC-9653 and $^{15}N_2$-$^{13}C_3$-phenytoin ($p < 0.05$).

STUDY: Evaluation of the Pharmacokinetic Interaction Between Diazepam and CI-982 in Healthy Male Volunteers

PROTOCOL NUMBER: 982-011 (9653-87-11)

RESEARCH REPORT NUMBER: RR 744-00031

STUDY DESIGN: single center, randomized, nonblind, 3-way crossover study in healthy males. Solutions were infused undiluted by Harvard Syringe Pumps into indwelling catheters in the same arm. Treatments were separated by at least 13 days. The treatments were:

A) fosphenytoin (750 mg at 50 mg / min)
B) diazepam (10 mg/2 ml/5 min) followed 10 minutes later by fosphenytoin (750 mg at 50 mg / min)
C) diazepam (10 mg/2 ml/5 min)

SUBJECTS: The values below are approximate -- 11 individuals entered the study, but only 9 completed the PK portion; the table below is for the 11 who entered.

Variable (units)	Mean ± SEM	Range
Age (years)	25.1 ± 1.1	20 - 31
Height (cm)	180.1 ± 2.2	168.2 - 191.1
Weight (kg)	78.7 ± 2.8	69.8 - 99.4

All subjects were male Caucasians and non-smokers.

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. Heparin was used as an anti-coagulant in this study. Free fractions were determined by spiking with radiolabel and ultracentrifugation was performed at room temperature.

PROTOCOL VARIATIONS: There were no protocol variations. There were 2 dropouts. Subject #6 withdrew from the study after completing his first treatment (treatment B -- diazepam and fosphenytoin) following diagnosis of underlying borderline hypertension by hispersonal physician. Subject #10 was withdrawn from the study after participating in

treatments B and A (treatment B -- diazepam and fosphenytoin and treatment A -- fosphenytoin alone) because of a vasovagal episode during treatment A. Subjects 6 and 10 were included in the safety analysis but not in PK analysis.

SAFETY RESULTS: One subject (#10) experienced a vasovagal syncopal episode which included hypotension and bradycardia during Treatment A (fosphenytoin alone). These events required discontinuation of the study drug. This subject had previously completed treatment B (diazepam and fosphenytoin) without significant effects on heart rate, ECG intervals, or blood pressure. Follow-up evaluation of this episode, which included a 24 hour Holter monitor recording and a more extensive medical history, revealed no cardiologic abnormalities, but did detail a previously unreported episode of syncope during an intravenous drug study. In the investigator's clinical judgement, this episode was therefore related to the intravenous infusion but not to fosphenytoin. Ten of the 11 subjects who entered the study reported adverse clinical events in at least one treatment phase. These events are summarized below.

Symptom	9653 Site		Diazepam Site	
	Treatment Period			
	9653 Alone (N=9)	Diazepam and (N=11)	Diazepam Alone (N=9)	Diazepam and (N=11)
Subject's Evaluations				
Pain	1	0	1	2
Burning	0(*)	0(*)	4(*)	5(*)
Itching	1	1	1	0
Investigator's Evaluations				
Erythema	0	3	0	1
Swelling	0	1	0	2
Tenderness	2	3	1	3

TABLE 10. ADVERSE CLINICAL EVENTS SUMMARY
(NUMBER OF SUBJECTS REPORTING ADVERSE EVENT)

System and Adverse Event	Treatment		
	9653 Alone (N=18)	Diazepam Alone (N=11)	Diazepam and 9653 (N=11)
Number of Subjects Reporting an Adverse Event	6	10	7
Body as a Whole	1	2	2
Headache	0	0	2
Infection Site Inflamed[a]	0	1	1
Injection Site Reaction[a]	1	0	0
Cardiovascular	2	0	0
Bradycardia	1	0	0
Hypotension	2	0	0
Gastrointestinal	1	0	1
Dry Mouth	0	0	1
Nausea	1	0	0
Central Nervous System	3	3[b]	2
Dizziness	1	3	0
Paresthesia	1	0	2
Somnolence	1	0[b]	0
Slurred Speech	0	1	0
Skin	2	0	2
Pruritus	2	0	2
Special Senses	1	0	0
Vision Abnormality	1	0	0

(a) - Injection site evaluations during the first 72 hours are provided in Table 11.
(b) - Statistically significant difference between treatments diazepam alone P 9653 alone and diazepam alone P diazepam and 9653
All adverse events were considered by the investigator to be possibly or probably related to the treatment(s)

PHARMACOKINETIC and STATISTICAL METHODS:

Pharmacokinetic parameters o -9653, phenytoin, and diazepam were calculated using non-compartmental methods. Calculations were based on the free acid form of ACC-9653 and the acid form of phenytoin.

Maximum plasma concentration (C_{max}) and the time of maximum plasma concentration (T_{max}) were determined by observation.

The terminal or "apparent" disposition rate constant (λ_n) was calculated as the slope of the terminal portion of the log-linear concentration versus time curve.

The terminal or "apparent" disposition half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \frac{\ln 2}{\lambda_n}$$

Area under the plasma concentration versus time curve ($AUC_{0\to\infty}$) was calculated by the trapezoidal rule up to the last quantifiable concentration ($AUC_{0\to T}$) plus the residual area calculated as the ratio of the final plasma concentration divided by λ_n.

Clearance (CL) was calculated by:

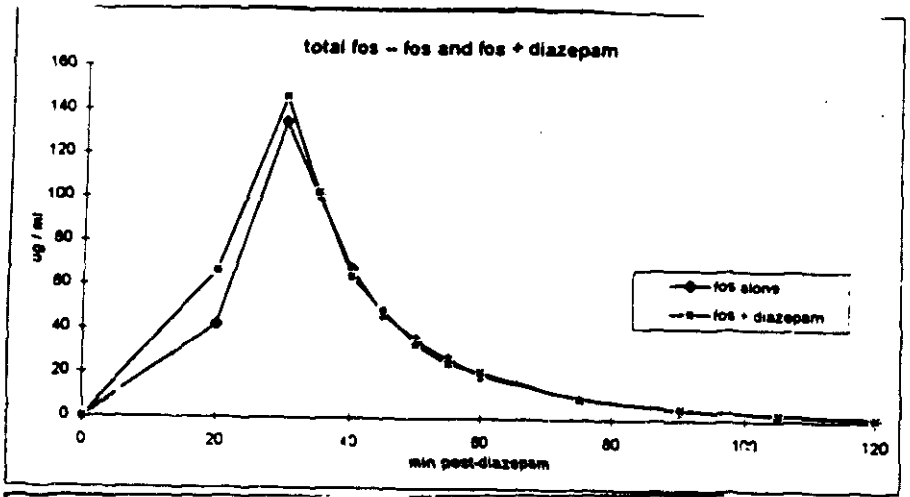
$$CL = \frac{Dose}{AUC_{0\to\infty}}$$

Volume of distribution (V_d) was calculated by:

$$V_d = \frac{CL}{\lambda_n}$$

CL and V_d values were standardized to each subject's weight.

PHARMACOKINETIC RESULTS:



times are relative to the start of diazepam infusion; fosphenytoin was started at 15 minutes

n = 7 - 9

TABLE 3. -9653 PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS (MEAN ± SD)

	Treatment	
Meter (units)	-9653 Alone (N=9)	Diazepam and -9653 (N=9)
C_{max} (µg/mL)	135 ± 20	146 ± 13
T_{max} (min)	15.6 ± 0.2	15.1 ± 0.3
λ_z (hrs^{-1})	2.85 ± 0.61	2.92 ± 0.75
$t_{1/2}$ (min)	15.2 ± 3.1(a)	15.8 ± 3.4(a)
AUC_{0-T} (µg*hr/mL)	53.5 ± 11.0	57.6 ± 9.5
$AUC_{0-\infty}$ (µg*hr/mL)	54.2 ± 11.4	58.1 ± 9.7
CL (L/hr)	19.1 ± 4.0	17.7 ± 3.2
CL (L/hr/kg)	0.246 ± 0.039	0.228 ± 0.033
V_z (L)	8.86 ± 1.58	8.27 ± 1.58
V_z (L/kg)	0.0883 ± 0.0146	0.0818 ± 0.0166

C_{max} - Maximum plasma concentration.

T_{max} - Time of maximum plasma concentration relative to the start of the -9653 infusion

λ_z - Terminal elimination rate constant

$t_{1/2}$ - Terminal elimination half-life

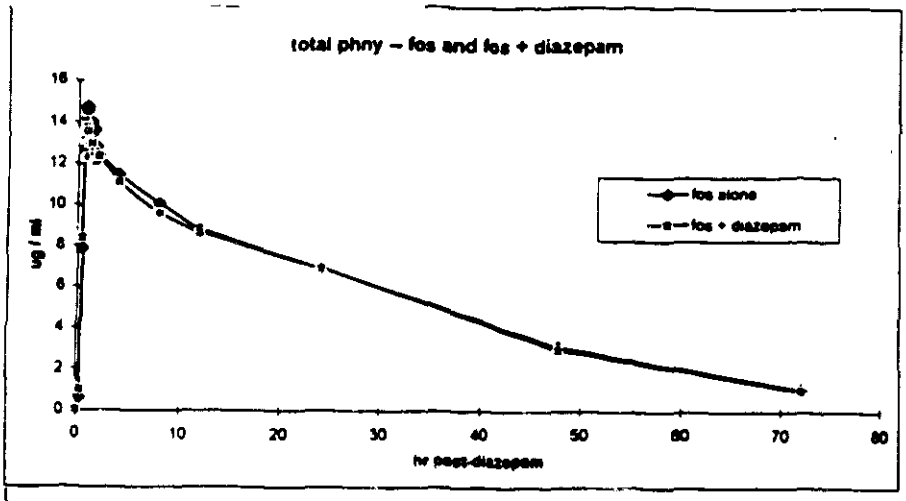
AUC_{0-T} - Area under the plasma concentration vs time curve from the start of t -9653 to the time of the last quantifiable concentration

$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from the start of t -9653 infusion to infinity

CL - Clearance.

V_z - Volume of distribution.

(a) Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 14.6 ± 3.2 and 14.3 ± 3.8 minutes for the -9653 treatment and the diazepam and -9653 treatment, respectively.



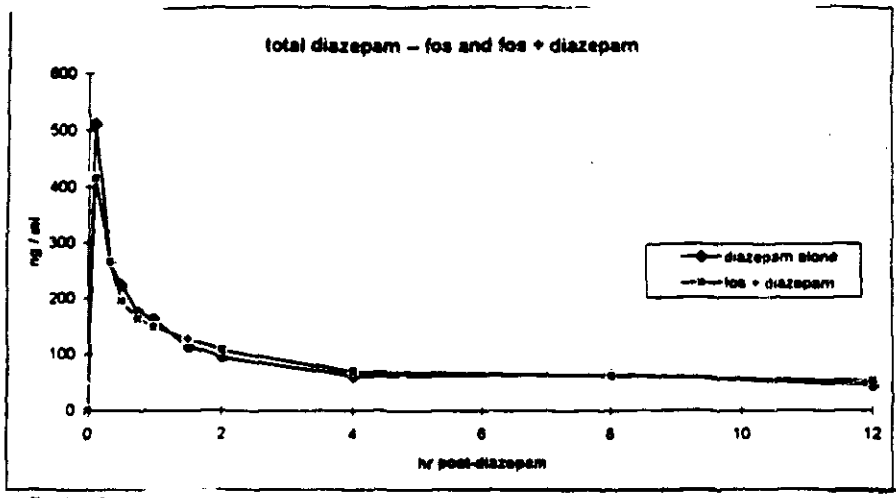
times are relative to the start of diazepam infusion; fosphenytoin was started at 0.25 hours

n = 7 - 9

TABLE 5. PHENYTOIN PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS (MEAN ± SD)

Parameter (units)	Treatment: 9653 Alone (N=9)	Diazepam and -9653 (N=9)
$C_{ss,max}$ (µg/mL)	18.4 ± 2.4	15.4 ± 2.8
$T_{ss,max}$ (min)	41.2 ± 16.9	55.6 ± 37.4
λ_n (hrs^{-1})	0.0360 ± 0.0078	0.0377 ± 0.0093
$t_{1/2}$ (hrs)	20.1 ± 4.6(a)	19.5 ± 5.1(a)
$AUC_{0-\tau}$	392 ± 64	384 ± 65
$AUC_{0-\infty}$	427 ± 92	417 ± 95

$C_{ss,max}$ - Maximum plasma concentration.
$T_{ss,max}$ - Time of maximum plasma concentration relative to the start of the 9653 infusion
λ_n - Terminal elimination rate constant.
$t_{1/2}$ - Terminal elimination half-life.
$AUC_{0-\tau}$ - Area under the plasma concentration vs time curve from the start o 9653 infusion to the time of the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from the start of t -9653 infusion to infinity.
CL - Clearance.
V_d - Volume of distribution.
(a) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 19.3 ± 4.2 and 18.4 ± 4.5 hours for \ 9653 treatment and the diazepam and \653 treatment, respectively.



times are relative to the start of diazepam infusion; fosphenytoin was started at 15 minutes

n = 8 - 9

TABLE 7. DIAZEPAM PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS (MEAN ± SD)

Parameters)	Treatment: Diazepam Alone (N=9)	Diazepam and 9853 (N=9)
C_{max} (µg/mL)	511 ± 239	466 ± 253
T_{max} (min)	18.8 ± 7.5	14.6 ± 9.6
λ_z (hrs^{-1})	0.436 ± 0.029	0.511 ± 0.031
$t_{1/2}$ (hrs)	26.9 ± 20.1	19.1 ± 13.8
AUC_{0-T} (µg•hr/mL)	1688 ± 1478	1766 ± 1326
$AUC_{0-\infty}$ (µg•hr/mL)	2998 ± 2428	2566 ± 1868
CL (L/hr)	5.31 ± 3.44	5.25 ± 2.52
CL (L/hr/kg)	0.0688 ± 0.0430	0.0663 ± 0.0281
V_z (L)	148 ± 72	113 ± 37
V_z (L/kg)	1.76 ± 0.73	1.46 ± 0.46

C_{max} - Maximum plasma concentration.
T_{max} - Time of maximum plasma concentration relative to the start of the diazepam infusion.
λ_z - Terminal elimination rate constant
$t_{1/2}$ - Terminal elimination half-life
AUC_{0-T} - Area under the plasma concentration vs time curve from the start of the diazepam infusion to the last quantifiable concentration.
$AUC_{0-\infty}$ - Area under the plasma concentration vs time curve from the start of the diazepam infusion to infinity.
CL - Clearance.
V_z - Volume of distribution.
(s) - Arithmetic mean and standard deviation. Harmonic mean ± pseudo standard deviation values of half-lives were 15.9 ± 11.1 and 13.6 ± 8.9 hours for the diazepam treatment and the diazepam and 9853 treatment, respectively.

Protocol Time (hr.min)[a]	9653 Percent Unbound Treatment: 9653 Alone	9653 Percent Unbound Treatment: Diazepam and ACC-9653	Phenytoin Percent Unbound Treatment: 9653 Alone	Phenytoin Percent Unbound Treatment: Diazepam and ACC-9653

(a) - Relative to the start of the diazepam infusion. 9653 was started at 15 minutes.
N=9 at all time points.
No statistically significant differences were observed between treatments ($p > 0.05$).

	Diazepam Percent Unbound Treatment

CONCLUSIONS: Co-administartion of fosphenytoin (750 mg/15 ml/15 min) and diazepam (10 mg/2 ml/5 min) resulted in plasma concentrations of fosphenytoin, phenytoin and diazepam similar to those observed when fosphenytoin or diazepam was administered alone. It should be noted that fosphenytoin was not administered at maximum dose and rate. The sponsor's labeling of fosphenytoin allows for doses up to 20 mg/kg (in a 70 kg individual this equals 1400 mg) and rates up to 225 mg/min. Thus the dose was approximately 50% of the labeled maximum, and the rate was approximately 25% of the labeled maximum. Similarly, Valium was not administered at maximum dose. The dose of Valium used was only 33% of the labeled maximum of 30 mg. Thus, conditions which have the greatest potential for pharmacokinetic and pharmacodynamic interaction (maximum dose and rate of both co-administered agents) were not addressed in the study.

SYNOPSIS

TITLE A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, RISING SINGLE-DOSE STUDY OF THE PHARMACOKINETIC AND TOLERANCE PROFILES OF INTRAVENOUS FOSPHENYTOIN SODIUM (CI-982) ADMINISTERED AT FIVE DIFFERENT INFUSION RATES TO HEALTHY SUBJECTS (PROTOCOL 982-18-0)

INVESTIGATOR

CI-982 ANALYST(S)

OBJECTIVES To evaluate, in healthy subjects, the safety and tolerance of escalating single doses and infusion rates of intravenously (IV) administered fosphenytoin compared with placebo and to define the pharmacokinetics of fosphenytoin and phenytoin following IV administration of fosphenytoin

STUDY DESIGN Randomized, double-blind, placebo-controlled, four-way crossover, tolerance, and pharmacokinetic study

DRUG TREATMENT Following a randomized, four-way crossover design, subjects received single IV infusion doses of fosphenytoin or placebo at weekly intervals. The first group received 600, 1200, or 1800 mg fosphenytoin at 18.75 mg/min (equivalent to 400, 800, or 1200 mg phenytoin at 12.5 mg phenytoin/min) or placebo (identical volume of fosphenytoin vehicle administered at the same rate as the fosphenytoin dose). Subsequent groups received these same doses of fosphenytoin and placebo at 37.5, 75, 150, and 225 mg/min (equivalent to 25, 50, 100, and 150 mg phenytoin/min). Escalation to the next dose and/or infusion rate was contingent on the absence of significant adverse events at the previous dose or rate.

SUBJECT CHARACTERISTICS AND DISPOSITION Twenty-one men ranging in age from 19 to 43 years (mean 26) participated in this study. Twenty subjects completed the study; one subject withdrew for personal reasons.

PHARMACOKINETICS In general, fosphenytoin plasma concentrations increased with dose and infusion rate, peaked near the end of infusion, and then declined with a $t_{\frac{1}{2}}$ of approximately 0.25 hour. Mean fosphenytoin AUC(0-∞) values decreased with increasing infusion rate; but increased with increasing dose, although less than expected for a drug with linear pharmacokinetics. When higher plasma fosphenytoin concentrations were achieved with increasing infusion rates, more free fosphenytoin was available for conversion to phenytoin resulting in increased fosphenytoin clearance.

Total phenytoin and free phenytoin pharmacokinetics were nonlinear. Mean total phenytoin Cmax values increased approximately proportionally with increases in dose. AUC(0-∞) values increased at a greater than dose-proportional rate; mean AUC(0-∞) values increased approximately

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five-fold over the three-fold range of doses. While Cmax and AUC(0-∞) values increased with dose, they did not increase with increased rates, providing further evidence that extent of fosphenytoin conversion to phenytoin was independent of fosphenytoin infusion rate.

Fosphenytoin displaced phenytoin from plasma protein binding sites resulting in a phenytoin free fraction that increased with increasing plasma fosphenytoin concentration. Displacement was greatest after administration of 1200 mg phenytoin equivalents fosphenytoin, leading to increases in phenytoin free fraction during the first hour after the start of infusion. During the first hour, similar free phenytoin Cmax values were seen at 12.5 to 50 mg phenytoin equivalents/min, whereas higher free phenytoin Cmax values temporally related to increased free fraction were observed at 100 and 150 mg phenytoin equivalents/min. Following conversion of fosphenytoin to phenytoin, free fraction, and plasma free phenytoin concentrations were similar at all infusion rates. Free phenytoin concentration-time profiles after administration of 1200 mg phenytoin equivalents fosphenytoin at the two highest rates were similar to those historically observed following administration of 1200 mg Dilantin at 50 mg/min.

Renal phenytoin and free phenytoin clearances were independent of dose and infusion rate. Less than 2% of dose was excreted as phenytoin. Thus, transient alterations in phenytoin free fraction did not affect overall renal clearance of phenytoin.

SAFETY Overall, 88% of fosphenytoin-treated subjects experienced adverse events compared with 15% of placebo-treated subjects. A total of 220 adverse events occurred following fosphenytoin treatment; most were mild in intensity and attributed to drug treatment. In general, the overall frequency of adverse events increased with fosphenytoin dose. Dizziness was the most frequently reported adverse event following fosphenytoin treatment. Other than mild nystagmus observed at 800 and 1200 mg phenytoin equivalents of fosphenytoin, significant drug-related changes were not observed in clinical laboratory parameters, physical examinations, electrocardiograms, or vital signs. No deaths or serious adverse events occurred, and no subject withdrew from the study as the result of an adverse event.

CONCLUSIONS Fosphenytoin is rapidly converted to phenytoin; rate and extent of conversion are independent of dose and infusion rate. Fosphenytoin displaces phenytoin from plasma proteins, especially at infusion rates greater than 50 mg phenytoin equivalents/min, resulting in increased free phenytoin concentrations for approximately 30 minutes after the start of infusion. Free phenytoin concentration-time profiles similar to those of parenteral phenytoin can be obtained by selecting the proper fosphenytoin infusion rate. Fosphenytoin doses of 400 to 1200 mg phenytoin equivalents at rates of 25 to 150 mg phenytoin equivalents/min are acceptably tolerated. However, as with Dilantin and other antiepileptic drugs, dizziness, paresthesia, and other CNS symptoms are often reported.

TABLE A. Mean (%RSD) Fosphenytoin Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Cmax (μg/mL)		tmax (hr)		t½ (hr)		AUC(0-∞) (μg · hr/mL)		CL (mL/min)		Vd_{area} (L)	
400	12.5	51.2	(10.6)	0.53	(0.00)	0.17	(17.57)	30.7	(13.2)	295.1	(12.9)	4.32	(10.89)
400	25	73.5	(6.7)	0.27	(0.00)	0.24	(15.31)	31.1	(10.0)	289.6	(10.7)	5.90	(13.01)
400	50	87.0	(7.4)	0.14	(6.42)	0.20	(15.41)	29.1	(14.4)	312.6	(15.0)	5.29	(6.48)
400	100	95.5	(6.5)	0.10	(30.00)	0.25	(25.77)	30.3	(7.1)	295.5	(7.0)	6.22	(20.82)
400	150	85.4	(24.7)	0.11	(21.20)	0.26	(21.59)	28.5	(22.3)	330.4	(23.1)	7.12	(9.33)
800	12.5	92.1	(9.2)	1.03	(11.32)	0.23	(12.68)	55.9	(10.3)	523.3	(9.7)	6.99	(10.03)
800	25	87.2	(3.3)	0.53	(0.00)	0.25	(24.06)	53.6	(3.4)	532.9	(3.5)	7.05	(22.32)
800	50	113.2	(6.7)	0.27	(1.62)	0.23	(7.37)	48.7	(10.8)	570.3	(10.0)	7.17	(13.36)
800	100	145.9	(12.2)	0.13	(0.00)	0.26	(28.65)	48.9	(23.0)	884.6	(22.7)	8.14	(10.62)
800	150	134.4	(14.8)	0.12	(27.84)	0.27	(10.84)	45.9	(12.7)	894.6	(11.1)	9.02	(14.24)
1200	12.5	56.2	(14.6)	1.15	(22.59)	0.24	(11.79)	91.0	(15.6)	800.8	(13.9)	6.27	(21.12)
1200	25	84.7	(7.3)	0.77	(7.33)	0.29	(30.64)	76.7	(7.0)	850.5	(6.6)	8.57	(31.29)
1200	50	116.0	(8.5)	0.38	(11.55)	0.23	(20.94)	63.3	(12.8)	429.2	(12.5)	8.23	(16.75)
1200	100	168.7	(10.5)	0.20	(0.00)	0.57	(76.88)	63.2	(13.9)	432.5	(14.9)	21.12	(74.27)
1200	150	168.5	(10.1)	0.13	(0.00)	0.25	(5.98)	53.3	(11.6)	508.1	(10.9)	10.85	(8.91)

Rate = Rate of fosphenytoin infusion.
Cmax = Maximum observed plasma fosphenytoin concentration.
tmax = Time of Cmax, times differ from end of infusion.
t½ = Elimination half-life.
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinite time.
CL = Systemic plasma clearance.
%RSD = Relative standard deviation (% of mean value).

Note: These are adjusted fosphenytoin values.

TABLE B. Mean (%RSD) Phenytoin Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Cmax (μg/mL)		tmax (hr)		t½ (hr)		AUC(0-∞) (μg · hr/mL)	
400	12.5	8.50	(10.65)	0.94	(9.79)	14.3	(49.9)	179.5	(41.1)
400	25	8.46	(6.96)	1.01	(59.83)	12.0	(11.8)	164.3	(20.7)
400	50	8.19	(9.47)	1.18	(52.59)	13.0	(26.5)	179.0	(29.9)
400	100	8.23	(10.63)	1.28	(41.27)	14.0	(18.7)	177.8	(20.2)
400	150	8.19	(8.50)	0.83	(55.94)	12.9	(11.7)	177.8	(14.7)
800	12.5	15.43	(12.19)	1.68	(20.41)	18.6	(56.5)	490.0	(37.8)
800	25	16.55	(11.82)	1.32	(41.48)	12.6	(8.8)	475.0	(19.2)
800	50	15.60	(13.72)	1.21	(37.33)	16.5	(37.1)	485.8	(28.9)
800	100	19.23	(23.58)	0.61	(84.45)	19.7	(16.0)	468.3	(24.7)
800	150	16.25	(6.66)	1.12	(34.55)	17.0	(21.1)	503.5	(18.4)
1200	12.5	23.48	(12.63)	2.50	(0.00)	25.1	(80.9)	1030.0	(42.8)
1200	25	24.00	(9.19)	1.62	(26.33)	17.6	(21.6)	920.0	(20.2)
1200	50	22.53	(4.85)	1.88	(11.55)	21.8	(40.5)	914.3	(29.2)
1200	100	22.88	(6.55)	1.22	(40.19)	28.9	(23.6)	940.8	(21.2)
1200	150	24.35	(7.67)	1.01	(50.65)	21.7	(35.3)	863.3	(25.8)

Rate = Rate of fosphenytoin infusion.
Cmax = Maximum observed plasma phenytoin concentration.
tmax = Time of Cmax, times differ from end of infusion.
t½ = Elimination half-life.
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinite time.
%RSD = Relative standard deviation (% of mean value).

TABLE C. Mean (%RSD) Free Phenytoin Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Cmax (μg/mL)		tmax (hr)		AUC(0-tldc) (μg·hr/mL)	
400	12.5	0.000	—	—	—	0.00	—
400	25	0.334	(58.6)	0.47	(77.0)	0.28	(173.2)
400	50	0.422	(25.0)	0.69	(70.8)	1.75	(39.4)
400	100	0.460	(26.6)	0.43	(41.5)	1.51	(30.4)
400	150	0.389	(23.4)	1.18	(92.1)	1.10	(14.1)
800	12.5	0.645	(20.9)	1.48	(22.2)	3.23	(63.0)
800	25	0.880	(24.7)	0.88	(42.2)	8.45	(48.4)
800	50	0.837	(20.3)	0.43	(43.6)	10.88	(30.1)
800	100	1.537	(47.3)	0.34	(59.8)	11.54	(48.4)
800	150	0.774	(16.6)	0.61	(24.0)	13.50	(25.8)
1200	12.5	1.083	(13.5)	1.78	(2.4)	18.61	(52.8)
1200	25	1.200	(10.3)	1.84	(69.2)	26.25	(8.1)
1200	50	1.313	(15.6)	0.63	(34.0)	22.90	(26.7)
1200	100	2.083	(55.2)	0.40	(52.7)	24.55	(14.8)
1200	150	1.720	(7.59)	0.22	(27.7)	27.73	(39.4)

Rate = Rate of fosphenytoin infusion.
Cmax = Maximum observed plasma free phenytoin concentration.
tmax = Time of Cmax, times differ from end of infusion.
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to time of the last detectable concentration.
%RSD = Relative standard deviation (% of mean value).
— = Indeterminable.

TABLE D. Mean (%RSD) Urinary Pharmacokinetic Parameters Following Intravenous Administration of 400-, 800-, and 1200-mg Phenytoin Equivalent Doses of Fosphenytoin to Healthy Subjects (982-018)

Dose (mg)	Rate (mg/min)	Phenytoin						p-HPPH			
		Ae (mg)		Ae% (%)		Clr (mL/min)		Ae (mg)		Ae% (%)	
400	12.5	3.14	(13.8)	0.85	(13.8)	0.346	(41.2)	81.6	(25.7)	19.3	(25.7)
400	25	2.84	(38.9)	0.77	(38.9)	0.288	(20.8)	49.5	(25.4)	11.7	(25.4)
400	50	3.22	(19.9)	0.88	(19.9)	0.328	(27.1)	58.4	(11.2)	13.8	(11.2)
400	100	3.77	(18.8)	1.03	(18.8)	0.377	(24.2)	61.2	(23.2)	14.5	(23.2)
400	150	3.24	(16.7)	0.88	(16.7)	0.329	(28.7)	64.2	(21.1)	15.2	(21.1)
800	12.5	8.83	(23.8)	1.20	(23.8)	0.365	(48.2)	141.6	(15.3)	16.8	(15.3)
800	25	8.12	(23.1)	1.10	(23.1)	0.290	(5.25)	128.6	(18.7)	15.2	(18.7)
800	50	9.40	(41.2)	1.28	(41.2)	0.340	(22.7)	107.0	(26.1)	12.7	(26.1)
800	100	9.52	(17.8)	1.29	(17.8)	0.385	(27.4)	115.8	(11.5)	13.7	(11.5)
800	150	8.89	(17.0)	1.21	(17.0)	0.320	(31.9)	133.0	(34.3)	15.8	(34.3)
1200	12.5	17.63	(36.0)	1.60	(36.0)	0.371	(62.4)	218.1	(19.5)	17.2	(19.5)
1200	25	16.13	(29.5)	1.46	(29.5)	0.301	(12.5)	172.9	(3.55)	13.7	(3.55)
1200	50	18.69	(30.9)	1.69	(30.9)	0.379	(8.60)	179.7	(22.4)	14.2	(22.4)
1200	100	16.77	(18.9)	1.52	(18.9)	0.350	(20.6)	174.2	(21.6)	13.8	(21.6)
1200	150	16.42	(33.4)	1.49	(33.4)	0.362	(44.8)	190.0	(39.5)	15.0	(35.9)

Ae = Amount excreted in urine.
Ae% = Amount excreted in urine expressed as percent of dose.
CLr = Renal clearance.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).

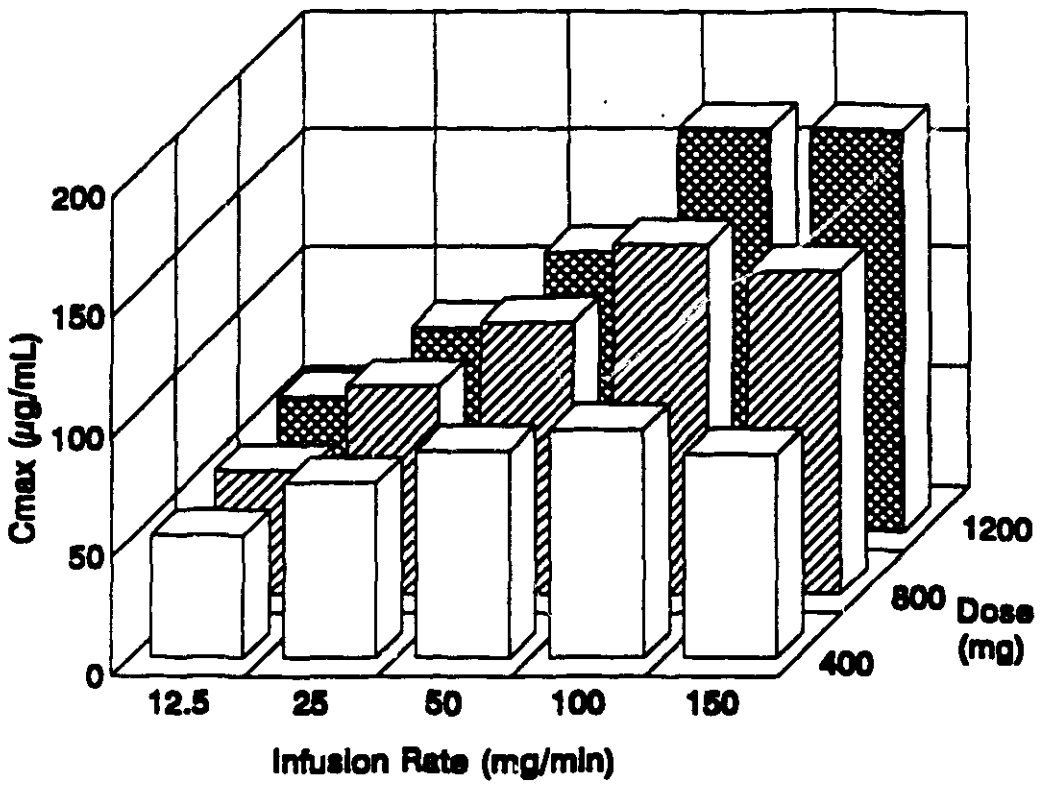


FIGURE A. Relationship Between Mean Fosphenytoin Cmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

Note: The Y-axis has been rescaled to reflect the adjusted fosphenytoin Cmax values.

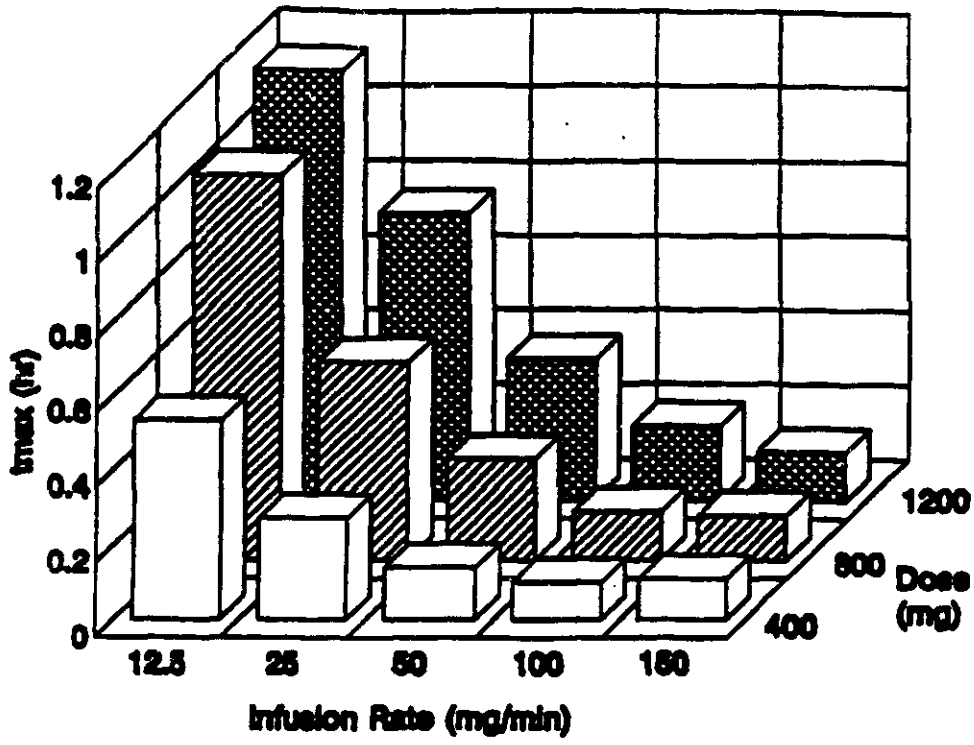


FIGURE B. Relationship Between Mean Fosphenytoin tmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

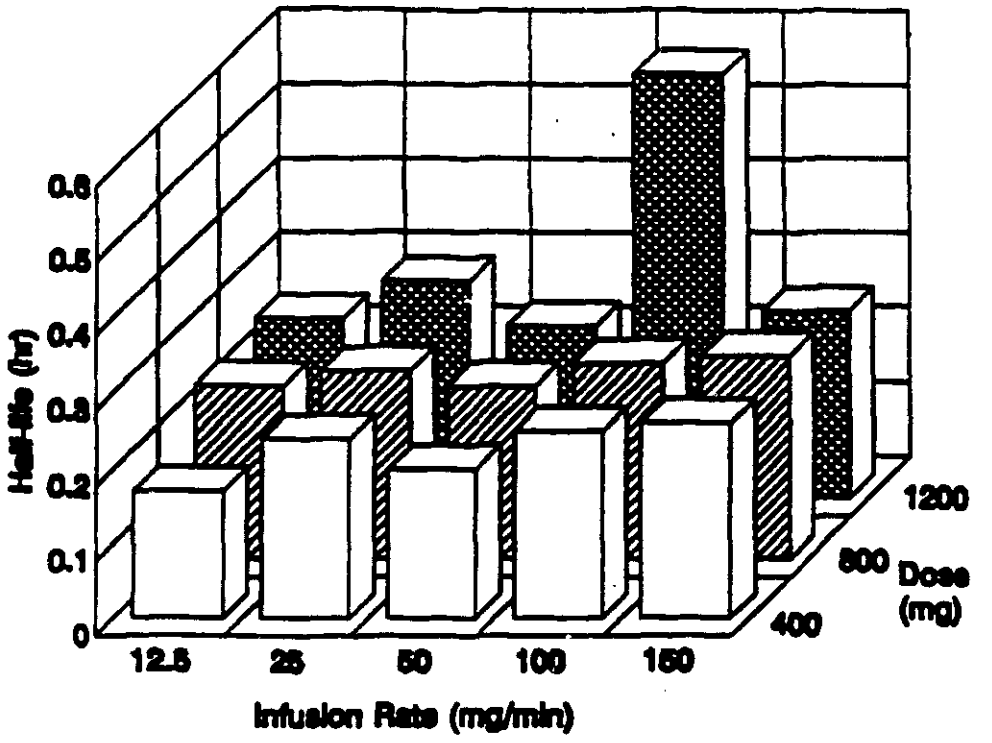


FIGURE C. Relationship Between Fosphenytoin Mean Half-Life Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

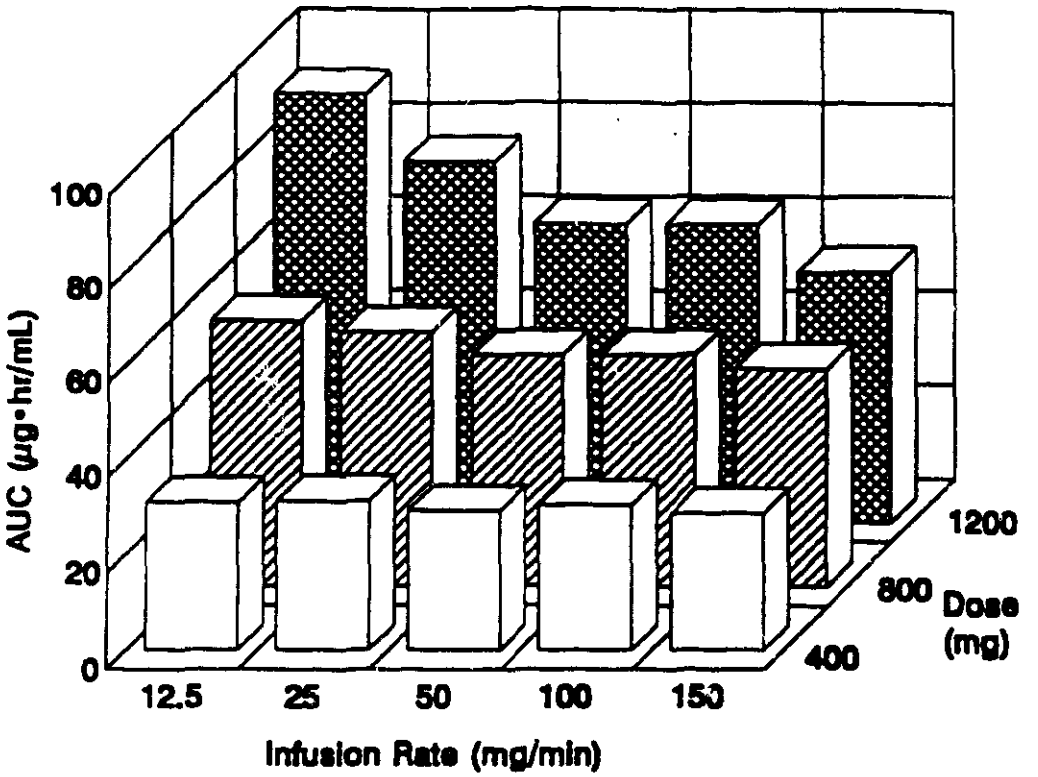


FIGURE D. Relationship Between Fosphenytoin Mean AUC(0-∞) Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

Note: The Y-axis has been rescaled to reflect the adjusted fosphenytoin AUC values.

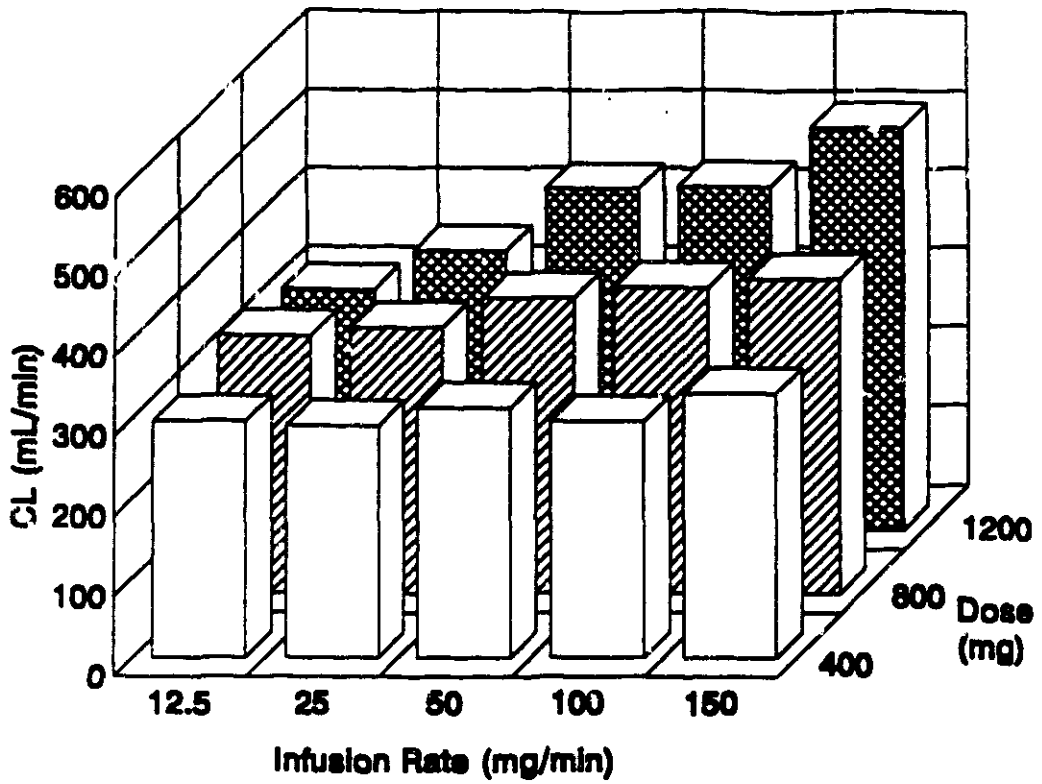


FIGURE E. Relationship Between Mean Fosphenytoin Clearance Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

Note: The Y-axis has been rescaled to reflect the adjusted fosphenytoin CL values.

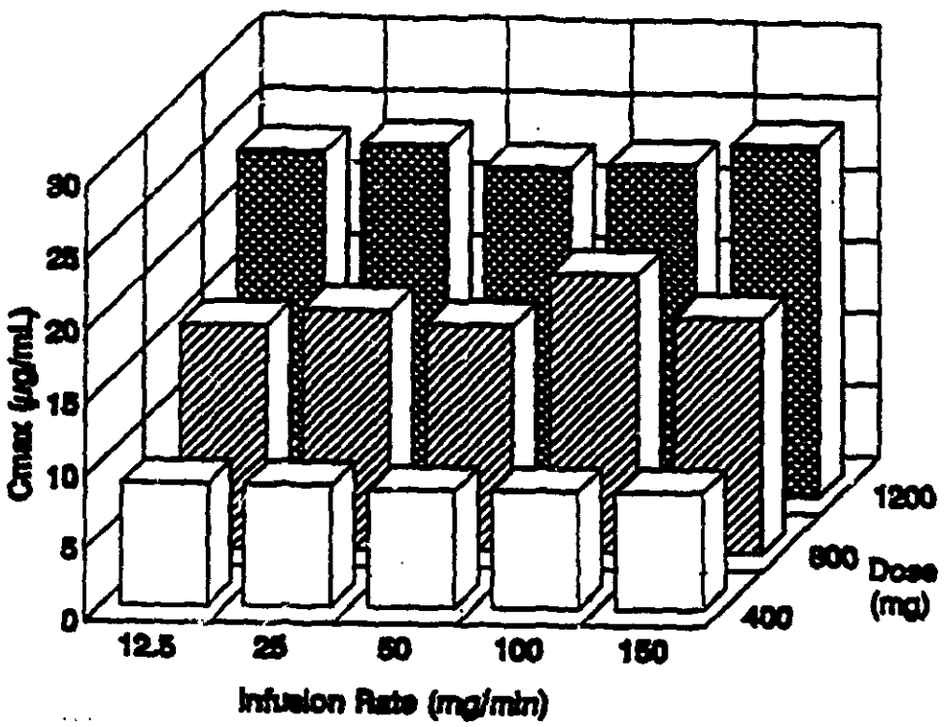


FIGURE F. Relationship Between Mean Total Phenytoin Cmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (*Protocol* 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

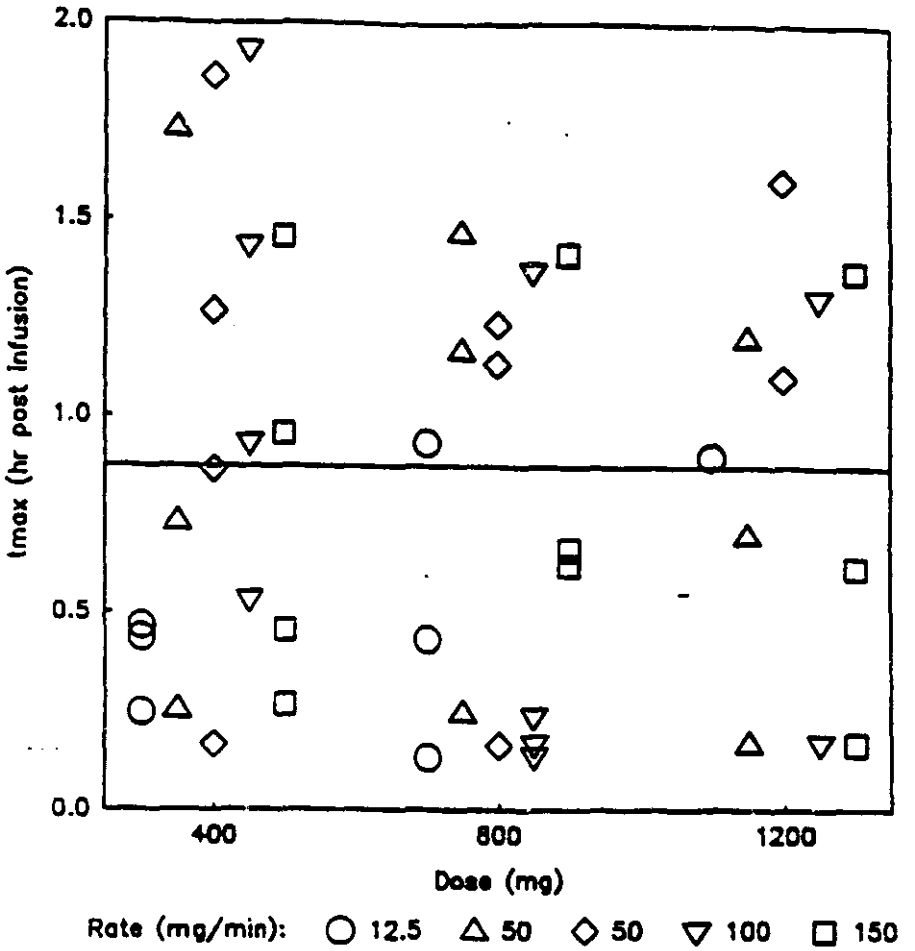


FIGURE G. Individual Phenytoin tmax Values (hour postinfusion) Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Horizontal line depicts mean value. Values may have been shifted slightly along the ordinate to facilitate resolution.

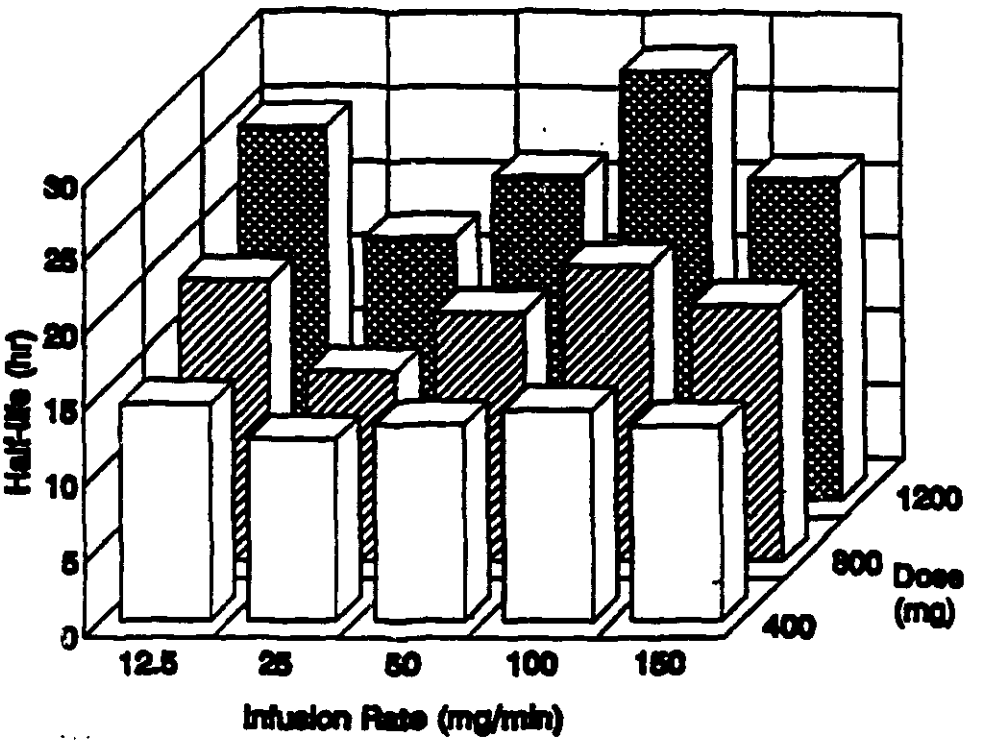


FIGURE H. Relationship Between Mean Phenytoin Half-Life Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

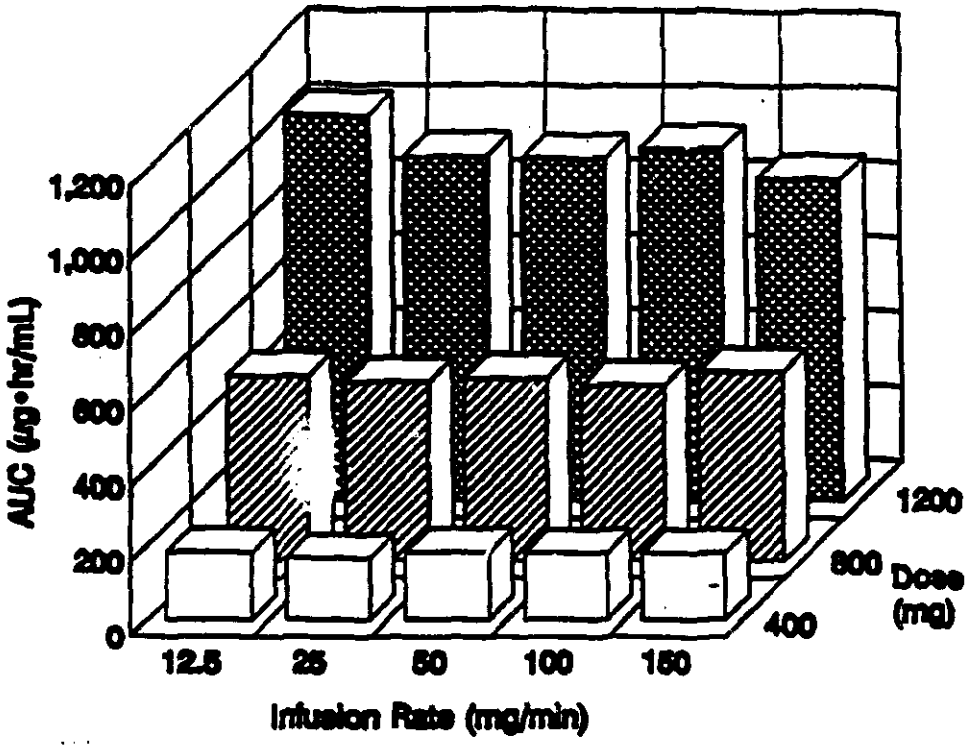


FIGURE I. Relationship Between Mean Phenytoin AUC(0-∞) Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

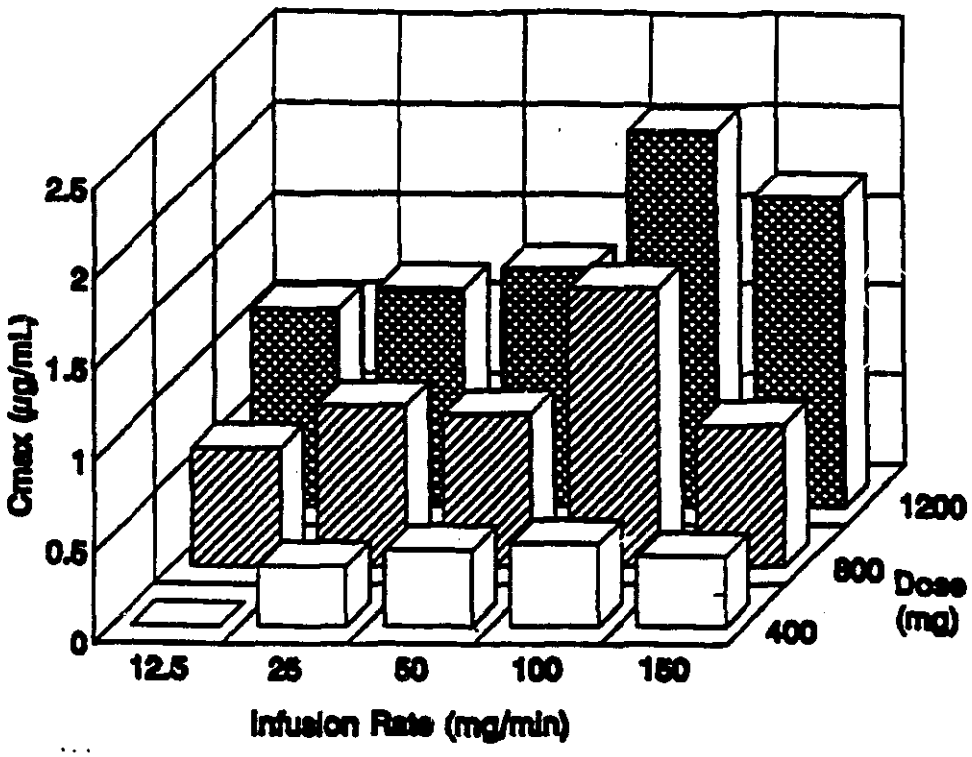


FIGURE 5. Relationship Between Mean Free Phenytoin Cmax Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

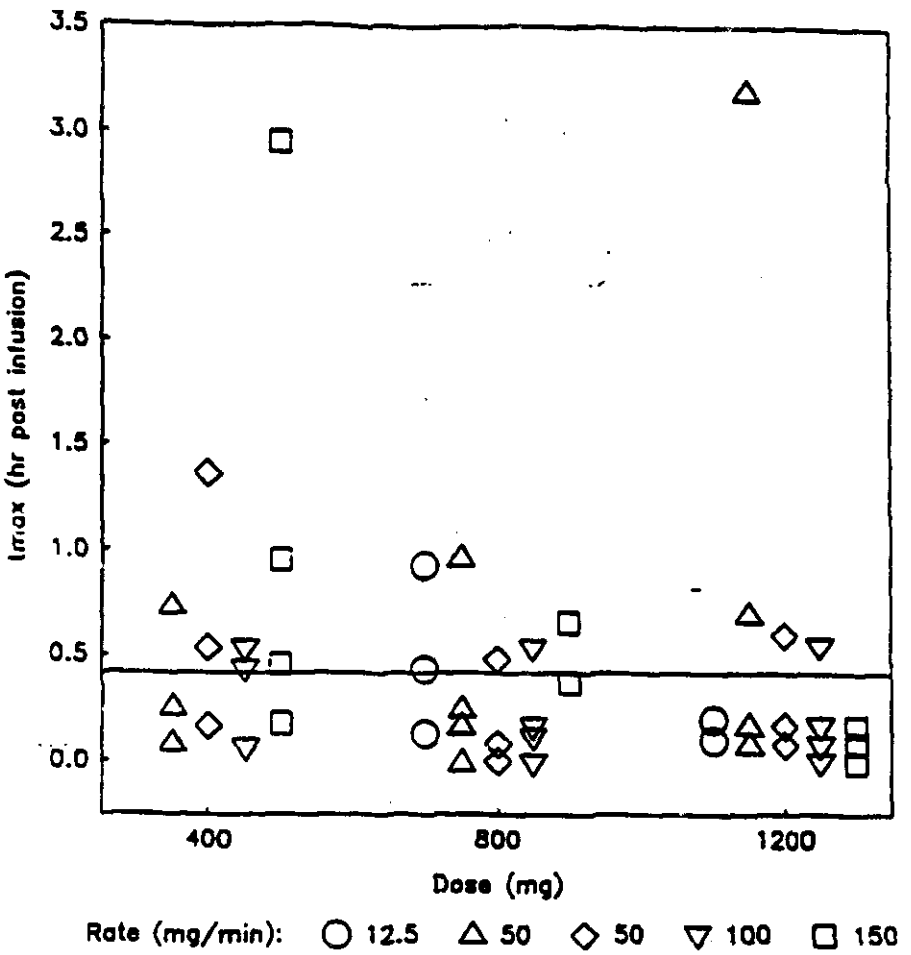


FIGURE K. Individual Free Phenytoin tmax Values (hour postinfusion) Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Horizontal line depicts mean value. Values may have been shifted slightly along the ordinate to facilitate resolution.

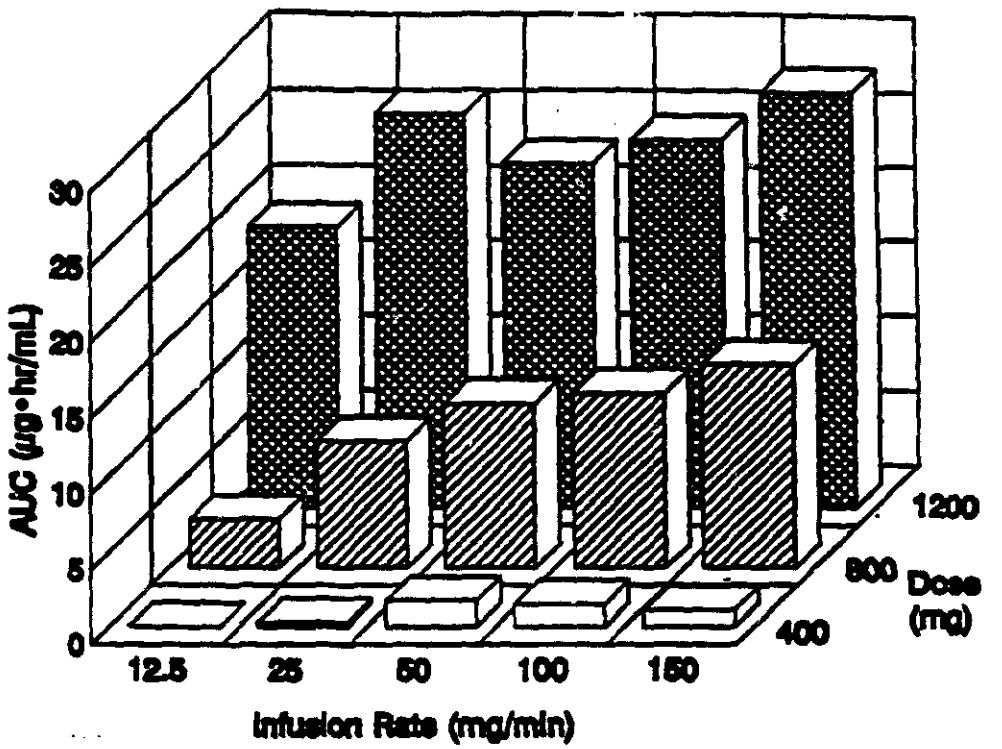


FIGURE L. Relationship Between Mean Free Phenytoin AUC(0-tldc) Values, Dose, and Infusion Rate Following Intravenous Administration of Fosphenytoin to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents.

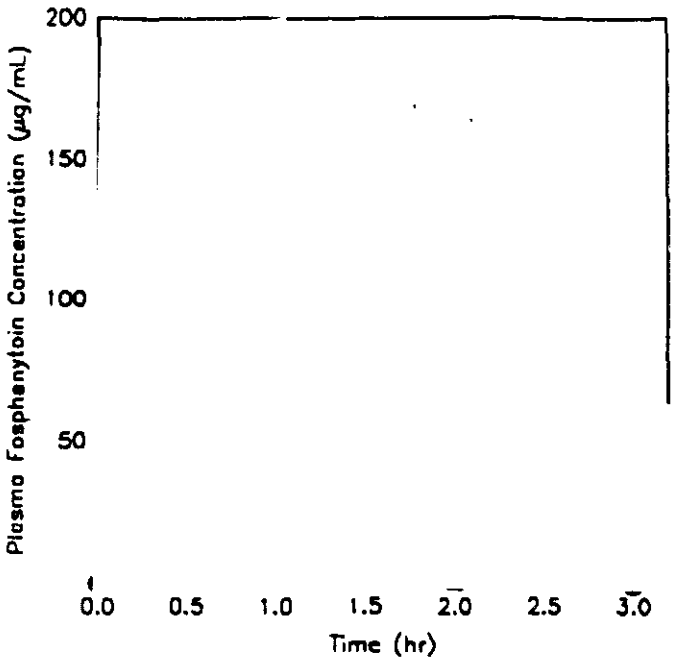
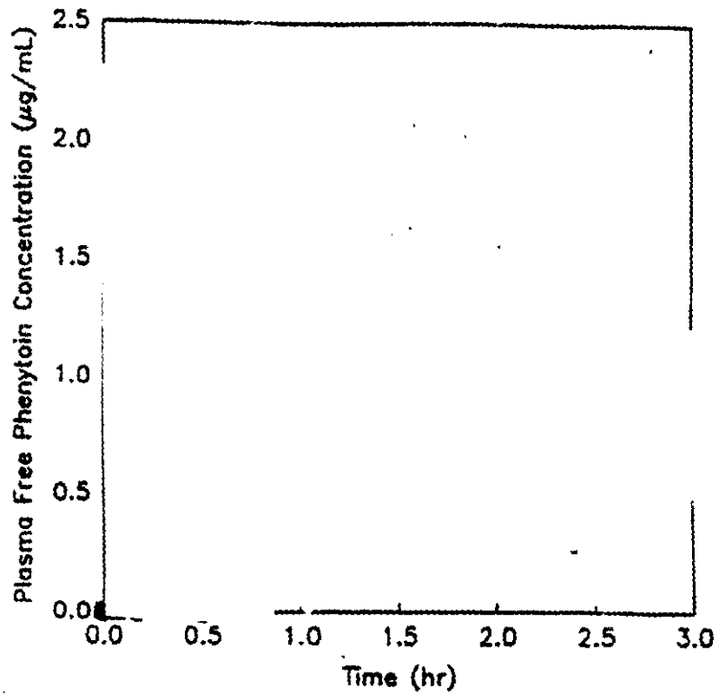


FIGURE O. Mean Plasma Fosphenytoin Concentration Versus Nominal Sample Collection Time Profiles Following Intravenous Administration of 1200 mg Fosphenytoin at 12.5 (○), 25 (●), 50 (△), 100 (▲), and 150 (□) mg/min to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Values depicted are mean of Period 4 data.

Note: The Y-axis has been rescaled to reflect the adjusted fosphenytoin concentration values.



Free Phenytoin

FIGURE Q. Mean Plasma ~~Fosphenytoin~~ Concentration Versus Nominal Sample Collection Time Profiles Following Intravenous Administration of 1200 mg Fosphenytoin at 12.5 (○), 25 (●), 50 (△), 100 (▲), and 150 (□) mg/min to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Values depicted a mean of Period 4 data.

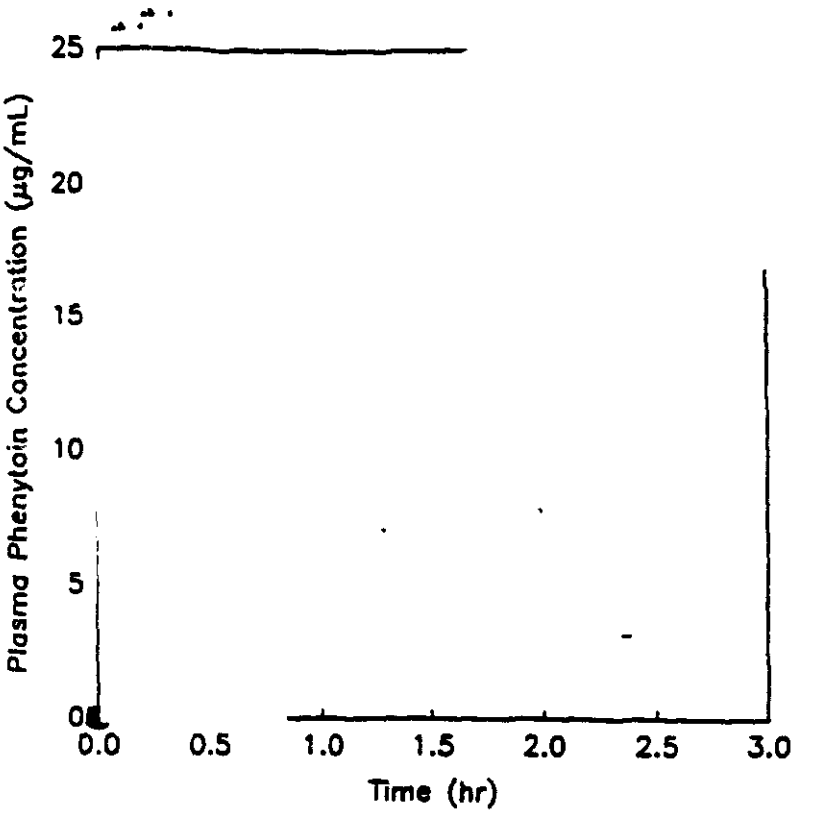


FIGURE P. Mean Plasma ~~Fosphenytoin~~ Phenytoin Concentration Versus Nominal Sample Collection Time Profiles Following Intravenous Administration of 1200 mg Fosphenytoin at 12.5 (○), 25 (●), 50 (△), 100 (▲), and 150 (□) mg/min to Healthy Subjects (Protocol 982-18)

Fosphenytoin doses and infusion rates are expressed as phenytoin equivalents. Values depicted are mean of Period 4 data.

concentrations generally occurred 30 minutes earlier than maximal total phenytoin concentrations. Despite displacement of phenytoin from plasma proteins by fosphenytoin, mean free phenytoin Cmax following fosphenytoin was 35% less than that following Dilantin, with the mean maximum difference occurring at the end of infusion. After conversion of fosphenytoin to phenytoin, plasma free phenytoin concentrations were similar for both treatments. At a molar equivalent dose and rat comparable free and total phenytoin AUC values were obtained following fosphenytoin and Dilantin.

SAFETY The nature and frequency of adverse events were similar after fosphenyt and Dilantin; few adverse events occurred following placebo. The most frequent adverse events after fosphenytoin and Dilantin were nystagmus, dizziness, and tinnitus. Injection-site symptoms (inflammation, pain, and reaction) were experien by fewer subjects following fosphenytoin (33%) than Dilantin (83%). There were deaths, serious adverse events, or withdrawals due to adverse events. No clinicall significant changes occurred in clinical laboratory parameters, physical examinatio electrocardiograms, or vital signs.

CONCLUSIONS A molar equivalent dose of fosphenytoin administered at 50 m phenytoin equivalents/min produces comparable free and total phenytoin AUC va but slightly lower and delayed maximal free and total phenytoin concentrations compared to those following Dilantin administered at the same rate. The similar free and total phenytoin concentration-time profiles suggests that fosphenytoin administered at 50 mg phenytoin equivalents/min should be a suitable substitute Dilantin in nonemergent situations. Fosphenytoin has a similar safety profile to Dilantin, but is better tolerated at the injection site.

SYNOPSIS

TITLE A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND DILANTIN®-CONTROLLED, SINGLE-DOSE STUDY OF THE PHARMACOKINETIC AND TOLERANCE PROFILES OF INTRAVENOUS FOSPHENYTOIN SODIUM (CI-982) IN HEALTHY SUBJECTS (PROTOCOL 982-20-0)

INVESTIGATOR

CI-982 ANALYST

OBJECTIVE To compare the pharmacokinetics of phenytoin following single doses of intravenously administered fosphenytoin and Dilantin, and to evaluate the safety and tolerance of fosphenytoin compared with Dilantin and placebo

STUDY DESIGN Randomized, double-blind, 3-way crossover, pharmacokinetic and tolerance study

DRUG TREATMENT Each subject received 1200 mg Dilantin, a molar equivalent dose of fosphenytoin, and placebo; each treatment was separated by a 1-week washout period. Fosphenytoin was infused at 50 mg phenytoin equivalents/min (75 mg/min) and Dilantin at 50 mg/min. Subjects were randomized so that only 2 subjects received each treatment (fosphenytoin, Dilantin, or placebo) at any one time.

SUBJECT CHARACTERISTICS AND DISPOSITION Twelve men ranging in age from 18 to 49 years (median 30) entered and completed this study.

PHARMACOKINETICS Plasma fosphenytoin, total phenytoin, and free phenytoin concentrations were quantified using validated liquid chromatographic methods. Plasma fosphenytoin concentrations peaked near the end of the infusion. Rapid conversion of fosphenytoin to phenytoin was apparent from the short mean fosphenytoin t½ value of 0.29 hour. For the first hour after dosing, total phenytoin concentrations following fosphenytoin were lower than those following Dilantin due to the time required for conversion of fosphenytoin to phenytoin. Mean phenytoin AUC(0-tldc) values following fosphenytoin were approximately 8% less than those following Dilantin, probably due to differences in total phenytoin clearance as a function of plasma phenytoin concentration rather than incomplete conversion of fosphenytoin to phenytoin.

Free phenytoin tmax values after fosphenytoin were influenced by fosphenytoin displacement of phenytoin from plasma proteins as maximal free phenytoin

TABLE 5. Mean (%RSD) Free Phenytoin Pharmacokinetic Values Following Intravenous Administration of 1200-mg Phenytoin Equivalent Doses of Fosphenytoin and Dilantin Infused at 50 mg/min Phenytoin Equivalents

Pharmacokinetic Parameter	Fosphenytoin N = 12		Dilantin N = 11	
Cmax, μg/mL	2.6	(20.4)	4.6	(33.2)
tmax, hr	0.5	(35.2)	0.5	(22.2)
AUC(0-tldc), μg · hr/mL	66.1	(30.9)	74.1	(24.8)
AUC(0-∞), μg · hr/mL	73.1	(34.1)	82.8	(28.9)
AUC_{extrap}, %	8.9	(44.7)	9.8	(51.8)
λz, hr^{-1}	0.034	(22.9)	0.031	(25.6)
t½, hr	21.7	(30.1)	24.3	(32.2)
CL, mL/min	275	(28.9)	238	(26.4)
Vd_{area}, L	484	(13.0)	476	(23.4)

%RSD = Relative standard deviation (% of mean value).

TABLE 6. Comparison of Mean Free Phenytoin Pharmacokinetic Parameters Following Intravenous Administration of 1200-mg Phenytoin Equivalent Doses of Fosphenytoin and Dilantin Infused at 50 mg/min Phenytoin Equivalents

Parameter	Fosphenytoin (Test)			Dilantin (Reference)			Ratio of Least-Squares Means (Test/Reference)	90% Confidence Interval[a]
	Mean	%RSD	N	Mean	%RSD	N		
Cmax, μg/mL	2.58	20.4	12	4.04	33.2	11	64.6[b]	53.8 - 77.8
tmax, hr	0.49	35.2	12	0.46	22.2	11	108.2	94.7 - 121.7
AUC(0-tldc), μg · hr/mL	66.1	30.9	11	74.1	24.8	11	87.2[b]	83.0 - 91.7

Mean = Arithmetic mean of untransformed data.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).
[a] Ninety percent confidence intervals for ratio (test/reference) of treatment least-squares mean values
[b] Ratio represents antitransforms of difference between treatment least-squares means of natural log transformed parameters values (test-reference) expressed as a percentage.

Mean free phenytoin AUC(0-tldc) following fosphenytoin administration was 13% less than that following Dilantin. As previously discussed for total phenytoin, this small difference in AUC(0-tldc) is probably the result of differences in clearance as a function of free phenytoin concentration rather than incomplete conversion of fosphenytoin to phenytoin. Free phenytoin AUC(0-tldc) met commonly used

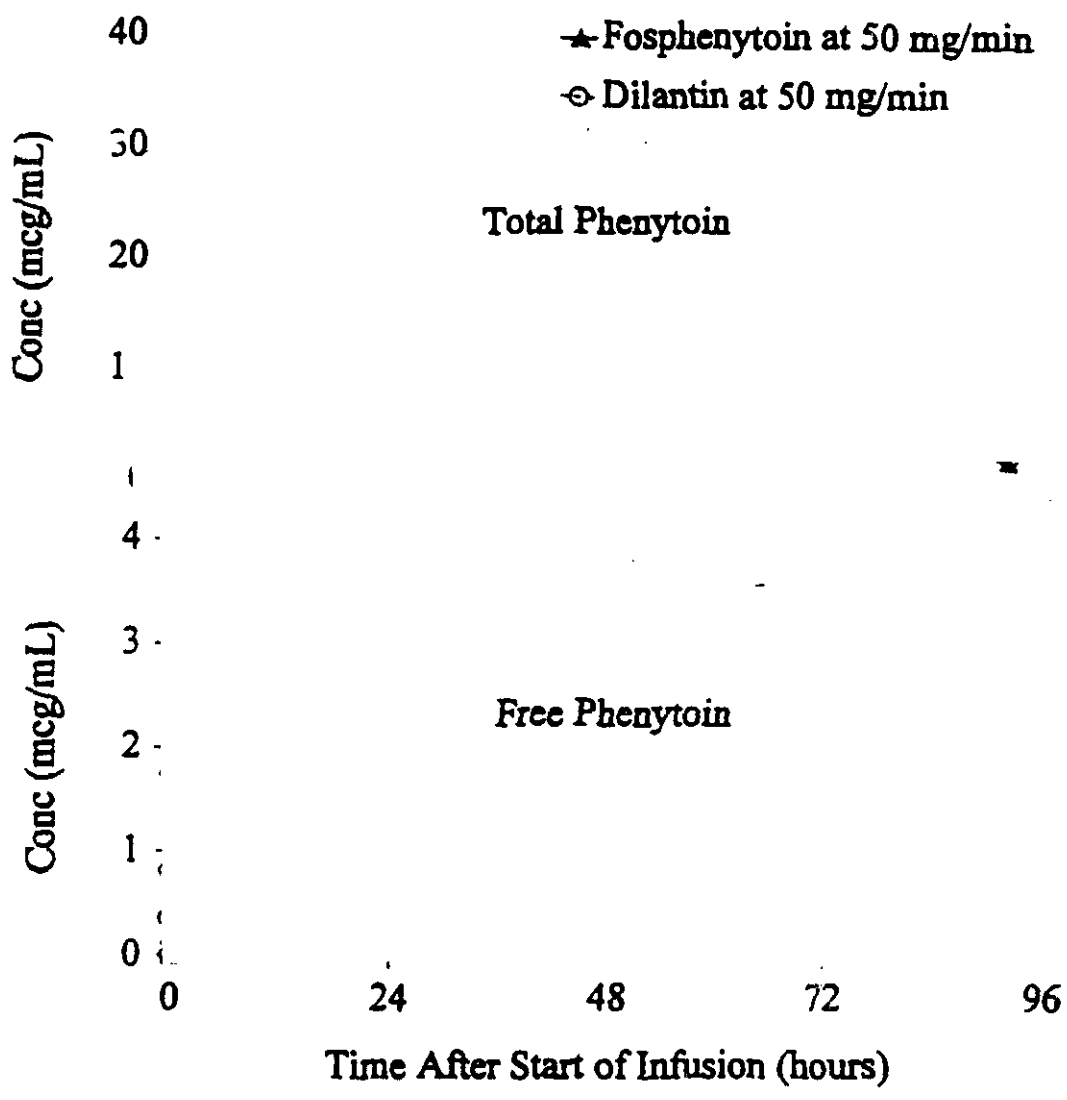


FIGURE 2. Mean Total and Free Phenytoin Concentrations Following Intravenous Administration of 1200-mg Phenytoin Equivalent Doses of Fosphenytoin and Dilantin Infused at 50 mg/min Phenytoin Equivalents to 12 Healthy Subjects

3 Pages
Purged

STUDY: A Randomized, Nonblind, Dilantin-Controlled, Single-Dose Study of the Pharmacokinetic Profile and Tolerance of Intravenous Fosphenytoin Sodium (CI-982) in Healthy Subjects

PROTOCOL NUMBER: 982-24-0

RESEARCH REPORT NUMBER: RR 744-00152

STUDY DESIGN: Randomized, nonblind, 3-way crossover study in healthy males between 18 and 50 yrs. of age

TABLE 1. Treatment Sequences for Drug Administration[a]

Sequence		Week 1	Week 2	Week 3
1	Treatment	Fosphenytoin	Fosphenytoin	Dilantin
	Rate	100	150	50
2	Treatment	Fosphenytoin	Dilantin	Fosphenytoin
	Rate	150	50	100
3	Treatment	Dilantin	Fosphenytoin	Fosphenytoin
	Rate	50	100	150

[a] Infusion rates are in milligram phenytoin equivalents per minute for fosphenytoin and milligrams per minute for Dilantin.

SUBJECTS: 12 healthy males (10 white, 2 other), ages 20 - 42

DOSAGE FORM: see Formulation Summary: Appendix 3

ASSAY: see Analytical Methods Summary: Appendix 4. EDTA was used as an anti-coagulant and ultrafiltration was performed at 37° C in this study.

PROTOCOL VARIATIONS: There were no protocol variations.

SAFETY RESULTS:

SAFETY The nature of adverse events was similar after fosphenytoin and Dilantin. Nystagmus occurred with similar frequency following both treatments. However, paresthesia and pruritus were noted more frequently following fosphenytoin than Dilantin, and dizziness occurred more often following Dilantin than fosphenytoin. Pruritus increased in frequency as fosphenytoin infusion rate increased. Injection-site symptoms (inflammation, pain, reaction, hypersensitivity) were experienced by fewer subjects following fosphenytoin (42%) than Dilantin (100%). There were no deaths, serious adverse events, or withdrawals due to adverse events. No clinically significant changes occurred in clinical laboratory parameters, physical examinations, electrocardiograms, or vital signs.

PHARMACOKINETIC AND STATISTICAL METHODS:

Fosphenytoin, total phenytoin, and free phenytoin pharmacokinetic parameters were calculated for each subject and each treatment by noncompartmental analysis of plasma concentration-time data.[10] Actual sample collection times were used for pharmacokinetic parameter calculations. Maximum observed plasma fosphenytoin, total phenytoin, and free phenytoin concentrations (Cmax) and the time each occurred (tmax) were recorded as observed. Area under plasma analyte concentration-time curve (AUC) was estimated using the linear trapezoidal method. AUC(0-tldc) was calculated from time zero to the time of the last detectable concentration (ldc). The apparent first-order terminal rate constant (λz) was estimated as the absolute value of the slope of a linear regression of natural logarithm (ln) of plasma analyte concentration on time during the terminal elimination phase of the plasma analyte concentration profile. Apparent terminal half-life ($t\frac{1}{2}$) was calculated as $\ln(2)/\lambda z$. AUC(0-∞) was calculated as the sum of corresponding AUC(0-tldc) and $ldc/\lambda z$ values. Due to the recognized nonlinearity of total and free phenytoin elimination, total and free phenytoin AUC(0-∞), λz, and $t\frac{1}{2}$ values were not reported.

Similarity between treatments observed while qualitatively comparing mean parameter values led to use of the following conventional statistical analysis plan for the assessment of bioequivalence which was performed using a validated computer system.[10] Ln(Cmax) and ln[AUC(0-tldc)] values for free phenytoin were the primary parameters evaluated for pharmacokinetic equivalence using established bioequivalence criteria. Secondary parameters (Cmax, tmax, and AUC[0-tldc]) for free phenytoin were also analyzed. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, subject within sequence, period, and treatment effects. The sequence effect was assessed using the subject within sequence mean square from the ANOVA as the error term to form the appropriate 2-sided F-test. Period effects were tested using residual error variance; a p-value <0.05 was considered significant. Statistical tests were performed using Type III sum of squares from the general linear model (GLM) procedure of SAS (SAS Releases 5.18 and 6.07, SAS Institute Inc, Cary, North Carolina, USA). Least-squares treatment mean values were determined for each parameter. Program code and output are stored in databooks listed in Table 1 in Appendix C.1.

Bioequivalence was concluded if estimates of the 90% confidence interval for the ratio of test (fosphenytoin) to reference (Dilantin) least-squares mean values, based on log-transformed Cmax and AUC(0-tldc) data, were between 80% and 125%.[13] This was equivalent to using the two 1-sided tests procedure.[14]

PHARMACOKINETIC RESULTS: The mean concentration-time profiles for fosphenytoin, total phenytoin and free phenytoin are shown below.

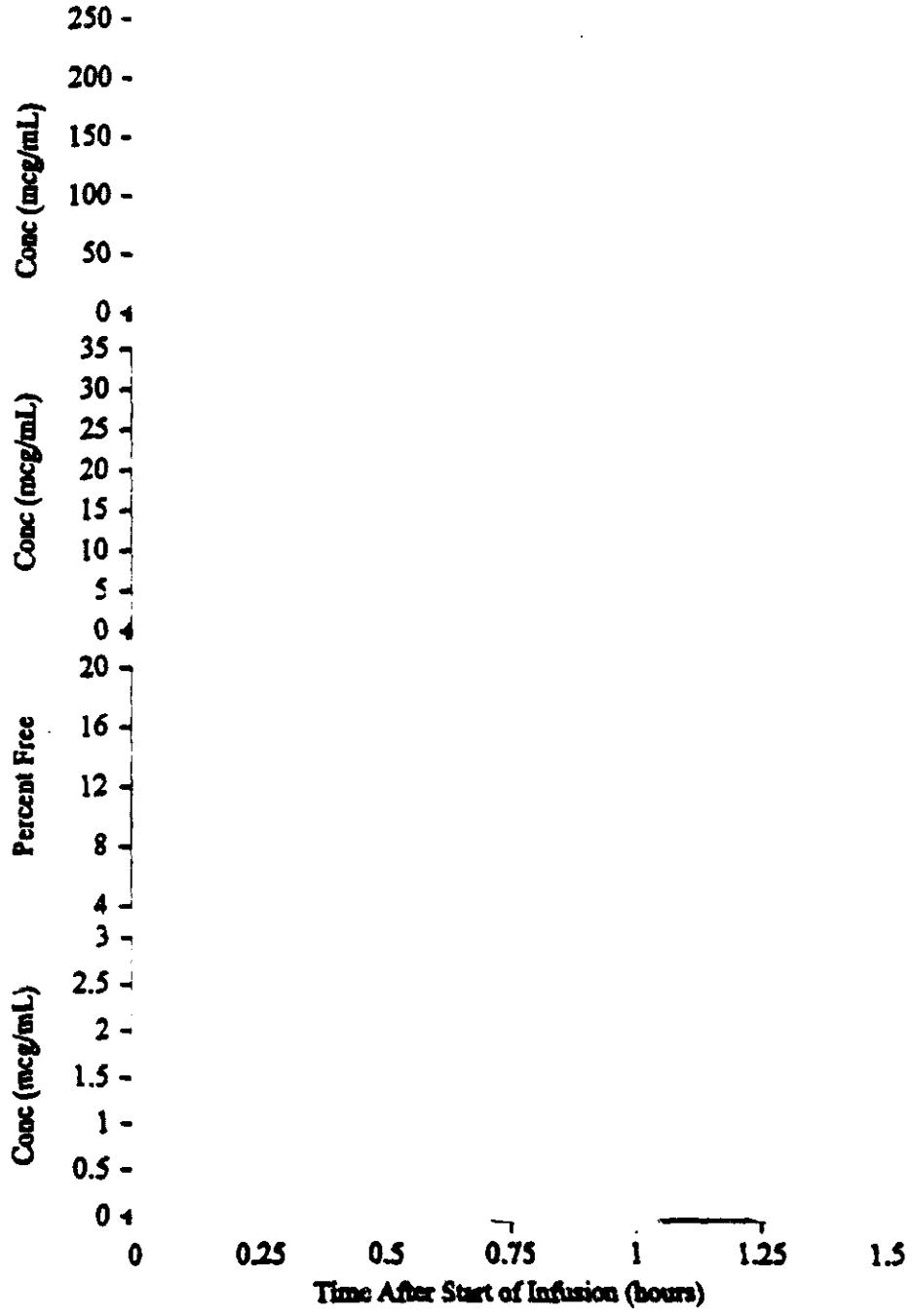


FIGURE 1. Mean Fosphenytoin (Panel A), Total Phenytoin (Panel B), and Free Phenytoin (Panel D) Concentrations and Mean Phenytoin Free Fraction (Panel C) Following Intravenous Administration of 1200 mg Phenytoin Equivalent Doses of Fosphenytoin Infused at 100 and 150 mg/min Phenytoin Equivalents and Dilantin Infused at 50 mg/min (N = 12)

The following table demonstrates that using the two one-sided confidence interval approach and the 80 - 125 % confidence interval criteria, fosphenytoin at (phenytoin equivalent) 1200 mg and 150 mg/min is bioequivalent to Dilantin at 1200 mg and 50 mg/min with regard to free phenytoin AUC and Cmax. Fosphenytoin at 100 mg/min is equivalent with regard to extent of exposure (AUC) but not rate (Cmax).

PK PARAMETERS ARE FOR FREE DRUG

Pharmacokinetic Parameter	Fosphenytoin		Dilantin[a]		Ratio	90% CI
	at 100 mg PE/min					
ln(Cmax)[b], μg/mL	2.72		3.21		84.7	72.7 - 98.8
ln[AUC(0-tldc)][b], μg · hr/mL	78.8		85.5		92.2	88.4 - 96.2
Cmax, μg/mL	2.78	(22)	3.30	(26)	84.2	NA
tmax, hr	0.524	(37)	0.526	(17)	99.6	NA
AUC(0-tldc), μg · hr/mL	79.5	(14)	87.1	(22)	91.3	NA
	at 150 mg PE/min					
ln(Cmax)[b], μg/mL	3.08		3.21		96.0	82.1 - 111.7
ln[AUC(0-tldc)][b], μg · hr/mL	84.5		85.5		98.8	94.8 - 103.2
Cmax, μg/mL	3.18	(28)	3.30	(26)	96.4	NA
tmax, hr	0.576	(59)	0.526	(17)	109.5	NA
AUC(0-tldc), μg · hr/mL	85.5	(17)	87.1	(22)	98.2	NA

Ratio = Ratio (test/reference) of treatment least-squares mean values expressed as a percentage.
90% CI = 90% confidence estimate for ratio (test/reference) of treatment least-squares mean values expressed as a percentage.
PE = Phenytoin equivalents.
NA = Not applicable.
[a] At 50 mg/min
[b] Values represent antilogs of log-transformed data

Because extent of exposure at early time points is important in therapy of status epilepticus, the sponsor was asked to evaluate cumulative AUC across time. The results are shown on the following 2 pages.

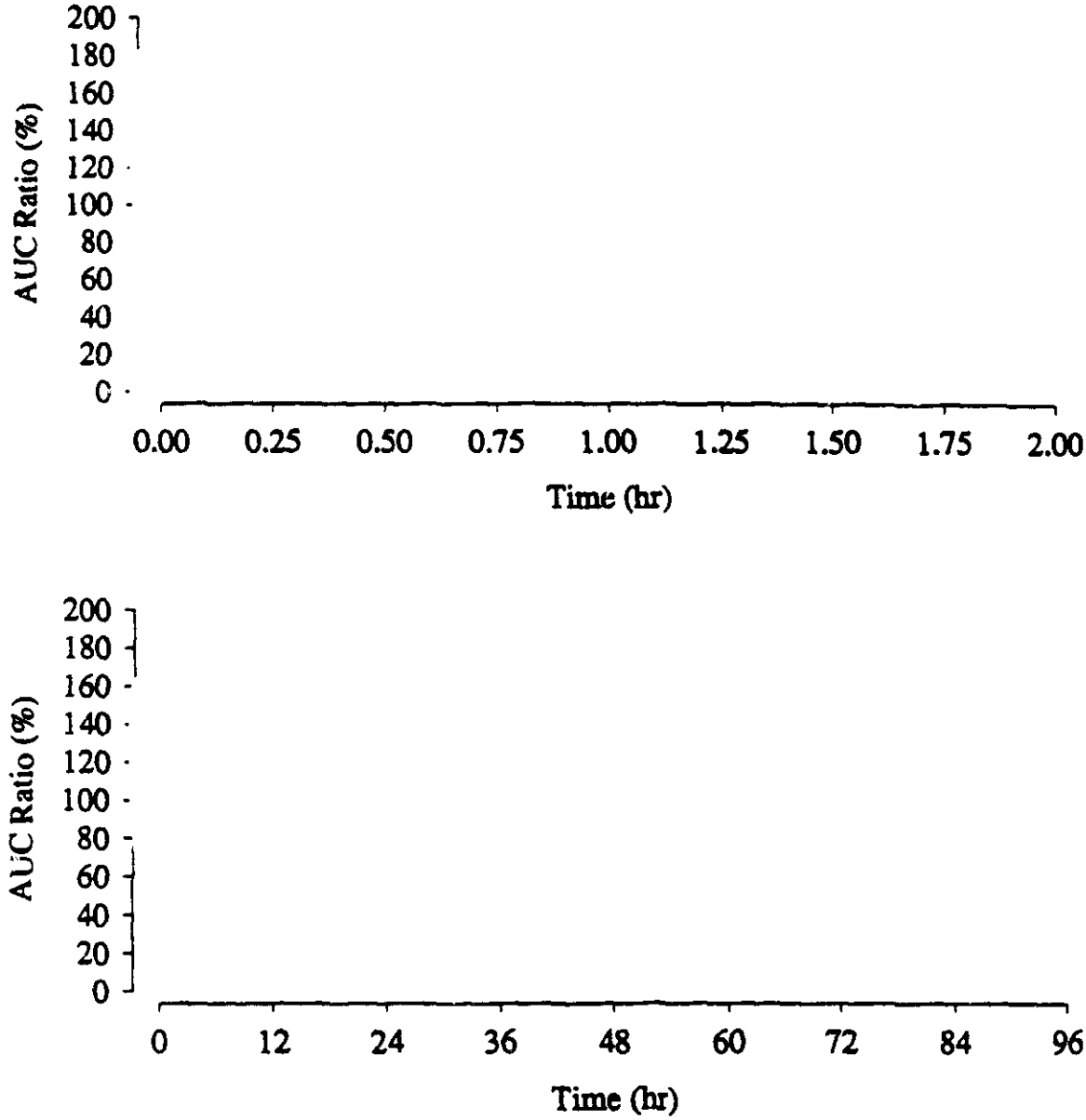


FIGURE 13. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 150 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

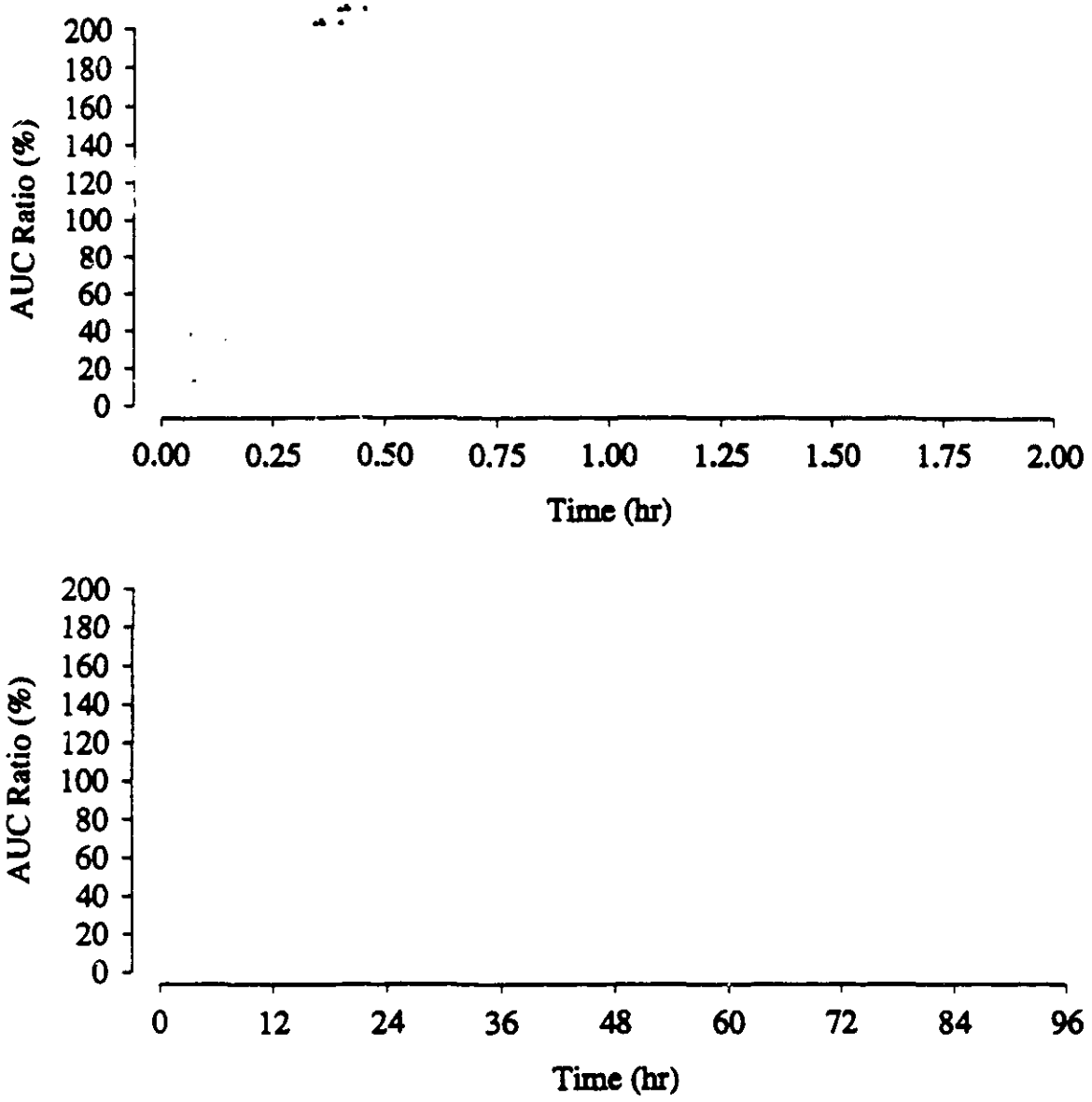


FIGURE 14. Cumulative Free Phenytoin AUC Ratio Analysis: Study 982-24

Mean ratios of AUC for test treatment (fosphenytoin at 100 mg/min)/AUC for reference treatment (Dilantin at 50 mg/min) are plotted along with the corresponding 90% confidence intervals. The dashed vertical lines represent the customary 80% and 125% confidence interval boundaries for bioequivalence testing and the 100% reference line. Time Axis 0-2 (top panel) and 0-96 (bottom panel) hours.

Note: All doses and dose rates are expressed in phenytoin equivalents.

The above figures demonstrate that, at the 150 mg/min rate of fosphenytoin, AUC of free phenytoin from fosphenytoin reaches that of free phenytoin from Dilantin at approximately 8 min. post-start-of-infusion., rises above that of Dilantin, and then falls to be approximately equal to that of Dilantin within 30 minutes post-start-of-infusion. This approximate equality is then maintained over the remainder of the time course. At 100 mg/min fosphenytoin, cumulative AUC of free phenytoin takes approximately 1.5 hrs. to reach the 80 - 125 % band.

As forementioned, the cumulative AUC from fosphenytoin is greater than that from Dilantin for approximately 10 - 20 minutes. However, examination of the concentration-time profiles (Panel D -- page 127) shows that the reason for the increased AUC is because fosphenytoin delivers free phenytoin more rapidly than Dilantin, and not because Cmax is increased. An additional point is that the differences in cumulative AUC between the 100 and 150 mg rates is due to the first 15 minutes post-initiation-of-infusion. From that point onward, the differences between the 100 and 150 mg/min infusion rates are minimal.

These analysis' show that, at 100 - 150 mg/min, free phenytoin from fosphenytoin closely approximates, but does not duplicate, free phenytoin from Dilantin at 50 mg/min.

CONCLUSIONS: The concentration-time profile of free phenytoin from 1200 mg of fosphenytoin administered at 100 or 150 mg/min is comparable to that following 1200 mg of phenytoin administered at 50 mg/min. The 150 mg/min rate meets equivalence criteria for Cmax and AUC, whereas the 100 mg/min rate meets criteria for AUC only.

If cumulative AUC is examined, the 150 mg/min rate meets equivalence criteria from 30 minutes onward, the 100 mg/min rate from 90 minutes onward. At time periods longer than 90 minutes the AUC of free phenytoin from fosphenytoin at either administration rate are equivalent to free phenytoin from 50 mg/min Dilantin.

STUDY: Pharmacokinetic meta analysis of fosphenytoin clinical trials

RESEARCH REPORT NUMBER: RR-X 764-02114

OBJECTIVE: To compare systemic exposure of phenytoin, 1) after dosing fosphenytoin and Dilantin®, 2) between patients and healthy subjects, 3) between arterial and venous phenytoin, and 4) the effects of age, gender, and race on the pharmacokinetic profile of fosphenytoin.

STUDY DESIGN: The data from clinical studies 982-13 to 982-16 and healthy volunteer studies 982-18, 982-20 and 982-24 were utilized.
1) Phenytoin population pharmacokinetics was carried out using a nonlinear mixed effect model to evaluate the effects of dosing regimen, body weight, time, age, gender, and serum albumin concentration on phenytoin clearance and distribution in a linear pharmacokinetic model. The studies 982-14 and 982-15 used in the analysis were from routine therapeutic drug monitoring. Only samples collected more than 6 hours after fosphenytoin administration were used (to avoid cross reactivity with immunoassay).
2) Graphical analysis of patient/subject differences were made by subsetting free phenytoin, total phenytoin and fosphenytoin concentration time profiles by dose and infusion rate and visually inspecting for patterns and/or differences among patients and healthy subjects. All the above studies were included.
3) Comparison of arterial and venous plasma concentrations for fosphenytoin, total phenytoin and free phenytoin were made in 6 neurosurgery patients. Plots were visually inspected for trends.
4) Patient sub-populations were graphically analyzed by subsetting plasma concentration profiles by route of administration and then further subsetting by age, gender, and race and visually inspecting for patterns and/or differences among patients.

RESULTS:
1) A linear pharmacokinetic model served as a suitable alternative to the generally applicable non-linear model given the restrictions in the range of doses and plasma phenytoin concentrations available from these clinical trials.

Consistent with previous clinical experience, phenytoin clearance and volume of distribution exhibit a direct relationship with weight. Mean trough phenytoin levels decline over time (Fig 1) and this is also reflected in the individual plots (Fig 2). Modeling suggests this decline in mean plasma phenytoin concentration is most likely explained in terms of an increase in phenytoin clearance in those patients remaining in the studies for more than just a few days rather than a tendency for patients with intrinsically high clearance to remain in the study longer (Fig 2 and Bayes estimates).

Modeling for difference in extent of systemic availability suggests that fosphenytoin delivers 15% less phenytoin than Dilantin, however, this may be due to model misspecification of the i.m. dosage.
2) Graphical presentation of free phenytoin, total phenytoin, and fosphenytoin concentration-time profiles by dose/infusion rate does not suggest the presence of sub-populations or specific individuals for which these levels are atypical.
3) Graphical comparison of plasma arterial and venous concentration time profiles for free phenytoin, total phenytoin and fosphenytoin do not show any differences.

4) Graphical analysis of patient sub-populations did not suggest the presence of sub-populations or specific individuals for which fosphenytoin concentration time profiles were atypical (Fig 3).

CONCLUSIONS: The observed trend for concentrations to drop within individuals suggests a time dependent increase in clearance in phenytoin clearance which has been observed previously in febrile patients and trauma patients. This does not appear to be related to fosphenytoin administration. The observation that intravenous fosphenytoin is 15% less bioavailable than Dilantin is not of concern because the improved fit of the data to the model including this bioavailability term is moderate. No further unusual trends where observed.

Visual inspection of plasma arterial and venous concentration-time profiles for fosphenytoin show no obvious differences which is consistent with the fact that phenytoin is a low extraction ratio drug.

Visual inspection of fosphenytoin concentration time profiles does not show any apparent differences across age, gender, race or in any of the sub-groups. This is consistent with the fact that phosphatase activity is extensive and differences in individuals is unlikely to make much difference in the conversion of fosphenytoin to phenytoin.

The conversion of fosphenytoin to phenytoin is consistent and essentially complete. There is no evidence of atypical phenytoin pharmacokinetics due to differences in fosphenytoin disposition between individuals.

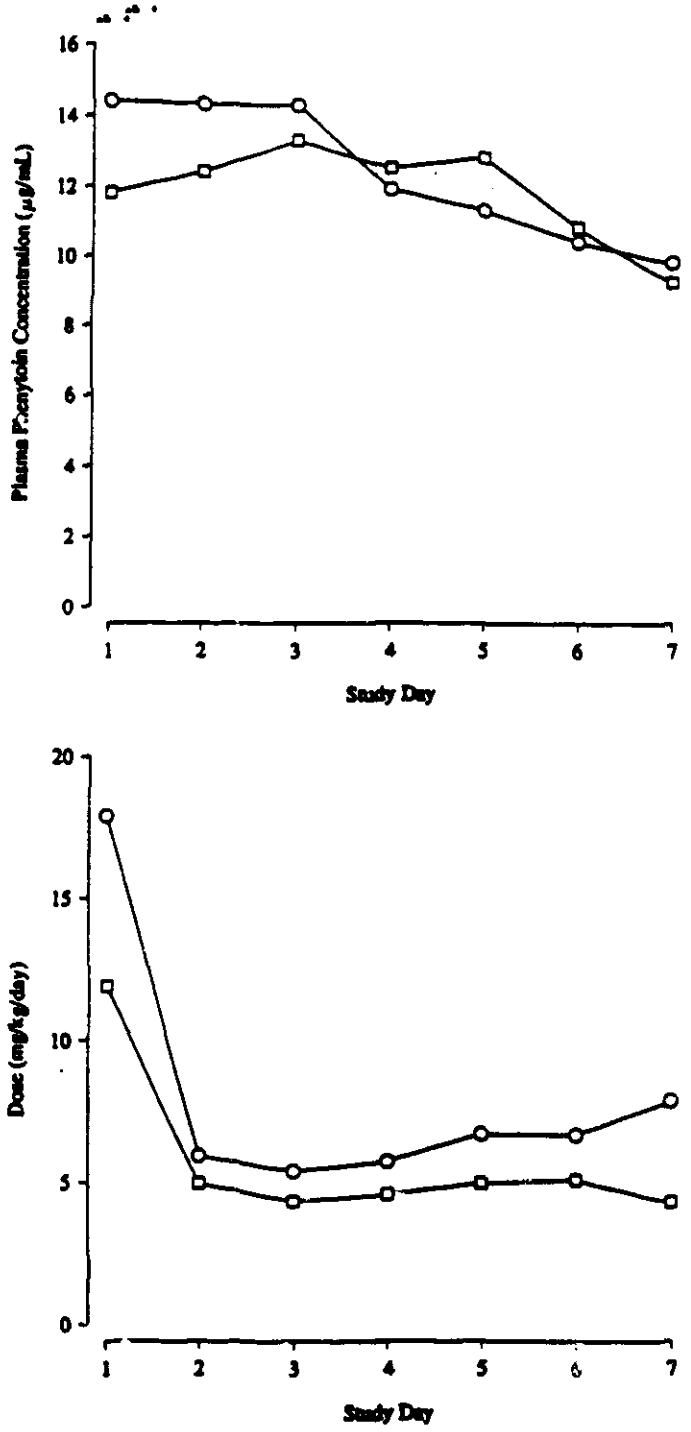
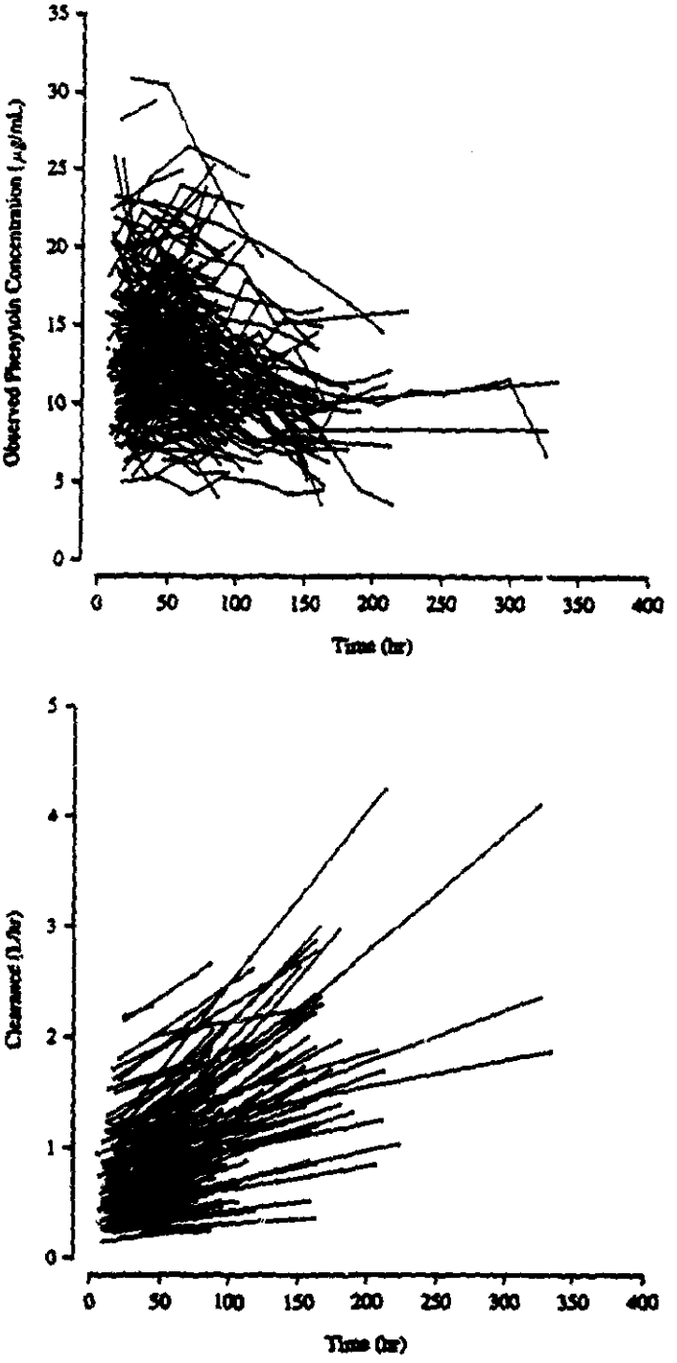


FIGURE 1 Mean Plasma Phenytoin Concentration (Top) and Mean Dose (Bottom) Versus Study Day for (□) Protocol 982-14 (Intramuscular) and (○) Protocol 982-15 (Intravenous)



2

FIGURE X Plasma Phenytoin Concentration (Top) and Post Hoc Estimated Clearance (Bottom) Versus Time for Protocols 982-14 (Intramuscular) and 982-15 (Intravenous). Lines Connect Data by Patient.

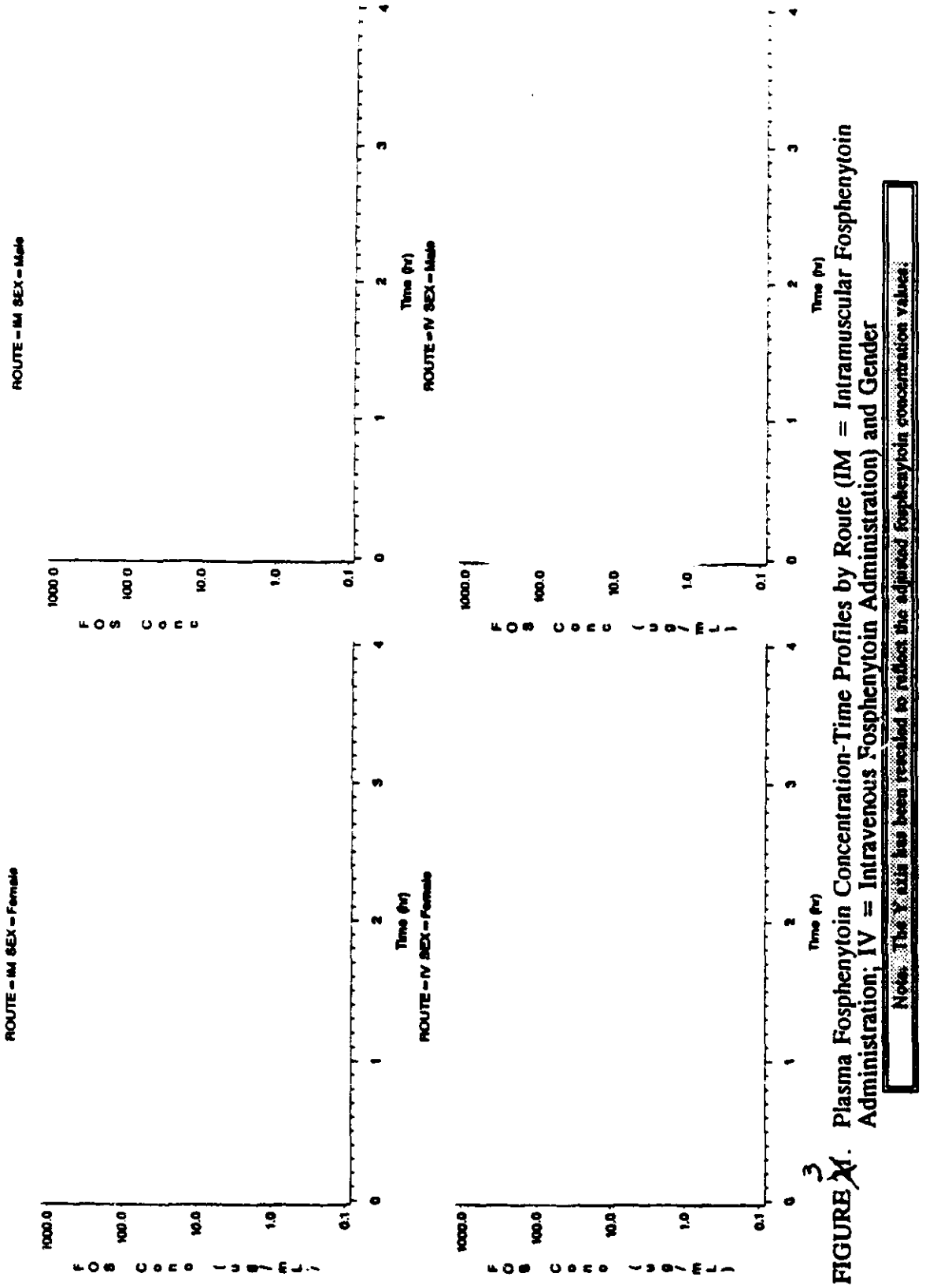


FIGURE 3. Plasma Fosphenytoin Concentration-Time Profiles by Route (IM = Intramuscular Fosphenytoin Administration; IV = Intravenous Fosphenytoin Administration) and Gender

Note: The 7 min has been rounded to reflect the adjusted fosphenytoin concentration values.

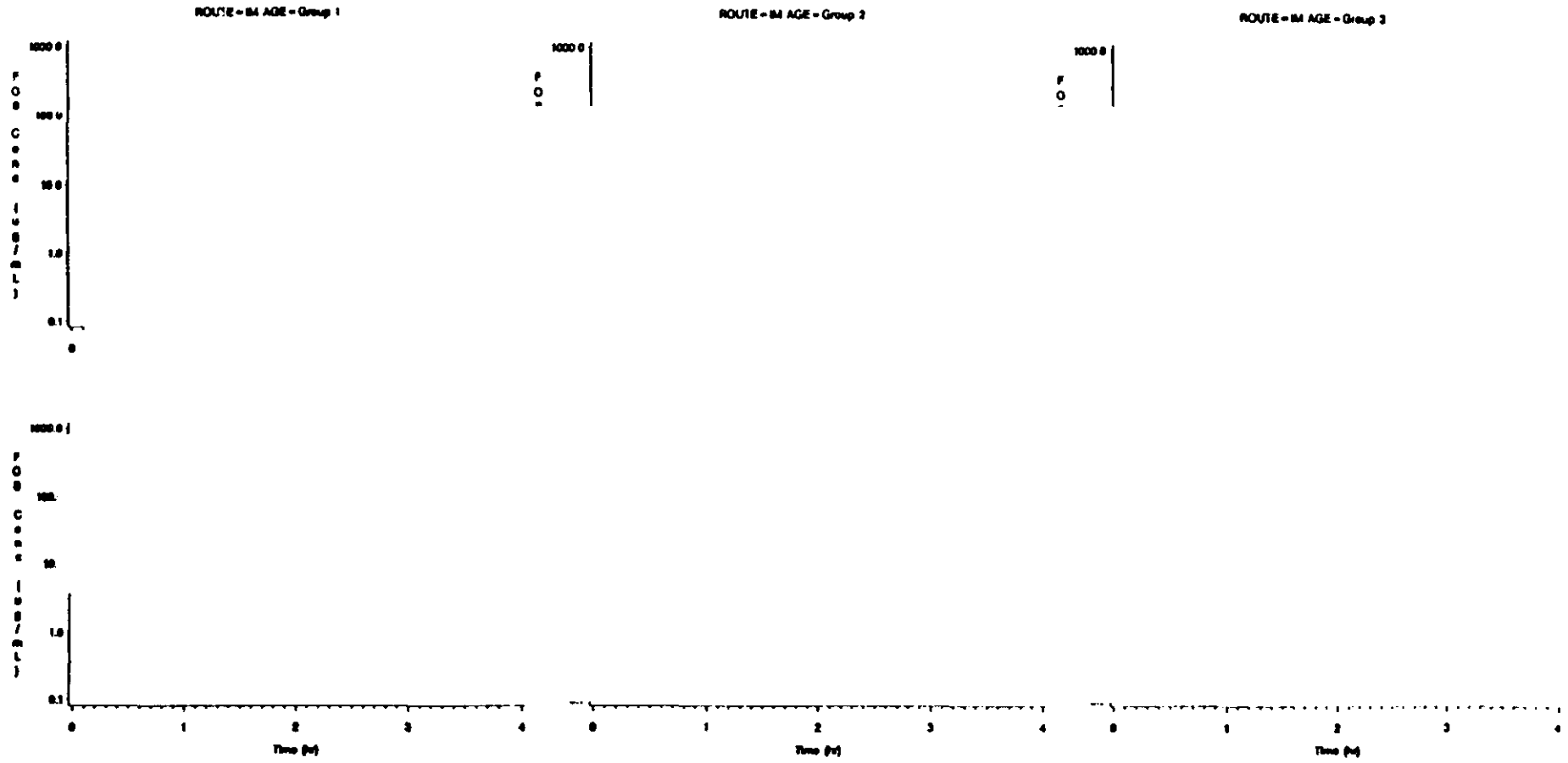


FIGURE 22. Plasma Fosphenytoin Concentration-Time Profiles by Route (IM = Intramuscular Fosphenytoin Administration; IV = Intravenous Fosphenytoin Administration) and Age Group (Group 1 = Age ≤40; 2 = 40 < Age ≤65; 3 = Age >65 yr)

Note: The Y axis has been rescaled to reflect the adjusted fosphenytoin concentration values.

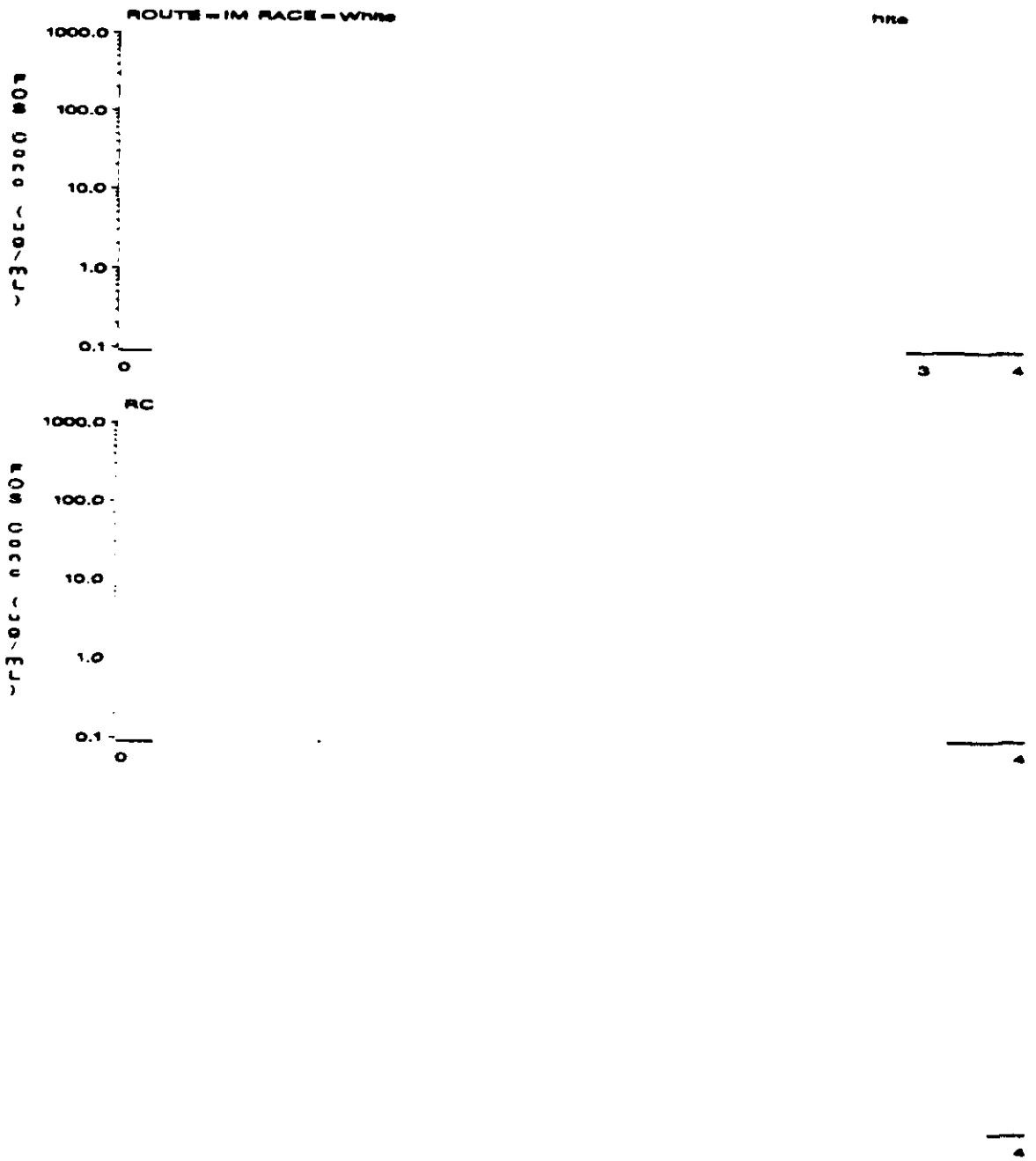


FIGURE 3. Plasma Fosphenytoin Concentration-Time Profiles by Route (IM = Intramuscular Fosphenytoin Administration; IV = Intravenous Fosphenytoin Administration) and Race

Note: [redacted]

note: Fosphenytoin concentrations and parameters reported in the this review have been corrected. They **DO NOT** suffer from the errors detailed in the **Important Note** on p. 3.

STUDY: Characterization of fosphenytoin and phenytoin human plasma protein binding in vitro

RESEARCH REPORT NUMBER: RR 764-02124

OBJECTIVES: To determine the protein binding characteristics of fosphenytoin and phenytoin using standard **in vitro** methodologies.

STUDY DESIGN: Plasma samples were spiked with fosphenytoin (up to 800 μg/mL) and phenytoin (up to 80 μg/mL) and total and unbound drug concentrations were determined via ultrafiltration and HPLC. NONMEM was used to fit the data to a variety of binding models.

RESULTS: The following pertinent conclusions can be made (see Figures 1 - 5):

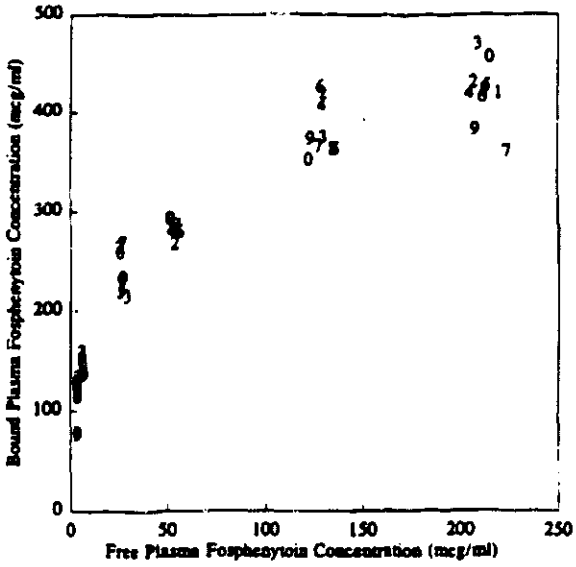
1. Fosphenytoin binding is best described by a model which incorporates 2 saturable binding sites. Fosphenytoin binds to the site of highest affinity with a binding constant of approximately 1.1 μg/mL, suggesting that this is the approximate unbound plasma concentration above which nonlinear binding may be observed. The second site has a much lower affinity (Kd > 100 μg/mL) suggesting that binding at this site will be linear at typical in vivo plasma fosphenytoin concentrations.

2. Phenytoin binding is best described by a model which incorporates 1 saturable binding site and 1 linear binding site. The affinity constant for the saturable binding site is approximately 30 μg/mL.

3. Fosphenytoin (at free concentrations above approximately 1.0 μg/mL or total concentrations above approximately 75 μg/mL) is capable of displacing phenytoin from the high affinity binding sights whereas phenytoin (at total concentrations below 80 μg/mL) does not significantly displace fosphenytoin.

4. These results are qualitatively consistent with the results of in vivo studies. However, quantitatively there are some inconsistencies. These inconsistencies are likely due to deficiencies in the in vivo studies (including the performance of ultrafiltration at non-physiological temperatures, the use of heparin as the anticoagulant, and the use of contaminated radiolabeled drugs).

10. FIGURES



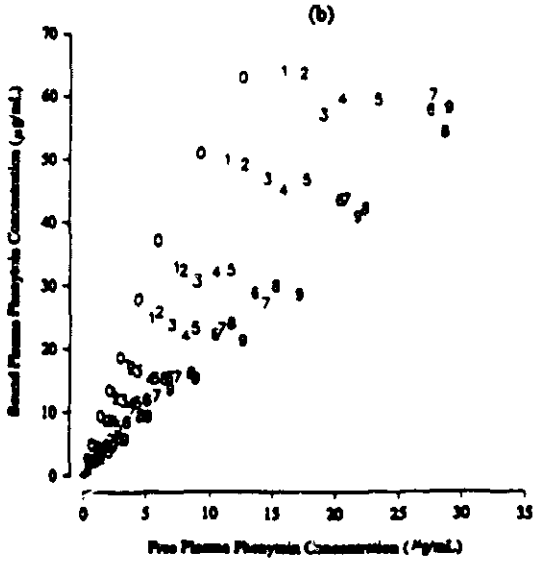


FIGURE 1. Plasma Protein Binding and Displacement Plots for Fosphenytoin (a) and Phenytoin (b). Symbol references nominal displacer concentration with 0 indicating no displacer present and 9 indicating the maximum amount: 80 µg/mL phenytoin in (a) and 800 µg/mL fosphenytoin in (b). See Table 2 for complete range of nominal concentrations.

Note: Panel A: The X and Y axes have been rescaled to reflect the adjusted fosphenytoin concentration values.

4 Pages
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APPENDIX 3

COMPREHENSIVE FORMULATION SUMMARY

The composition of the drug product intended for market is the same as that identified in the attached as Formulation 1 Fosphenytoin Injection 75 mg/ml. Other than the ^{13}C-labeled fosphenytoin (Formulation X) used in Study 982-10, Formulation 1 was the only fosphenytoin formulation used in clinical trials.

List of All Formulations Used in Clinical Studies
(Sorted by Study Number)
(Page 1 of 2)

Study No. 982-	Formulation No.	Formulation Name/Strength	Lot No.	Batch Size	Site of Manufacture
001	1	Fosphenytoin Injection 75 mg/mL	[a]	[a]	PR[b]
001	1P	Placebo for Fosphenytoin	[a]	[a]	PR[b]
002	1	Fosphenytoin Injection 75 mg/mL	Z86-6-8	[a]	PR[b]
002	[c]	Dilantin Injection 50 mg/mL	05726	[c]	[c]
003	1	Fosphenytoin Injection 75 mg/mL	[a]	[a]	PR[b]
003	1P	Placebo for Fosphenytoin	[a]	[a]	PR[b]
005	1	Fosphenytoin Injection 75 mg/mL	[a]	[a]	PR[b]
006	1	Fosphenytoin Injection 75 mg/mL	Z86-1-8	[a]	PR[b]
006	[c]	Dilantin Injection 50 mg/mL	05726	[c]	[c]
007	1	Fosphenytoin Injection 75 mg/mL	Z87-3-1	[d]	PR[b]
010	X	$^{13}C_3$-Fosphenytoin Injection	Z88-5-4	[d]	PR[b]
010	Y	$^{15}N_2$-$^{13}C_3$-Phenytoin Injection	Z88-5-5	[d]	PR[b]
011	1	Fosphenytoin Injection 75 mg/mL	Z87-3-1	[d]	PR[b]
011	[c]	Valium Injection 5 mg/mL	[c]	[c]	[c]
012	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester[e]
012	1P	Placebo for Fosphenytoin	CM 345120	150 L	Rochester
012	[c]	Dilantin Injection 250 mg/5 mL	03060	[c]	Rochester
013	9PA1	Placebo Capsule	CL 002017	500,000 Caps	MOPS[f]
013	11A3	Dilantin Capsule 100 mg	CM 223070	105,000 Caps	PR[g]/MOPS
013	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
013	1P	Placebo for Fosphenytoin	CM 345120	150 L	Rochester
014	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester

[a] Not specified. Study conducted by
[b] Manufactured at
[c] Commercially available product.
[d] Not specified. Study conducted by
[e] Rochester, Michigan
[f] Morris Plains, New Jersey

List of All Formulations Used in Clinical Studies
(Sorted by Study Number)
(Page 2 of 2)

Study No. 982-	Formulation No.	Formulation Name/Strength	Lot No.	Batch Size	Site of Manufacture
015	1	Fosphenytoin Injection 75 mg/mL	CM 0020192	17,000 Amps	Rochester
015	46	Dilantin Injection 250 mg/5 mL	CM 057031	480 L	Rochester
015	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
016	1	Fosphenytoin Injection 75 mg/mL	CM 0020192	17,000 Amps	Rochester
016	1	Fosphenytoin Injection 75 mg/mL	CR 0200193	5,000 Vials	Rochester
017	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
017	[c]	Dilantin Injection 250 mg/5 mL	03060	[c]	Rochester
018	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
020	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
020	1P	Placebo for Fosphenytoin	CM 345120	150 L	Rochester
020	[c]	Dilantin Injection 250 mg/5 mL	03060	[c]	Rochester
021	46	Dilantin Injection 250 mg/5 mL	CM 057031	480 L	Rochester
021	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
021	[c]	Sodium Chloride Injection USP	66-429-DK	[c]	Abbott
022	1	Fosphenytoin Injection 75 mg/mL	CM 0020192	17,000 Amps	Rochester
022	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester
024	46	Dilantin Injection 250 mg/5 mL	CM 057031	480 L	Rochester
024	1	Fosphenytoin Injection 75 mg/mL	CM 344120	100 L	Rochester

[a] Not specified. Study conducted b
[b] Manufactured a
[c] Commercially available product.
[d] Not specified. Stu
[e] Rochester, Michigan
[f] Morris Plains, New Jersey
[g] Powder blend made

3 Pages
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APPENDIX 4

3 Pages
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APPENDIX 5

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 6, 1995

FROM: Associate Director,
Division of Scientific Investigations (HFD-340)

SUBJ: Review of EIRs Covering
NDA # 20-450, Fosphenytoin Sodium (Cerebyx®) Injection, sponsored by Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co.

TO: Paul D. Leber, M.D.
Director, HFD-120
Division of Neuropharmacological Drug Products

At the request of HFD-120, the Division of Scientific Investigations initiated audits of three pharmacokinetics and bioequivalency studies. These audits were expedited due to the User Fee status of this NDA.

The clinical portion of study 982-014 was performed at the University of Tennessee, Memphis, TN. The clinical portions of studies 982-018 and 982-024 were performed a
The analytical portions of all three studies were performed at
Following the inspections, Forms 483 (attached) were issued. Our evaluation of these findings is as follows:

1. Reported fosphenytoin concentrations were in error since the water content of the fosphenytoin reference standard was not taken into account in calculations.

4 Pages
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protein-binding, unbound phenytoin, and percentage unbound phenytoin, be reviewed for corroboration independent of the data evaluated here.

In light of the nonlinear kinetics for fosphenytoin and phenytoin, a dosing error up to 5% combined with analytical errors up to 10% may need to be considered when interpreting pharmacokinetics.

After you have reviewed the material, we request that this transmittal memo be appended to the original NDA submission. Please forward a copy of your review to HFD-340 for our files.

C.T. Viswanathan

C. T. Viswanathan, Ph.D.

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-450

Cerebyx®

(Fosphenytoin Sodium Injection)

HFD-120 REVIEW DIVISION

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-102

DATE COMPLETED: August 30, 1994

ENVIRONMENTAL ASSESSMENT

1. **Date:**

EA dated:	06/30/1994
NDA filed:	07/14/1994
Consult to HFD-102	07/27/1994
Assigned:	08/19/1994
Telecon:	08/22/1994
Faxed response:	08/22/1994

2. **Name of applicant/petitioner:**

Warner-Lambert Company

Adequate.

3. **Address:**

201 Tabor Road
Morris Plains, NJ 07950

Adequate.

4. **Description of the proposed action:**

a. **Requested Approval:**

Warner Lambert has filed an NDA for Cerebyx® (Fosphenytoin Sodium).

DEFICIENT. The drug product name and drug substance names are incorrect. This occurs throughout the rest of the document.

b. **Need for Action:**

The product will be used in the treatment and control of seizures in patients with status epilepticus.

Adequate.

c. **Production Locations:**

i. **Proprietary Intermediate(s):**

None

ii. **Drug Substance:**

Address: Parke-Davis Holland Chemical Facility
188 Howard Avenue
Holland, Michigan 49424

Facility Description & Adjacent Environment:
A brief facility description is provided. The facility is located in an industrial and commercial area which includes residential, light industry and retail business. It is adjacent to the Macatawa River and is in the Eastern Deciduous Forest Ecoregion (climax forest beech-maple).

Adequate.

iii. **Finished Dosage Form:**

Address: Parke-Davis Rochester Facility
870 Parkdale Avenue
Rochester, Michigan 48307

Facility Description & Adjacent Environment:
A brief facility description is provided. The facility is located adjacent to a city park, residential areas and light manufacturing.

Adequate.

d. **Expected Locations of Use (Drug Product):**

Not discussed. **DEFICIENT.**

e. **Disposal Locations:**

The fate of returned or expired drug product or rejected drug substance is not discussed. **DEFICIENT.**

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance: Fosphenytoin **DEFICIENT.** Should be identified as the sodium salt.

Drug Product: Not listed. Adequate as the drug product is identified elsewhere in the EA.

Chemical Name: 5,5-diphenyl-3-[(phosphonooxy)-methyl]-2,4-imidazolidinedione **DEFICIENT.** Should be identified as the sodium salt.

CAS #: 92134-98-0. The Library (Roy) confirms that this number is the CAS for Fosphenytoin Sodium.

Molecular Weight: 362.28 g/mole (free acid)
406.24 g/mole (sodium salt)

Molecular Formula: $C_{16}H_{15}N_2O_6P$ (free acid)
$C_{16}H_{13}N_2O_6PNa_2$ (sodium salt)

Structural Formula: Not included. **DEFICIENT.**

Physical Descrip.: fine white solid (drug substance)

Additives: No information provided. **DEFICIENT.**

Impurities: No information provided. **DEFICIENT.**

6. **Introduction of substances into the environment: For the site(s) of production:**

   a. **Potential Emitted substances:**

   A list of raw materials used in the synthesis of the bulk drug and the composition of the drug product is provided in the non-confidential portion of the EA. **Note: the company will be given the opportunity to move this information to a confidential appendix, although they may choose to leave it where it is.**

   The company was requested (telecon 8/22/1994) to provide a flow diagram for the synthesis of the drug substance and the manufacturing process for the drug product. This was faxed on 8/22/1994. An official copy should be provided. **DEFICIENT.**

   b. **Controls (Air, Liquid Effluent, Solid):**

   DEFICIENT. See Attachments 1 and 2.

c. Compliance with Federal, State and Local Emission Requirements:

A list of applicable environmental regulations are included and they state that the Rochester and Holland Michigan facilities are substantially in compliance with all applicable regulations (page 28). Adequate. They do not discuss meeting compliance with occupational exposure requirements. **DEFICIENT.**

d. Effect of Approval on Compliance with Current Emissions Requirements:

DEFICIENT. See Attachments 1 and 2.

e. Estimated Expected Emitted Concentration/Quantities:

DEFICIENT. See Attachments 1 and 2.

The maximum expected environmental concentration for Fosphenytoin has been calculated at 4.6×10^{-5} ppm (46 ppt), based on the 5th year manufacturing estimate of 5,115 pounds. Adequate. The EA document refers to this as the minimum EEC. **DEFICIENT.**

7. **Fate of emitted substances in the environment:**

Parent Compound:	Fosphenytoin Sodium (99.2% conversion to phenytoin)
In vivo:	Phenytoin
Metabolites:	Hydroxyphenytoin

The approximate percent excreted as phenytoin and hydroxyphenytoin should be provided if known. **DEFICIENT.**

The Tier 0 testing provided indicates Tier 1 (aquatic) testing for Fosphenytoin and Hydroxyphenytoin and Tiers 1 (aquatic) and 2 (terrestrial) testing for Phenytoin. See Attachment 3.

No information was provided regarding hydrolytic stability or dissociation constants for the compounds of interest. **DEFICIENT.**

Insufficient information is provided regarding the test methods for water solubility and partition coefficient. **DEFICIENT.** For water solubility information such as the methodology used (e.g., undersaturation/oversaturation), the study site, the temperature at which the solubility was determined and the HPLC method should be provided. For the partition coefficient information such as the test methodology, the study site, concentration at which the study was performed (2 different ones needed) and the HPLC method should be provided.

Although not necessary, the photolytic degradation of Fosphenytoin Sodium was determined. The conclusion (page 17, 1st sentence in second paragraph) should be revised to indicate that photolysis is not a primary removal mechanism of Fosphenytoin Sodium from the environment. **DEFICIENT.**

Fosphenytoin Sodium is aerobically biodegraded in the aquatic compartment to Phenytoin. Phenytoin does not biodegrade in the aquatic compartment and does not to absorb to soil. The company states that Hydroxyphenytoin aerobically biodegrades rapidly in the aquatic compartment and that it has been proven/demonstrated to completely degrade to CO_2. The data provided does not support these statements. **DEFICIENT.** (See Attachments 4 and 5)

8. **Environmental effects of released substances:**

See Attachments 4 and 5.

Neither Fosphenytoin, Phenytoin or Hydroxyphenytoin inhibit microbial growth at concentrations expected in the environment nor are they acutely toxic to *Daphnia magna*. (See Attachment 4).

Adequate.

9. **Use of resources and energy:**

   a. **Production:**

      Production of the material will result in a 1% or less increase in production levels or energy usage over current levels at both the Holland and Rochester facilitates. Adequate.

   b. **Effect on Endangered/Threatened Species:**

      None. Adequate.

c. **Effect on Properties Listed/Eligible for National Register of Historic Places:**

None. Adequate.

10. **Mitigation measures:**

The Emergency Plan, Pollution Incident Protection Plan (PIPP) and Spill Prevention Control and Countermeasure Plan (SPCC) for the Holland Facility is provided.

The Emergency Response Plan for the Rochester Facility is provided.

Safe handling guides and MSDS's are provided to personnel.

Material is disposed as indicated under # 6.

Adequate.

11. **Alternatives to the proposed action:**

They state that the proposed action will have no impact on the environment and the one alternative is no action (approval) by the FDA.

DEFICIENT. They can not say it will have no impact, only the FDA can in the FONSI.

12. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

A list is provided. **DEFICIENT.** They state that no consultants were used, but include in the list is a consultant (performed many of the environmental test) for this EA. also did some basic testing is support o. They also state that the *Curricula vitae* for the listed individual are attached. But they were not included.

13. **Certification:**

Provided. Adequate.

14. **References:**

References are provided. Adequate.

15. **Appendices:**

The appendices are not identified as confidential or non-confidential, although some individual pages are stamped as confidential. **Note: the company will be reminded about the confidentiality issues.**

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 1**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-1995

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: CEREBYX®
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

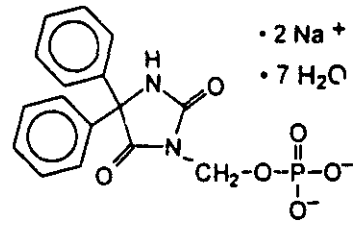
PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx ___ OTC

JUN - 7 1995

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

$C_{16}H_{13}N_2O_6PNa_2 \cdot 7H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

Phenytoin starting material is synthesized under DMF , which is currently under review and contains some major deficiencies. In general, the deficiencies in the NDA appear to be minor, however some control issues need to be resolved. For one intermediate in the fosphenytoin synthesis, there is no data to show that it is not present as an impurity in the drug substance. The proposed impurity limits for the drug product need to be evaluated.

CONCLUSIONS & RECOMMENDATIONS:

Establishment Evaluations, Microbiology and Environmental Assessment are still pending as is Methods Validation [this cannot be initiated until we obtain a satisfactory response to questions about possible impurities in the n.d.s., see Item 3 of draft letter]. Due to these issues, and manufacturing deficiencies in both the NDA and DMF the NDA is Not Approvable for Chemistry at this time.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/05-JUN-1995
HFD-120/CSO/RNighswander
HFD-120/SBlum/Init: 6/7/95

Martha R Heimann 6/7/95
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.001

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Cerebyx®

(fosphenytoin sodium)

Injection

NDA 20-450

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL
DRUG PRODUCTS (HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-250

Cerebyx®

(fosphenytoin sodium)

Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Cerebyx®**, **Warner-Lambert Company** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fosphenytoin sodium is a synthetic drug which is administered as an injectable solution in the treatment and control of seizures in patients with status epilepticus. The drug substance will be manufactured at Parke-Davis Holland Chemical Facility, Holland, Michigan. The drug product will be manufactured at Parke-Davis Rochester Facility, Rochester, Michigan. The finished drug product will be used in hospitals and clinics.

Fosphenytoin sodium is a prodrug which is rapidly and completely converted to phenytoin *in vivo*. Patient excretions contain a small percentage of the dose as phenytoin (<5%), some dihydrodiol phenytoin (~7-11%) and the major metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) (~67-88%). Small amounts of fosphenytoin sodium may enter the environment due to manufacture. Chemical and physical test results indicate that fosphenytoin sodium, phenytoin and, the major metabolite, p-HPPH will most likely be restricted to the aquatic environment.

Hydrolysis of fosphenytoin and phenytoin and photolysis of fosphenytoin sodium is expected to be slow under environmental conditions. Fosphenytoin is rapidly biotransformed to phenytoin under biodegradation test conditions, phenytoin is not chemically converted and p-HPPH can be completely biodegraded, although the biodegradation is not rapid.

As fosphenytoin and the major metabolites are expected to persist in the aquatic environment for some time, the toxicity of fosphenytoin sodium, phenytoin and p-HPPH to aquatic organisms was characterized. Acute static toxicity studies in water fleas (*Daphnia magna*) indicate that the drug substance is generally not toxic to aquatic organisms at concentrations of at least 5 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Microbial inhibition studies indicate that environmental microorganisms are not inhibited at concentrations of at least 7 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned drug product will be disposed of at a licensed incineration facility. Out-of-specification drug product and drug substance will be reprocessed or disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

6/9/95 Nancy B. Sager
DATE Prepared By
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

6/26/95 Robert A. Jerussi
DATE Concurred
Robert A. Jerussi V Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment I: Environmental Assessment
Attachment II: Material Safety Data Sheet (drug substance)

ATTACHMENT I

ITEM 3.6.
Freedom of Information Environmental Assessment for
Fosphenytoin Sodium Injection

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FREEDOM OF INFORMATION ENVIRONMENTAL ASSESSMENT FOR FOSPHENYTOIN SODIUM INJECTION

1. DATE

November 29, 1994

2. NAME OF APPLICANT

Warner-Lambert Company

3. ADDRESS OF APPLICANT

201 Tabor Road
Morris Plains, New Jersey 07950

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Description of the Proposed Action

Warner-Lambert has filed a New Drug Application for Cerebyx® (Fosphenytoin sodium). The drug substance is Fosphenytoin sodium. The New Drug Application requests approval of Fosphenytoin Injection for the treatment and control of seizures in patients with status epilepticus.

4.2. Need for the Action

Approval of this application will result in production and distribution of Cerebyx® in the United States. Approval will offer patients in the United States an effective therapy for treatment and control of seizures in patients with status epilepticus in hospitals and clinics. Because of the therapeutic benefits associated with its availability and use, approval is sought and preferable to nonapproval. It is estimated

that 1.5 million people are identified as suffering from epilepsy in the United States with an estimated yearly increase of approximately 70,000 to 130,000 patients.

4.3. Locations Where the Products Will be Produced

Bulk drug substance will be manufactured at the following Warner-Lambert facility:

Parke-Davis Holland Chemical Facility
188 Howard Avenue
Holland, Michigan 49424

The Parke Davis Holland Chemical facility is located on approximately 50 acres of land in the Township of Holland (1990 population—17,523), in Ottawa County, Michigan, approximately 30 miles west of Grand Rapids. The site is just north of the city of Holland and consists of approximately 15 buildings and employs an average work force of 300 employees. It is adjacent to the Macatawa River near the river's confluence with Lake Macatawa. Lake Macatawa flows into Lake Michigan approximately 4.5 miles downstream from the facility. The plant is located in an industrial and commercial area which includes residential, light industry, retail business and beech-maple forests.

The Holland facility receives its potable water from Holland Township. Holland Township obtains its potable water from the city of Wyoming, the city of Holland, and in rural areas, from ground water. Wyoming obtains water from Lake Michigan via an intake structure located approximately 6 miles northwest of the facility and about 6 miles north of Lake Macatawa's outlet to Lake Michigan. The city of Holland obtains its potable water from Lake Michigan via an intake located about 0.75 miles off-shore and about 5 miles west of the facility and 2 miles north of Lake Macatawa's outlet to Lake Michigan. The facility pumps its sanitary wastes to the Holland Municipal Waste Treatment Facility.

Process water for noncontact cooling is obtained from an intake located on the channel leading to the Macatawa River on the east side of the facility.

The Holland facility is located on a former beach and associated offshore deposits of a higher stage of Lake Michigan. These areas have locustrine sand and gravel deposits and may include intercalated clay. Eolian sand and organic soils may be present. The area is in the Eastern Deciduous Forest Ecoregion, and the climax forest is beech-maple[1]. The site slopes from a high in the north of 605 feet to the Macatawa River in the south, which has an approximate elevation of 579 feet. The site is mostly paved or covered with buildings.

Drug product formulation, packaging and testing will be performed at the following Warner-Lambert facility:

Parke-Davis Rochester Facility
870 Parkedale Avenue
Rochester, Michigan 48307

The Parke-Davis Rochester facility is located on 80 acres of land in Oakland County, Michigan in the northeast corner of the City of Rochester (1990 population—7,096). It is approximately 30 miles north of Detroit, Michigan. The facility consists of 40 buildings and employs an average workforce of 500 people. The closest neighboring structure is over 800 feet away. The facility is surrounded by a city park to the south, a public roadway and residential area to the north, light manufacturing to the east, and vacant property followed by residential neighborhoods to the west. The site is approximately 35 miles upstream from the confluence of the Clinton River and Lake St. Clair. See Appendix 1 for Site Location Map and Site Plan.

Returned and unused drug product will be returned via the Warner-Lambert Drug Distribution System. Material with inadequate shelf-life for distribution will be sent to the following facilities:

Warner-Lambert Company
400 W Lincoln Avenue
Lititz, PA 17543

Returned products will be destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

Material that does not meet specifications will be either reprocessed at the manufacturing sites specified and submitted as a supplement to the NDA or destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

5.1. Chemical Names

5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

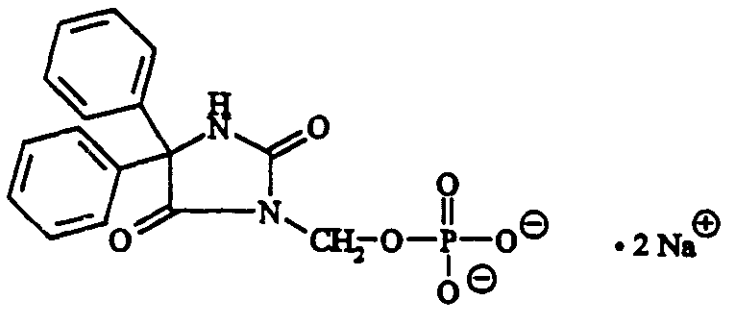
CAS Registry Number 92134-98-0

5.2. Synonym Names

Cerebyx®

Fosphenytoin sodium (USAN)

5.3. Structural Formula



5.4. Description

Fine white solid

5.5. List of Potential Impurities

Phenytoin
Dibenzylphosphate
Diphenylglycine
Diphenylhydantoic Acid
Diphenylimidazolidinone
Diphenylglycinamide
(2,5-dioxo-4,4-diphenyl-2,4-imidazolidinyl-1-yl) methoxy]methoxy]phosphoric acid bis(phenylmethyl)ester
2,4-Imidazoldinedione,3,3'-methylenebis[5,5-diphenyl-
(4-cyclohexyl-2,5-dioxo-4-phenyl-1-imidizolidinyl)methyl ester, disodium salt.

A material safety data sheet (MSDS) for Fosphenytoin sodium is provided in Appendix 2.

5.6. Ultraviolet Spectrum

The apparent maximum UV absorbance in water and methanol is 200 and 204 nm, respectively. Spectra are provided in Section 15(a)3.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Fosphenytoin sodium is synthesized in the Holland, Michigan facility. The following chemicals with their corresponding CAS numbers are used in the production of Fosphenytoin sodium.

6.1. Materials Emitted into the Air in Holland, Michigan Plant

Ambient air quality at the Holland, Michigan facility is not routinely monitored. Indoor air quality is monitored. In addition, the facility has a number of other air permits that are not associated with hazardous waste management but are associated

with the specific batch manufacturing processes conducted at the site. Emission permit applications have been submitted for the Fosphenytoin sodium process. The permit (air, liquid, and solid) numbers, requirements, expiration dates, and other pertinent information are summarized in Appendix 3. Refer to Appendix 4 for where emission permits apply in the flow diagrams of synthetic route and manufacturing direction for drug substance and drug product, respectively.

6.2. Materials Disposed as Solid Waste in Holland, Michigan Plant

Solid waste is generated in the bulk pharmaceutical production at the Holland plant in 2 forms. Waste cakes from process solution filtration, and mixed wastewater filtration. The former solids are isolated from Niagara (stacked plate) pressure filters, and are primarily activated carbon and diatomaceous earth filter aid from decolorizing operations. The latter type is a product of process wastewater filtration. Suspended solids present in the wastewater are removed after pH adjustment by passing the water through a rotary precoat filter. Sludge from the wastewater is peeled off the filter along with diatomaceous earth filter aid. Both of these sludges are combined in roll-off hoppers and disposed of in a hazardous waste landfill.

The solid waste and waste solvent for our Holland, Michigan facility are disposed by the following contractors:

Waste Stream	Vendor Name	Address
Waste Solids	Chemical Waste Management	Adam's Center Landfill 4636 Adams Center Road Fort Wayne, IN 46806
Waste Solvent	EWR Inc	PO Box 160 Ceal City, IL 60416
Waste Solvent	Systech Environmental Corporation	11397 County Road 176 Paulding, OH 45879
Off-Specification Pharmaceutical Substance	Chemical Waste Management	Trade Waste Incinerator #7 Mobile Avenue Sauget, IL 62201

6.3. Materials Disposed as Liquid in Holland, Michigan Plant

Aqueous emissions are regulated by Michigan Minerals Wells Act, Safe Drinking Water Act, and the Resource Conservation and Recovery Act. Compliance with these statutes has been achieved by obtaining Underground Injection Control permits from US EPA MI-139-1W-0003, MI-139-1W-0004, and MI-139-1W-0005. For noncontact cooling water discharges, NPDES Permit MI-0004715 has been granted. The permit numbers, authorizing agencies, and other pertinent information are also summarized in Appendix 3.

A storm water retention pond is located in the southwest corner of the Holland, Michigan site next to the Macatawa River. This pond receives surface runoff from the west part of the site, except runoff from certain roofs and all secondary containment areas, which is sent to the chemical waste treatment system. The unlined retention pond has no outlet, but water leaves it through the soil. A description of the wastewater treatment system is provided in Appendix 5. Water from this treatment system is disposed of by deepwell injection for which Permits MI-139-1W-0003, MI-139-1W-004, and MI-139-1W-0005 have been granted.

The Fosphenytoin sodium is received in bulk form from the Parke-Davis facility located in Holland, Michigan, and the following chemicals with their CAS numbers are used in the production of Fosphenytoin solutions for injection.

6.4. Material Disposed of as Liquid - Rochester, Michigan

Liquid wastes are containerized and transported after on-site storage to Drug & Laboratory Disposal, Inc (D&L), located in Plainwell, Michigan. D&L is an EPA licensed Treatment and Disposal facility meeting the requirements of 40 CFR Part 265 and is a licensed Michigan Act 136 Liquid Industrial Waste Hauler. D&L treats the waste as follows; the liquid waste is bulked and treated by flocculation to remove all solids, the liquids are decanted and sent to a licensed fuel blender for incineration.

6.5. Materials Disposed of into the Sewage Treatment System in Rochester, Michigan

For the Rochester, Michigan site, mixing tank residues and spent rinsate solutions containing de minimis concentrations of Fosphenytoin sodium will be discharged to the Detroit Wastewater Treatment Plant. Excess bulk Fosphenytoin solution will be containerized and placed into temporary storage in the hazardous waste storage shed prior to transport to a licensed hazardous waste incinerator for destruction. Excess buffer solutions will be neutralized prior to discharge into the sewer system. The application for the wastewater permit has been submitted to Detroit Water and Sewage Department (DWSD). The pertinent information on the liquid emission permit is summarized in Appendix 6. Approval of this product will not exceed the limit for this permit.

6.6. Materials Disposed of as Solid Waste in Rochester, Michigan

The glass vials and ampoules used in the production of Fosphenytoin for injection may become solid wastes due to inspection failures, QC failures, and sterility failures. Filled vials and ampoules which fail inspections and testing will be stored and scheduled for crushing. After crushing, the liquids are separated from the crushed glass and containerized. The separated liquids are sent off-site for incineration. The crushed glass is rinsed and then sent to a licensed Class II landfill located in Michigan. The disposition of solid waste is under a registered hazardous waste generator identification number, MID 005380126. Pertinent information of this registration is also summarized in Appendix 6.

6.7. Materials Disposed of as Hazardous Waste Materials in Rochester, Michigan

Parke-Davis' Rochester facility is a registered generator of hazardous wastes. All solid and hazardous waste associated with production of Fosphenytoin sodium Injection will be managed as hazardous waste utilizing a licensed waste hauler and disposal facility (Drug and Laboratory Disposal, Inc). This contractor is an EPA licensed treatment and disposal facility located at Plainwell, Michigan. There is no compliance issue regarding the generation, hauling, or disposal of this material.

Off-specification (including rejected) and excess Fosphenytoin sodium will be containerized and stored in the Hazardous Waste Storage Shed prior to transport to a licensed hazardous waste incinerator. Storage of this waste shall not exceed 90 days from initial placement in the storage shed. All waste shipments shall be properly manifested using Michigan Department of Natural Resources Uniform Manifests. Manifest copies will be kept and submitted as required by Michigan Public Act 64.

6.8. Materials Emitted into the Air in Rochester, Michigan

Air-borne particulates may be generated during the formulation process, although such an occurrence is unlikely. Bulk Fosphenytoin sodium powder is weighed-out in the Drug & Chemical Dispensing area prior to delivery to the bulk formulation room. The Drug & Chemical area is equipped with several in-line HEPA filtering systems capable of 99% particulate removal efficiencies prior to discharge to the ambient atmosphere. In the bulk formulation room, Fosphenytoin sodium is added directly to the injection solution containing; water for injection; buffer solutions; and tromethamine. The resulting mixture is agitated to completely mix the ingredients. The mixing occurs in an enclosed formulation tank, thus minimizing potential air releases. Vapor pressures of all ingredients are very low and none are expected to vaporize during handling and mixing. Nevertheless, application of air emission permits has been granted for HEPA filters in Drug and Chemical Dispensing and solution manufacturing areas. The numbers authorizing agencies, requirements, and other pertinent information are summarized in Appendix 6. All employees working with Fosphenytoin Injection production will adhere to Warner-Lambert's Safe Handling Guideline for Fosphenytoin sodium (Appendix 7) which require the use of personal protective equipment. Additionally, Industrial Hygiene monitoring will be conducted to verify that worker exposures to all Fosphenytoin Injection ingredients are below Occupational Exposure Guidelines (OEGs).

6.9. Compliance With Regulatory Statues and Emission Standards

The Holland, Michigan, Parke-Davis facility maintains compliance with the following federal, state, and local regulations. The increase in waste generation and emissions due to Fosphenytoin sodium production will be negligible and will not adversely impact our ability to comply with these rules.

Federal: Resource Conservation & Recovery Act (RCRA)
Emergency Planning & Community Right To Know Act (EPCRA)
Hazardous Materials Transportation Act (HMTA)
Superfund Amendments & Reauthorization Act (SARA)
Clean Air Act Amendments (CAAA)
Clean Water Act (CWA)

State: MI PA 64 - Hazardous Waste Management Act
MI PA 641 - Solid Waste Act
MI PA 245 - Clean Water Act
MI PA 348 - Clean Air Act
MI PA 368 - Medical Waste Act
MI PA 136 - Liquid Industrial Waste Act

Local: Holland Charter Township Ordinance 106
- Wastewater Discharge Regulations
- These rules cover the discharge of sanitary sewage from the Holland plant.

The Rochester facility has maintained substantial compliance with all of the above regulations, and production of Fosphenytoin Injection will not adversely affect current compliance status. In addition, the Rochester facility has also maintained substantial compliance with the following state and local regulations:

State: MI PA 307 - Environmental Response Act
MI PA 478 - Leaking Underground Storage Tank Act

Local: City of Detroit Industrial Wastewater Discharge Ordinance

Discharges to the sanitary sewer system are expected from mixing tank rinse water, disposal of cleaning solutions, and discarding of excess buffer solutions. The quantities and components reaching the waste water treatment plant are not expected to exceed effluent quality limits as set by the City of Rochester. All buffer solutions will be neutralized prior to discharge, and only hot deionized/distilled water is used as a cleaning agent. The City of Rochester regulates industrial discharges and requires that industry monitor their effluent at least twice per year to demonstrate compliance. The Rochester facility has maintained compliance with this ordinance.

The Rochester waste water treatment plant has a maximum capacity of 2.5 million gallons per day and is a B-rated plant utilizing an activated sludge process. The Rochester plant offers primary and secondary treatment, and disinfects by chlorination followed by dechlorination prior to discharge into the Clinton River. After June 1, 1994, the City of Rochester will be sending its sanitary and industrial discharges to the City of Detroit's waste water treatment plant. The Detroit plant has a maximum capacity of 1.2 billion gallons per day and is currently receiving 800 million gallons per day. The Detroit waste water treatment plant utilizes an activated sludge process and offers primary and secondary treatment, and chlorination for disinfection prior to discharge into the Detroit River.

Finished product waste is expected to be generated. Crushed glass will be sent to an approved Class II landfill. The MDNR Solid Waste Division administers landfill compliance. Finished product liquids are separated from crushed glass and are drummed and stored on-site pending transport to a licensed hazardous waste incinerator. The waste finished product is regulated by MI PA 64 and also administered by the MDNR—Solid Waste Division as hazardous liquid waste. Parke-Davis Sterile Products has been issued EPA Generator ID MID 005380126 as a generator of hazardous wastes.

Applicable exposure and emission limits for the Rochester facility are shown in the Table below.

6.10. Maximum Expected Emitted Concentration

Calculation of a maximum EEC is based on release of the Drug Substance uniformly within the US using the equation presented by the Pharmaceutical Manufacturers Association in their guidance document for preparation of environmental assessments and an estimated fifth-year production of _____ pounds of Fosphenytoin sodium.

ppm (in US environment) = lbs/year x (8.9×10^{-9})
derived from ppm = (A)(B)(C)(D)(E)(F)
where:

A = pounds produced divided by 1 year (fifth-year production estimate).
B = 1 year by 365 divided days (length of year).
C = 1 day-person divided by 150 gallons (average daily water use per person in US).
D = 1 divided by 246,000,000 persons (population of US).
E = 1 gallon divided by 8.34 pounds (weight of a gallon of water).
F = 1,000,000 (conversion to parts per million).

The maximum expected emitted concentration in the US is calculated to be:

ppm (in US environment) =
ppb (in US environment) =
ppt (in US environment) =

Estimated environmental concentrations and exposures as a result of drug product use.

Calculations were performed in order to estimate the worst-case concentration of Fosphenytoin that could possibly be present in the United States. The estimate assumes that all Fosphenytoin Injection produced for sale in the US (based on fifth-year postapproval production estimates, _____ lbs) will be administered to patients and disposed of directly into sewage systems. This calculation overestimates the environmental concentration of Fosphenytoin sodium in at least 2 ways: (1) It assumes that all the Fosphenytoin produced will be sold and used by patients, and that none will be left unsold, unused by patients, or will expire or be returned for disposal outside sewage treatment systems, and (2) It assumes that all of the Fosphenytoin sodium Injection administered to patients will be excreted into sewage treatment systems. Patient metabolism will obviously reduce the quantity of Fosphenytoin sodium reaching the environment, as will discharge into private septic systems. Nonetheless, 46 parts per trillion is calculated to be the "maximum" expected environmental concentration in the US following the estimate presented above.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Fosphenytoin sodium is a prodrug which is readily converted quantitatively to phenytoin (dilantin) by patients. Based on a review article on the metabolism of

phenytoin (Appendix 8), it is expected that Fosphenytoin sodium to be largely metabolized to hydroxylated phenytoin. The major metabolite, 5-(4-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) excreted in urine, accounted for 67% to 88% of administered dose. The other urinary metabolite is dihydrodiol phenytoin which only accounted for about 7% to 11% of the dose. Less than 5% of the dose is expected to be excreted in urine as unchanged phenytoin. Accordingly, data were developed on Fosphenytoin, phenytoin and p-hydroxyphenytoin (HPPH).

7.1. Hydrolysis of Fosphenytoin Sodium

Hydrolytic stability: Hydrolysis of Fosphenytoin disodium had been studied at various pHs and buffer concentrations by V. J. Stella (Appendix 9). The rate constant is contained in the table below:

Effect of Buffer Concentration on the Rate of Hydrolysis of Fosphenytoin Sodium at Various pH Values[a]

Buffer	Buffer Conc, M	Apparent First-Order Rate Constant (κ), x $10^{4}h^{-1}$	κ_{obs} at Zero Buffer Conc, x $10^{4}h^{-1}$
Acetate			
pH 3.9	0.025	50.1	
	0.05	50.7	
	0.1	62.1	44.4
Phosphate			
pH 6.5	0.02	13.4	
	0.03	15.2	
	0.04	18.3	8.3
pH 7.4	0.01-0.04	2.9[b]	2.9
pH 8.1	0.02-0.04	1.1[b]	1.1

[a] μ = 0.5, 70°C.
[b] No buffer catalysis

Studies of the hydrolysis of phenytoin was described in the Analytical Profiles of Drug Substances Volume 13, Page 429 (Appendix 10). After refluxing phenytoin in 2.5 N HCL for 7 hours, essentially complete recovery of starting material was obtained. Phenytoin heated 24 hours at 170°C to 18°C in 20% NaOH(5 N) gave 82% yield of diphenylglycine. Stability study of phenytoin injection had shown the

presence of dihenylhydantoic acid as a decomposition product along with diphenylglycine.

7.2. Dissociation Constants

The ionization constant (pKa) for Fosphenytoin sodium, phenytoin and p-hydroxlphenytoin is listed below:

Compound	pKa
Fosphenytoin sodium	6.2 ± 0.017 (n = 3)
Phenytoin[a]	8.31, 8.33
HPPH	8.22

[a] Reported in Analytical Profile of Drug Substances Vol 13, P 426 (1984) (Appendix 10).

The study report is provided as Appendix 11.

Physico-Chemical Data Summary Table

Fosphenytoin sodium

Molecular Formula and Weight: $C_{16}H_{15}N_2O_6P$, 362.28 g/mole, free acid
$C_{16}H_{13}N_2O_6PNa_2$, 406.24 g/mole, sodium salt

Phenytoin

Molecular Formula and Weight: $C_{15}H_{12}N_2O_2$, 252.27 g/mole, free acid
$C_{15}H_{11}N_2O_2Na$, 274.25 g/mole, sodium salt

Hydroxyphenytoin (HPPH)

Molecular Formula and Weight: $C_{15}H_{12}N_2O_3$, 268.27 g/mole

7.3. Solubility

Solutions of Fosphenytoin sodium were mixed on a rotary wheel for 1 hour at 24 rpm. Samples were filtered and quantified by HPLC yielding the following results.

Buffer System	pH	Solubility (mg/mL)	Final pH
0.25 M $NaC_2H_3O_2$	4.0	78.5	4.37
	5.0	140.2	6.39
0.05 M Na_2HPO_4	6.0	148.7	7.04
	7.0	134.5	7.60
	8.0	137.2	8.50
0.05 M $Na_2B_4O_7$	9.0	141.3	9.35
	10.0	121.7	10.28

The complete test report including the HPLC procedure, study site, and temperature is provided in Appendix 12.

The water solubility of phenytoin has been published in Analytical Profiles of Drug Substances, edited by Klaus Flory, Volume 13, Page 417 (1984). Information presented below for phenytoin was taken from this reference (Appendix 10). Information regarding buffer composition and final pH were not available, however, the relatively low solubilities observed suggest that the final pH values were similar to the pH of the buffers.

pH	Solubility (mg/mL)
1.6	0.02
4.4	0.02
5.0	0.01
5.9	0.02
6.9	0.02
8.0	0.01
9.0	0.10
10.0	0.96
11.0	9.6
12.0	96

Solubility: Solutions of Hydroxyphenytoin were mixed on a rotary wheel for 1 hour at 24 rpm. Samples were filtered and quantified by HPLC yielding the following results.

The complete test report including HPLC method, study site, and temperature is provided in Appendix 11.

Buffer System	pH	Solubility (mg/mL)
0.05 M NaH_2PO_4	4.0	0.013
	5.0	0.014
	6.0	0.014
0.05 M Na_2HPO_4	7.0	0.014
	7.5	0.016
	8.0	0.022
0.05 M $Na_2B_4O_7$	9.0	0.104
	10.0	1.19

7.4. Partition Coefficient

Fosphenytoin sodium, phenytoin and hydroxyphenytoin were equilibrated with equal volumes of octanol and aqueous buffer. An internal standard, acetophenone, was added to each container and mixed on a rotary wheel for 30 minutes at 24 rpm. Each phase was analyzed by HPLC with the following results.

Buffer System Hydroxyphenytoin	$\log(K_{ow})$ Fosphenytoin	$\log(K_{ow})$ Phenytoin	$\log(K_{ow})$
0.05 M Phosphate, pH 4.0	-1.10	2.48	1.96
0.05 M Phosphate, pH 7.4	-2.03	2.40	1.91
0.05 M Borate, pH 9.1	-3.06	1.34	0.82

The complete test reports are provided as Appendices 11 and 12.

7.5. Vapor Pressure

The vapor pressures of Fosphenytoin sodium, phenytoin, and hydroxyphenytoin were determined following the procedures in FDA Environmental Assessment Technical Assistance Handbook Section 3.07. The gas saturation method was used for each compound, and for each compound the vapor pressure was determined to be less than 1.3×10^{-5} Pa (1.0×10^{-7} torr). The complete final report on the vapor pressure of Fosphenytoin, Study Number 10320-0993-6129-740, Report Number 94-6-5318 is attached as Appendix 13. The complete final report on the vapor pressure of phenytoin, Study Number 10320-0394-6140-740, Report Number 94-6-5308 is attached as Appendix 14. The complete final report on the vapor pressure of hydroxyphenytoin, Study Number 10320-0394-6144-740, Report Number 94-6-5307 is attached as Appendix 15.

7.6. Sorption/Desorption

The propensity for human drug substances to be transported from disposal sites is determined by factors contributing to their distribution, mobility, and persistence in the environment. Partitioning between solid and aqueous phases influences mobility by controlling sorption and leaching rates. A measure of a compound's tendency to sorb and desorb readily can predict the ultimate disposition of residues as either bound to soil/sludge, or as freely soluble material.

Fosphenytoin sodium, phenytoin, and hydroxyphenytoin were studied to determine their sorption and desorption properties following the FDA Environmental Assessment Technical Assistance Handbook Section 3.08. Three soil types were used with both reagent water to mimic "soft" water, and 0.01 M $CaCl_2$ to approximate "hard" water.

For Fosphenytoin sodium, at a solution to soil ratio of 5:1, results showed that the mean percent sorbed for all 3 soil types ranged from 19.0% to 42.4% in $CaCl_2$ and from 8.68% to 29.9% in reagent water. When desorption was tested, none of the sorbed Fosphenytoin sodium could be removed from reagent water or $CaCl_2$. This indicated that Fosphenytoin sodium was strongly bound to the 3 types of soils tested, but the low desorption was probably due to rapid degradation occurring in the samples. Since radiolabeled Fosphenytoin sodium was not available for this study,

water and soil concentrations were determined by using HPLC with UV detection. The preliminary screening portion of the study demonstrated that minor differences in sorption occurred between reagent water and $CaCl_2$ solution for all 3 soil types. Results of the preliminary study are summarized below.

	K_d		K_{oc}	
Soil Type	$CaCl_2$	Water	$CaCl_2$	Water
Washington	6.29	9.60	972	1480
Kansas	149	42.8	10100	2910
Wisconsin	46.9	23.5	1450	727

Washington soil: 46% sand, 47% silt, 7% clay, 1.1% organic matter, pH 7.8, cation exchange capacity 23.6 meq/100 g.

Kansas soil: 10% sand, 47% silt, 43% clay, 2.5% organic matter, pH 5.5, cation exchange capacity 34.4 meq/100 g.

Wisconsin soil: 48% sand, 37% silt, 15% clay, 5.5% organic matter, pH 7.1, cation exchange capacity 17.2 meq/100 g.

Consistent with the FDA Handbook, advanced isotherm testing was conducted with all 3 soils in both water types, since binding at a 5:1 ratio would have demonstrated greater than 25% sorption. Due to the relatively high sorption observed in the screening phase, solution to soil ratios of 50:1 and 100:1 were used in the advanced isotherm test (50:1 for Washington, 100:1 for Kansas and Wisconsin). Results of the definitive test conducted at concentrations ranging from 50.7 to 3.02 mg/L are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	11.8	1820	1.25	0.997
Kansas	43.2	2940	1.59	0.976
Wisconsin	6.10	188	0.953	0.801

Results of the definitive test conducted at concentrations ranging from 49.4 to 3.80 mg/L in 0.01 M $CaCl_2$ are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	23.1	3,570	1.85	0.866
Kansas	315	21,400	1.99	0.995
Wisconsin	51.2	1,580	71.75	0.941

The complete final report on the sorption/desorption of Fosphenytoin sodium, Study Number 10320-0993-6128-710, Report Number 94-6-5352 is attached as Appendix 16.

For phenytoin, the same testing was performed using soils from the same lots. At a solution to soil ratio of 5:1, results showed that the mean percent sorbed for all 3 soil types ranged from 10.1% to 43.0% in $CaCl_2$ and from 2.04% to 45.0% in reagent water. When desorption was tested, 51.6 to 87.4% and 63.4 to 100% of the sorbed phenytoin could be removed from reagent water and $CaCl_2$, respectively. This indicated that phenytoin was only slightly bound to the 3 types of soils tested. The preliminary screening portion of the study demonstrated that no significant difference in sorption occurred between reagent water and $CaCl_2$ solution for all 3 soil types. Results of the preliminary study are summarized below.

	K_d		K_{oc}	
Soil Type	$CaCl_2$	Water	$CaCl_2$	Water
Washington	0.604	0.303	93.3	46.8
Kansas	1.16	1.01	78.5	68.8
Wisconsin	3.61	3.41	112	105

Consistent with the FDA Handbook, advanced isotherm testing was only conducted with the Wisconsin soil in $CaCl_2$ since desorption was greater than 75% for the other

2 soils. Results of the definitive test conducted at concentrations ranging from 10 to 0.6 mg/L are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	NA	NA	NA	NA
Wisconsin	3.46	107	1.06	0.996

The complete final report on the sorption/desorption of phenytoin sodium, Study Number 10320-0394-6141-710, Report Number 94-6-5314 is attached as Appendix 17.

For hydroxyphenytoin, the same testing was performed using the soil from the same lots. At a solution to soil ratio of 5:1, results showed that the mean percent sorbed for all 3 soil types ranged from 13.7% to 53.3% in $CaCl_2$ and from 3.54 to 43.8% in reagent water. When desorption was tested, 45.8% to 61.2% and 30.5% to 100% of the sorbed hydroxyphenytoin could be removed from reagent water and $CaCl_2$, respectively. This indicated that hydroxyphenytoin was only slightly bound to the 3 types of soils tested. The preliminary screening portion of the study demonstrated that no significant difference in sorption occurred between reagent water and $CaCl_2$ solution for all 3 soil types. Results of the preliminary study are summarized below.

	K_d		K_{oc}	
Soil Type	$CaCl_2$	Water	$CaCl_2$	Water
Washington	0.851	0.487	131	75.3
Kansas	1.92	2.09	130	142
Wisconsin	4.81	3.55	149	110

Consistent with the FDA Handbook, advanced isotherm testing was only conducted with the Kansas and Wisconsin soils in $CaCl_2$ since desorption was greater than 75%

for the other soil. Results of the definitive test conducted at concentrations ranging from 1.2 to 0.08 mg/L are summarized below.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	1.85	124	1.20	0.993
Wisconsin	3.33	103	1.19	0.998

The complete final report on the sorption/desorption of hydroxyphenytoin, Study Number 10320-0394-6145-710, Report Number 94-5-5286 is attached as Appendix 18.

7.7. Photolysis

Fosphenytoin sodium was studied to determine its potential for photolysis following the FDA Environmental Assessment Technical Assistance Handbook Section 3.10. Photolysis as a pathway for degradation can be important from an environmental perspective since most pharmaceuticals will enter the environment in a dissolved form, whether from discharge from the site of production or from patient use. Photolysis occurs when a dissolved compound absorbs light and degrades through energy transfer.

Photolysis was investigated at 3 pHs, 5.0, 7.0, and 9.0 for a 30-day period. Results demonstrated that Fosphenytoin sodium is relatively resistant to photolysis. The half-lives were determined to be 112 days at pH 5, 193 days at pH 7, and 86 days at pH 9. Correlation coefficients ranged from 0.586 to 0.654 and are consistent with half lives 3 to 6 times longer than the experimental period. These data indicate, that photolysis in aqueous solution is not a primary removal mechanism for Fosphenytoin sodium in the environment.

The complete final report on the photodegradation of Fosphenytoin sodium, Study Number 10320-0394-6138-720, Report Number 94-6-5328 is attached as Appendix 19.

7.8. Biodegradation in Water

Biodegradation is a process by which organic chemicals may be significantly reduced in their structural complexity in the environment through biological means. Knowledge of the potential for biodegradation of a chemical is often critical in the assessment of environmental exposure and impact of the chemical. The objective of the study was to determine the potential for biodegradation of Fosphenytoin sodium under standard laboratory conditions. The biodegradation studies were conducted according to modified methods and procedures based in part on the information published in the FDA Technical Assistance Handbook, Section 3.11.

Aerobic biodegradation studies in water were performed with Fosphenytoin sodium, [^{14}C]phenytoin and [^{14}C]hydroxyphenytoin. Test flasks were incubated at 22°C in the dark to minimize the potential for photolysis, and inoculated with a bacterial population obtained from a publicly owned sewage treatment plant. The study design was a batch activated sludge simulation in which activated sludge was removed from a local waste water treatment works and used in a concentration similar to that found in most treatment plants, 3,000 mg solids per liter of solution. (The study design recommended in the handbook is based on a solids concentrations several orders of magnitude lower). The studies were conducted in triplicate with glucose as a positive reference control, and negative blank controls. The quantity of carbon dioxide ($^{14}CO_2$) released as a result of microbial degradation in the sludge/water was measured. HPLC measurements were performed periodically to determine whether partial degradation of Fosphenytoin sodium, had occurred.

From the Fosphenytoin sodium flasks, the cumulative CO_2 collected over 28 days was negligible relative to the dose initially applied. Volatile organic products also were not detected from these flasks. From the glucose flasks, greater than 60% of the dosed radioactivity was collected as CO_2. While these results showed no evidence for the complete biodegradation of Fosphenytoin sodium to carbon dioxide, analysis of the test solutions containing Fosphenytoin sodium were performed using HPLC

throughout the study. Results of these analyses indicated complete biotransformation to phenytoin occurred in the first day.

The complete final report on the aerobic aquatic biodegradation of Fosphenytoin sodium, Study Number 10320-1093-6136-731, Report Number 94-6-5349 is attached as Appendix 20.

From the [^{14}C]phenytoin flasks, the cumulative $^{14}CO_2$ collected over 42 days was negligible relative to the dose initially applied. ^{14}C-volatile organic products also were not detected from these flasks. From the ^{14}C-glucose flasks, greater than 60% of the dosed radioactivity was collected as $^{14}CO_2$. Analysis of the test solutions containing [^{14}C]phenytoin were performed using HPLC-RAM throughout the study and indicated that no chemical conversion occurred during the study.

The complete final report on the aerobic aquatic biodegradation of phenytoin, Study Number 10320-0394-6142-731, Report Number 94-6-5337 is attached as Appendix 21.

From the [^{14}C]hydroxyphenytoin flasks, the cumulative $^{14}CO_2$ collected over 42 days was approximately 10% of the dose initially applied. ^{14}C-Volatile organic products were not detected from these flasks. From the ^{14}C-glucose flasks, greater than 60% of the dosed radioactivity was collected as $^{14}CO_2$. These results demonstrated conclusively that the complete biodegradation of [^{14}C]hydroxyphenytoin to carbon dioxide can occur using organisms commonly found in publicly owned treatment plants. However, this biodegradation is not rapid. Analysis of the test solutions containing [^{14}C]hydroxyphenytoin were performed using HPLC-RAM throughout the study and indicated that approximately 30% of the applied test substance had degraded to more polar products. This characterization of polarity was made by comparison of HPLC retention times.

The complete final report on the aerobic aquatic biodegradation of hydroxyphenytoin, Study Number 10320-0394-6146-731, Report Number 94-6-5323 is attached as Appendix 22.

The environmental distribution of Fosphenytoin sodium should place in the aquatic phase. The low vapor pressure demonstrates that the atmospheric compartment will not be significantly affected by release of Fosphenytoin. With the extremely low solids level of sewage treatment plants, Fosphenytoin and its degradation products will be present primarily in the hydraulic phase. The ultimate fate of Fosphenytoin is determined in part by the metabolism in patients and the biodegradation in water. Metabolism data indicates that Fosphenytoin is completely modified by patients to the hydroxy derivative, hydroxyphenytoin. Biodegradation data shows that hydroxyphenytoin will easily degrade when exposed to common bacteria indigenous to sewage treatment plants. Therefore, fosphenytoin and its degradation products will not persist in the environment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Production, use and discharge of Fosphenytoin sodium into the environment will pose no adverse effect on humans, animals, plants or environmentally significant organisms. All organisms tested indicated that no threat to any of them are possible at concentrations at or near those calculated to occur upon approval of this NDA.

As a measure of the toxicity of any chemical, the determination of the lowest concentration that inhibits microbial growth is important because of possible ramifications if that concentration is exceeded in the environment. Three microbial growth inhibition studies were conducted according to the methods and procedures published in the FDA Technical Assistance Handbook, Section 4.02. The microbial inhibitory concentrations (MICs) of Fosphenytoin sodium, phenytoin and hydroxyphenytoin were determined for each of 5 species. For all 3 compounds, preliminary tests using concentrations of 0.1 to 1000 ppm (0.1 mg/L to 1000 mg/L) showed no effects to all 5 species investigated at all concentrations tested including 1000 mg/L. Based on the results of the preliminary exposure, definitive tests were not conducted. The MICs reported were defined as the lowest concentrations of these materials that completely inhibited the growth of the test organism.

Species	Fosphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

The complete final report on the microbial growth inhibition of Fosphenytoin sodium, Study Number 10320-0594-6155-770, Report Number 94-6-5293 is attached as Appendix 23.

Species	Phenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

The complete final report on the microbial growth inhibition of phenytoin, Study Number 10320-0594-6156-770, Report Number 94-6-5294 is attached as Appendix 24.

Species	Hydroxyphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

The complete final report on the microbial growth inhibition of hydroxyphenytoin, Study Number 10320-0594-6157-770, Report Number 94-6-5295 is attached as Appendix 25.

The acute toxicities (concentration at which 50% of the organisms are affected or EC_{50}) of Fosphenytoin sodium, phenytoin and hydroxyphenytoin to *Daphnia magna* (a freshwater invertebrate), were investigated. This organism is often tested and considered to be 1 of the most sensitive aquatic species available for standardized aquatic studies. The no observed effect concentration (NOEC) was determined as well as the EC_{50}. The NOEC is defined as the highest concentration at or below which there was no toxicant-related immobilization, or physical or behavioral abnormalities when compared to the control. The study was conducted according to the methods and procedures published in the FDA Technical Assistance Handbook, Section 4.08.

During the *Daphnia magna* acute toxicity study with Fosphenytoin sodium, immobilization or sublethal effects were observed among daphnids exposed to several of the measured concentrations (0% at 23, 48 and 94 mg/L, 10% at 190 mg/L, 75% at 380 mg/L, and 100% at 760 mg/L) following 24-hours of exposure. After 48-hours' exposure, 75% were immobilized at 190 mg/L, 95% at 380 mg/L, and 100% at the highest concentration, 760 mg/L. No immobilization was observed at lower concentrations or in the control solutions (some erratic behavior was noted at 94 mg/L). The outcome of the study was a calculated 48-hour EC_{50} for daphnids exposed to Fosphenytoin of 170 mg/L. The 48-hour NOEC for this study was determined to be 48 mg/L.

The complete final report on the *Daphnia magna* Static Acute Toxicity of Fosphenytoin sodium, Study Number 10320-0594-6154-110, Report Number 94-5-5273 is attached as Appendix 26.

During the *Daphnia magna* acute toxicity study with phenytoin, no immobilization or sublethal effects were observed among daphnids exposed to any of the measured concentrations (39, 23, 14, 8.3, and 4.9 mg/L) following 24-hours of exposure. The functional limit of solubility in the hardened freshwater used for this study was 39 mg/L, determined by stirring a saturated solution of phenytoin for 24 hours. After

48-hours' exposure, 20% were immobilized at the highest concentration, 39 mg/L. No immobilization was observed at lower concentrations or in either the solvent control or the control solutions. The outcome of the study was a calculated 48-hour EC_{50} for daphnids exposed to phenytoin of greater than 39 mg/L. The 48-hour NOEC for phenytoin was determined to be 23 mg/L.

The complete final report on the *Daphnia magna* Static Acute Toxicity of phenytoin, Study Number 10320-0993-6134-110, Report Number 94-6-5321 is attached as Appendix 27.

During the *Daphnia magna* acute toxicity study with hydroxyphenytoin, no immobilization or sublethal effects were observed among daphnids exposed to any of the measured concentration (28, 17, 10, 6.2, and 3.6 mg/L) following 24-hours of exposure. The functional limit of solubility in the hardened freshwater used for this study was 28 mg/L, determined by stirring a saturated solution of hydroxyphenytoin for 24 hours. After 48-hours' exposure, no immobilization was observed at any concentration or in either the solvent control or the control solutions. The outcome of the study was a calculated 48-hour EC_{50} for daphnids exposed to hydroxyphenytoin of greater than 28 mg/L. The 48-hour NOEC for hydroxyphenytoin was determined to be 28 mg/L.

The complete final report on the *Daphnia magna* Static Acute Toxicity of hydroxyphenytoin, Study Number 10320-0494-6153-110, Report Number 94-5-5271 is attached as Appendix 28.

The narrowest margin of safety for Fosphenytoin sodium is based on the NOEC for *Daphnia magna* (the most sensitive species tested) and is calculated by dividing 48 mg/L by [redacted] (the ~~minimum~~ maximum expected concentration based on distribution of all Fosphenytoin over the entire United States). This calculation results in a safety margin of 1,067,000. Similar safety margins for phenytoin and hydroxyphenytoin using the NOECs determined and [redacted]. The safety margin for phenytoin is 500,000 and for hydroxyphenytoin, 609,000.

Based on the documented rapid degradation pathways and the large safety margins (greater than 100,000), Fosphenytoin sodium has been shown to have no effect on the

external aquatic environment. Fosphenytoin sodium was shown to degrade in water with a half life of less than 1 day under microbially populated conditions similar to those seen in wastewater treatment plants. This clearly demonstrates that Fosphenytoin sodium will not persist in the environment. Furthermore, Fosphenytoin sodium was shown to have no effect on a wide variety of microorganisms at concentrations as high as 1000 mg/L. The LC_{50} to Daphnia magna was determined to be 170 mg/L and the no observed effect concentration was calculated to be 48 mg/L. This lowest risk concentration is more than 1,000,000 times higher than that which would occur if all the produced Fosphenytoin were used and discharged over the entire United States.

Metabolism data produced by Parke-Davis indicates that the entire quantity of Fosphenytoin sodium taken by patients is excreted as hydroxyphenytoin. Hydroxyphenytoin has been proven to biodegrade to more polar compounds and ultimately to carbon dioxide. Furthermore, no toxicity was observed for hydroxyphenytoin at the limit of solubility. Therefore, degradation pathways were determined for the parent drug substance Fosphenytoin, and the ultimately discharged metabolite, hydroxyphenytoin. The intermediate in degradation, phenytoin, which is formed *in vivo* transiently, was not observed to degrade under the laboratory conditions employed. Nonetheless, no environmental effects were observed at concentrations within 100,000-fold of the predicted environmental concentration.

9. USE OF RESOURCES AND ENERGY

In 1993, the Holland, Michigan manufacturing site used 19,643,113 kilowatts of electricity and 34.62 x 10^{10} BTU of steam to produce 1,085,153 kg of drug substances. The fifth-year production estimate for Fosphenytoin is pounds (11,253 kg) and represents an increase of 1.04%, on a kg basis.

The production of Fosphenytoin sodium represents less than 1% of the total pharmaceutical production at the Rochester facility. The proposed action will not alter land use since production will take place on premises currently owned by Parke-Davis and utilized for the manufacture of pharmaceutical products. The use of natural resources and energy for the manufacture of Fosphenytoin sodium is 0.1% of

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the present total plant usage and can be accommodated by the existing infrastructure. The Rochester facility generates its own electricity via a gas-fired turbine. In 1993, the total natural gas use was 465,098 billion cubic feet and the increase in consumption due specifically to the production of Fosphenytoin Injection is estimated to be less than 1%.

No impact will occur to endangered or threatened species. Since this activity does not involve the alteration, demolition, or construction of building or earth projects, approval will have no impact on property listed in the National Register of Historic Places.

10. MITIGATION MEASURES

The following measures are taken to prevent potential adverse environmental impacts:

- Use of MDNR permitted air purifying equipment to prevent air emissions from exceeding established Federal and State levels;

- Disposal of neutralized buffer solutions and wash/rinse water into the City of Rochester municipal sewer system which is treated by their tertiary wastewater treatment facility;

- Disposal of crushed glass wastes into a MDNR licensed Class II landfill;

- Destruction of all solid waste Fosphenytoin in a licensed hazardous waste incinerator;

- Material Safety Data Sheets for hazardous or potentially hazardous materials are made available to employees of Parke-Davis Company. These documents provide information on potential hazards, personal protective equipment, safe handling practices, and emergency procedures. Additionally, Parke-Davis distributes Safe Handling Guidelines for all new pharmaceuticals which describes the precautions which must be taken when handling these compounds.

Parke-Davis has a comprehensive occupational health and safety program. This includes conducting preplacement physical examinations of employees and periodic health surveillance examinations of all employees in manufacturing areas. Additionally, the company operates a health clinic to address any employee illness and/or injury occurring during the work day. The above procedures will serve to monitor employees for the development of conditions attributable to exposure.

The Rochester facility has an established Emergency Response Plan and Spill Prevention, Control & Countermeasure Plan and has conducted employee training in these procedures to effectively control and respond to releases of hazardous materials. Spill control stations equipped with absorbent materials and personnel protective equipment are located throughout the facility. A facility-wide Waste Management Plan has also been prepared and employees trained on their respective responsibilities. The Waste Management Plan includes procedures for hazardous, nonhazardous, pathological, flammable, and liquid industrial waste handling.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on the data summarized in this environmental assessment, the proposed action will have no impact on the environment. One alternative to the proposed action (drug approval) is no action by FDA. This will deprive humanity of potentially beneficial therapy, and also will have no impact on the environment.

12. LIST OF PREPARERS OF THE ENVIRONMENTAL ASSESSMENT

The following is a list of persons and respective qualifications, that participated in preparation of this Environmental Assessment document. Springborn Laboratories, Inc, was utilized as the consultant in the completion of this document.

M. K. Lemon CHMM Environmental Engineer
BS - Environmental Sciences
Certified Hazardous Materials Manager
Professional Experience - 13 years

A. Sommers	Industrial Hygienist MS - Occupational Health & Safety Professional Experience - 3 years
M. Nickolaus	Senior Associate Scientist - Technical Services BS - Management Professional Experience - 24 years
P. Fackler	Director, Environmental Chemistry PhD - Analytical Chemistry Professional Experience - 16 years
T. Bauer	Environmental Manager, B. S. Chemical Engineering Professional Experience - 15 years

Curricula vitae for these individuals are attached as Appendix 29.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of his knowledge for the preparation of the environmental assessment.

Date: November 29, 1994

Signature: Sean Brennan Sean Brennan

Title: Senior Director, Worldwide Regulatory Affairs

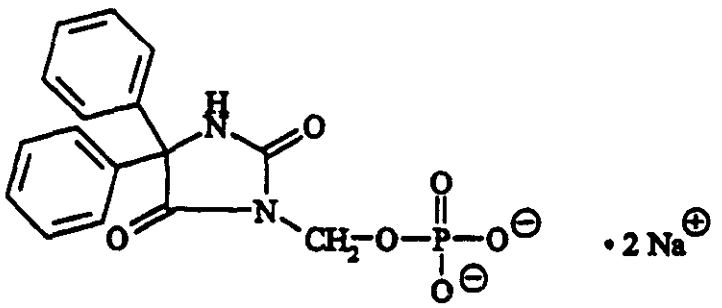
14. REFERENCES

1. Jose Philip, et al. Analytical Profiles of Drug Substances, edited by Klaus Florey, 1984;13:417.

15. APPENDICES

(a) Data Summary Tables

1. Structural Formula:



Chemical Names: 5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

CAS Registry Number 92134-98-0

Synonym Names: Cerebyx®
Fosphenytoin sodium (USAN)

2. Vapor Pressure:

Compound	Vapor Pressure
Fosphenytoin	Less than 1.3×10^{-5} pascal (1.0×10^{-7} torr)
Phenytoin	Less than 1.3×10^{-5} pascal (1.0×10^{-7} torr)
Hydroxyphenytoin	Less than 1.3×10^{-5} pascal (1.0×10^{-7} torr)

3. Ultraviolet Spectra

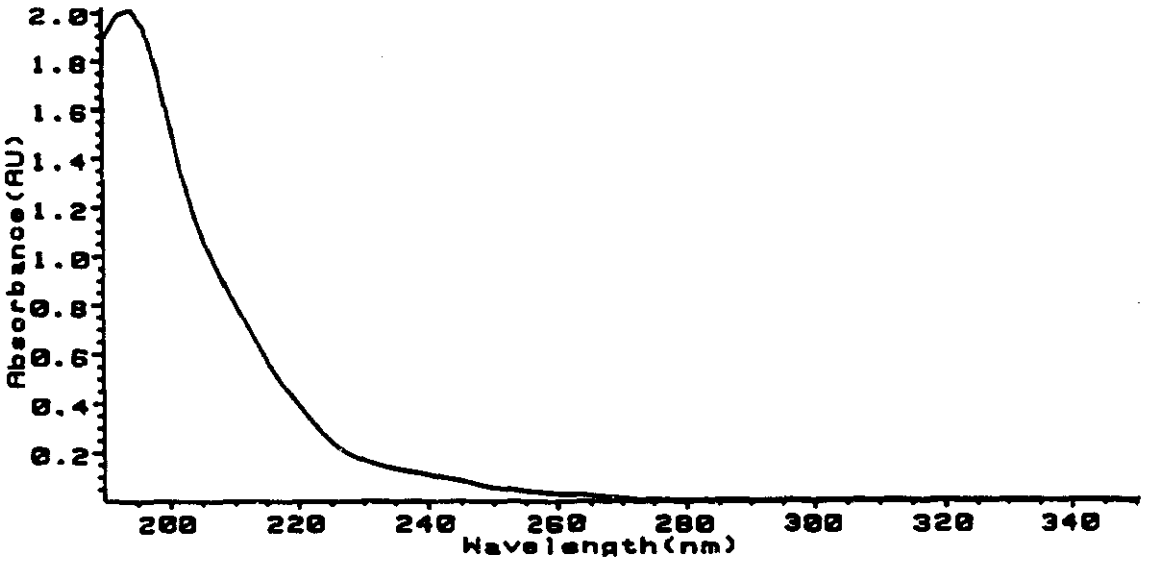


FIGURE 1. Ultraviolet Spectrum of Fosphenytoin Reference Standard II in Water (0.0165 mg/mL)

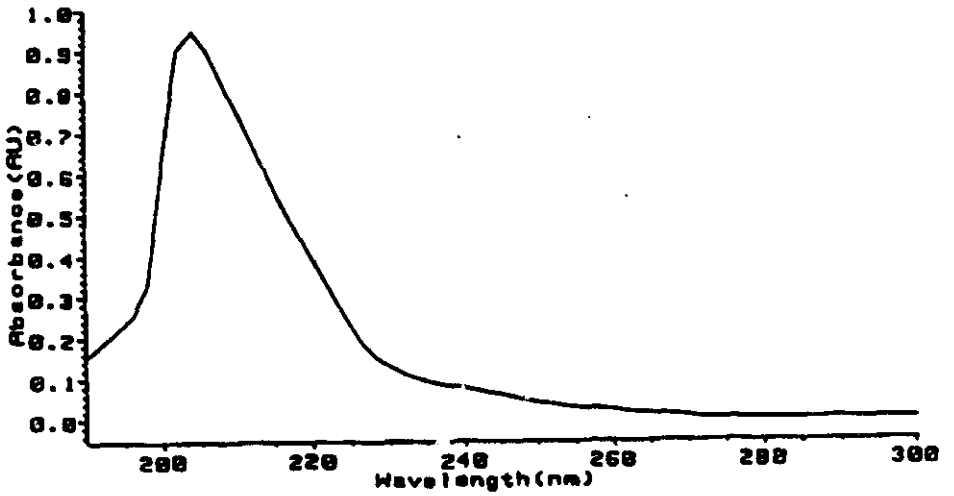


FIGURE 2. Ultraviolet Spectrum of Fosphenytoin Reference Standard II in Methanol, (0.0165 mg/mL)

4. Water Solubility:

Fosphenytoin Sodium

Buffer System	pH	Solubility (mg/mL)	Final pH
0.25 M $NaC_2H_3O_2$	4.0	78.5	4.37
	5.0	140.2	6.39
0.05 M Na_2HPO_4	6.0	148.7	7.04
	7.0	134.5	7.60
	8.0	137.2	8.50
0.05 M $Na_2B_4O_7$	9.0	141.3	9.35
	10.0	121.7	10.28

Phenytoin

pH	Solubility (mg/mL)
1.6	0.02
4.4	0.02
5.0	0.01
5.9	0.02
6.9	0.02
8.0	0.01
9.0	0.10
10.0	0.96
11.0	9.6
12.0	96

Hydroxyphenytoin (HPPH)

Buffer System	pH	Solubility (mg/mL)
0.05 M NaH_2PO_4	4.0	0.013
	5.0	0.014
	6.0	0.014
0.05 M Na_2HPO_4	7.0	0.014
	7.5	0.016
	8.0	0.022
0.05 M $Na_2B_4O_7$	9.0	0.104
	10.0	1.19

5. Partition Coefficient:

Buffer System	$\log(K_{ow})$ Hydroxyphenytoin	$\log(K_{ow})$ Fosphenytoin	$\log(K_{ow})$ Phenytoin
0.05 M Phosphate, pH 4.0	-1.10	2.48	1.96
0.05 M Phosphate, pH 7.4	-2.03	2.40	1.91
0.05 M Borate, pH 9.1	-3.06	1.34	0.82

6. Sorption/Desorption:

For Fosphenytoin sodium at concentrations range from 50.7 to 3.02 mg/L.

Soil Type	K_d	K_{oc}	n	r^2
Washington	11.8	1,120	1.25	0.997
Kansas	43.2	7,940	1.59	0.976
Wisconsin	6.10	188	0.953	0.801

Results at concentrations ranging from 49.4 to 3.8 mg/L in 0.0/M $CaCl^2$

Soil Type	K_d	K_{oc}	n	r^2
Washington	23.1	3,570	1.85	0.866
Kansas	315	21,400	1.99	0.995
Wisconsin	51.2	1,580	71.75	0.941

For phenytoin, advanced isotherm testing was only conducted at concentrations ranging from 10 to 0.6 mg/L with the Wisconsin soil in $CaCl_2$ since desorption was greater than 75% for the other 2 soils.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	NA	NA	NA	NA
Wisconsin	3.46	107	1.06	0.996

For Hydroxyphenytoin, advanced isotherm testing was conducted with Kansas and Wisconsin soils at concentrations ranging from 1.2 to 0.08 mg/L in $CaCl_2$ since desorption was greater than 75% for the Washington soil.

Soil Type	K_d	K_{oc}	n	r^2
Washington	NA	NA	NA	NA
Kansas	1.85	124	1.20	0.993
Wisconsin	3.33	103	1.19	0.998

7. Photolysis:

Photolysis for Fosphenytoin Sodium

pH	Half-Lives (Days)
5.0	112
7.0	193
9.0	86

8. Toxicology Studies of Fosphenytoin Sodium

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	Study Report NDA Location Volume	Study Report NDA Location Page
Acute Toxicity Studies								
Mouse (CD-1)	IV Infusion[c]	SAL		Fosphenytoin[a]	ACC	745-01722	1.12	114
5M + 5F, 120	(20 mL/kg)[d]	VC[e]		NOED = 33.3				
6 Weeks	14 Days	33.3	33	MNLD = 63.3				
		63.3	63	MLD = 156				
		120	120	Phenytoin				
		230	233	NOED = ND				
		433	440	MNLD = 63				
				MLD = 192				
Rat (SD)	IV Bolus	SAL		Fosphenytoin[a]	ACC	745-01726	1.12	147
5M + 5F, 120	(10 mL/kg)[f]	VC[g]	VC	NOED = 50				
7 Weeks	14 Days	50	45	MNLD = 153				
		73.3	65	MLD = 213				
		107	95	Phenytoin				
		153	145	NOED = ND				
		233	210	MNLD = 45				
		333	300	MLD = 90.4				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[d] Fosphenytoin dosing solution concentrations ranged from 2.50 to 32.5 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 22.0 mg/mL.

[e] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[f] Fosphenytoin dosing solution concentrations ranged from 7.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 4.50 to 30.0 mg/mL.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	Study Report NDA Location Volume	Study Report NDA Location Page
Acute Toxicity Studies (continued)								
Rat (SD)	IV Infusion[c]	SAL		**Fosphenytoin[a]**	ACC	745-01727	1.12	180
5M + 5F, 130	(10 mL/kg)[f]	50[g]	45	NOED = ND				
7 Weeks	14 Days	73.3	65	MNLD = 153				
		107	95	MLD = 242				
		153	145	**Phenytoin**				
		233	210	NOED = ND				
		333	300	MNLD = 210				
				MLD = 275[h]				
Rat (SD)	IV Infusion[c]	SAL		**Fosphenytoin[a]**	ACC	745-01725	1.12	214
5M + 5F, 120	(10 mL/kg)[i]	VC[e]		NOED = 33.3				
4 Weeks	14 Days	33.3	33	MNLD = 120				
		63.3	63	MLD = 258				
		120	120	**Phenytoin**				
		230	233	NOED = 33				
		433	440	MNLD = 120				
				MLD = 297				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[e] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[f] Fosphenytoin dosing solution concentrations ranged from 7.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 4.50 to 30.0 mg/mL.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[h] Estimate; value could not be calculated using Moving Average Interpolation or Probit Analyses Method.

[i] Fosphenytoin dosing solution concentrations ranged from 5.0 to 65 mg/mL. Phenytoin dosing solution concentrations ranged from 3.3 to 44 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	NDA Location Volume	NDA Location Page
Acute Toxicity Studies (continued)								
Rat (SD)	IM	SAL		**Fosphenytoin[a]**	ACC	745-01738	1.12	248
3M + 3F, 72	(5 mL/kg)[j,k]	33.3[g]	34	NOED = 33.3				
7 Weeks	14 Days	76.7	169	MNLD = 167				
		167	250	MLD = 278				
		247[l]	337[l]	**Phenytoin**				
		333[l]		NOED = 34				
				MNLD = 337				
				MLD = >337				
Rat (SD)	IP	SAL		**Fosphenytoin[a]**	ACC	745-01723	1.12	328
5M + 5F, 160	(10 mL/kg)[m]	VC[e]		NOED = 60				
6 Weeks	14 Days	33.3	33	MNLD = 177				
		60	60	MLD = 352				
		100	102	**Phenytoin**				
		177	178	NOED = 60				
		300	305	MNLD = 178				
		500	500	MLD = 339				
		850	860					

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[e] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[j] Dose volume for 337 mg/kg phenytoin group was 6.74 mL/kg.

[k] Fosphenytoin dosing solution concentrations ranged from 10 to 100 mg/mL. Phenytoin dosing solution concentrations ranged from 6.8 to 50 mg/mL.

[l] N = 5 rats/sex.

[m] Fosphenytoin dosing solution concentrations ranged from 5.0 to 75 mg/mL. Phenytoin dosing solution concentrations ranged from 3.3 to 50 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	Study Report NDA Location Volume	Study Report NDA Location Page
Acute Toxicity Studies (continued)								
Rat (SD)	IP	SAL		Fosphenytoin[a]	ACC	745-01720	1.12	358
5M + 5F, 140	(20 mL/kg)[a]	VC[c]		NOED = 100				
7 Days	14 Days	33.3	33	MTD = 100				
		60	60	MLD = 181				
		100	102	Phenytoin				
		177	178	NOED = 102				
		300	305	MTD = 102				
		500	500	MLD = 224				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[a] Fosphenytoin dosing solution concentrations ranged from 2.50 to 37.5 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 25.0 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Day	Dose (mg/kg) Fosphenytoin[a]	Dose (mg/kg) Phenytoin[b]	Results (mg/kg)	Lab	Study Report RR Number	NDA Location Volume	NDA Location Page
Escalating-Dose Toxicity Studies									
Rabbit (NZW)	IV Infusion[c]	1	6.7[e]	6.8	**Fosphenytoin[a]**	ACC	745-01721	1.12	386
6M + 6F, 24	(10 mL/kg)[o]	3	13.3	13.5	NOED = 40				
NA		6	20	20.2	MTD = 40				
		9	26.7	27	No Deaths				
		13	40	40.5	**Phenytoin**				
		15[p]	53.3	54	NOED = 27				
					MTD = 40.5				
					No Deaths				
Dog (beagle)	IV Bolus	1	6.7[g]	6	**Fosphenytoin[a]**	ACC	745-01728	1.12	412
2M + 2F, 8	(2 mL/kg)[q]	3	13.3	12	NOED = 13.3				
10 Months		5	26.7	24	MTD = 26.7				
		8[p]	40	36	No Deaths				
					Phenytoin				
					NOED = 6				
					MTD = 24				
					No Deaths				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[e] Vehicle = 1-arginine HCl, pH adjusted to 8.8.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[o] Fosphenytoin dosing solution concentrations ranged from 1.0 to 8.0 mg/mL. Phenytoin dosing solution concentrations ranged from 0.68 to 5.40 mg/mL.

[p] Animals observed for 14 days after last dose.

[q] Fosphenytoin dosing solution concentrations ranged from 5.0 to 30 mg/mL. Phenytoin dosing solution concentrations ranged from 3.0 to 18 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Observation Period	Day	Dose (mg/kg)		Results (mg/kg)	Lab	Study Report		
			Fosphenytoin[a]	Phenytoin[b]			RR Number	NDA Location Volume	Page
Escalating-Dose Toxicity Studies (continued)									
Dog (beagle)	IV Infusion[c]	1	6.7[g]	6	Fosphenytoin[a]	ACC	745-01729	1.12	471
2M + 2F, 8	(2 mL/kg)[d]	3	13.3	12	NOED = 13.3				
10 Months		5	26.7	24	MTD = 26.7				
		8[p]	40	36	No Deaths				
					Phenytoin				
					NOED = 12				
					MTD = 24				
					No Deaths				
Dog (beagle)	IM	1	6.7[g]	6.7	Fosphenytoin[a]	ACC	745-01742	1.12	527
3M + 3F, 12	(0.13-1.00 mL/kg)[r]	3	16.7	16.9	NOED = 33.3				
10 Months		7	33.3	33.7	MTD = 33.3				
		9[p]	50	50	No Deaths				
					Phenytoin				
					NOED = 6.7				
					MTD = >50				
					No Deaths				

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Duration of infusion = 30 minutes.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[p] Animals observed for 14 days after last dose.

[q] Fosphenytoin dosing solution concentrations ranged from 5.0 to 30 mg/mL. Phenytoin dosing solution concentrations ranged from 3.0 to 18 mg/mL.

[r] Fosphenytoin dosing solution concentration = 75 mg/mL. Phenytoin dosing concentration = 50 mg/mL.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Multidose Toxicity Studies						
Rat (SD) 5M + 5F, 60 6-7 Weeks	IV Bolus (10 mL/kg)[d] 7 Days	VC[g] 20 40 66.7 107 160	Deaths at 107 and 160 mg/kg. Dose-related lethargy, ataxia, and head tremors at ≥66.7 mg/kg. Decreased body weight gain and food consumption, glucosuria, and increased ALT, ALP, and BUN at 107 and 160 mg/kg. No pathologic findings. (ACC)	745-01730	1.13	001
Rat (SD) 10M + 10F, 100 8 Weeks	IV Bolus (10 mL/kg)[f] 2 Weeks	SAL VC[g] 13.3 33.3 100	Death, hypoactivity, dyspnea, dilated pupils, prostration, ataxia, hypothermia, decreased body weight gain in males, transient decreases in food consumption, increased urine volumes, and glucosuria in both sexes at 100 mg/kg. No pathologic findings. (IRDC)	745-01732	1.13	106
Rat (Wistar) 15M + 15F, 144[u] 6-7 Weeks	IV Bolus (2 mL/kg)[v] 4 Weeks[w]	VC[g] 20 40 100	No deaths. Ataxia, hypoactivity, and salivation at 40 and 100 mg/kg. Decreased body weight gain in males at 100 mg/kg. Reversible increases in ALT and ALP at 100 mg/kg. Increased liver:body weight in males at 100 mg/kg and females at all doses; reversible at 20 and 40 mg/kg. Reversible dose-related injection site irritation at ≥20 mg/kg and vacuolation of hepatocytes at 100 mg/kg. (SP)	250-01648	1.14	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[d] Fosphenytoin dosing solution concentrations ranged from 3.0 to 24 mg/mL.

[f] Fosphenytoin dosing solution concentrations ranged from 2.0 to 15 mg/mL.

[u] Three additional animals per sex included in control and/or drug-treated groups and utilized only for determination of drug concentrations.

[v] Fosphenytoin dosing solution concentrations ranged from 15 to 75 mg/mL.

[w] Five animals per sex per group were euthanatized after a 4-week withdrawal period (Week 8).

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[A] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Multidose Toxicity Studies (continued)						
Rat (SD) 5M + 5F, 90[W] 7-9 Weeks	IM (0.7-3.3 mL/kg)[X] 2 Weeks	SAL 33.3 66.7 100 133 167	Deaths at 133 and 167 mg/kg. Dose-related lethargy, prostration, ataxia, and/or tremors at ≥66.7 mg/kg. Decreased body weight gain, transient decreases in food consumption, and increased urine volumes in males at ≥100 mg/kg. Injection-related gross pathologic changes in muscle in 1 animal each at 100 and 167 mg/kg. (DCC)	745-01745	1.14	338
Rat (SD) 10M + 10F, 150[Y] 7 Weeks	IM (0.4-2.0 mL/kg)[X] 13 Weeks	SAL PHT[Z] 20 40 100	Increased liver weights in females at all doses. Deaths, dilated pupils, hypoactivity, excessive salivation, decreased body weight, increased AST, ALT, and ALP, hyperglycemia, glucosuria, and intracytoplasmic hepatocellular vacuolation with fosphenytoin at 100 mg/kg. Similar findings were noted with phenytoin. Local irritation with both compounds. (IRDC)	745-01744	1.15-16	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[A] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[W] Three additional animals per sex included in control and/or drug-treated groups and utilized only for determination of drug concentrations.

[X] Fosphenytoin dosing solution concentration = 75 mg/mL.

[Y] Five additional animals per sex per group utilized only for determination of drug concentrations.

[Z] Phenytoin Sodium Injection, USP, administered at 100 mg/kg, dosing solution concentration = 50 mg/mL; group terminated at Week 9.

Tabular Summary of Toxicology Studies
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Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Multidose Toxicity Studies (continued)						
Dog (beagle) 2M + 2F, 24 11-12 Months	IV Bolus (2.0 mL/kg)[aa] 7 Days	VC[g] 6.7 13.3 20 26.7 33.3	No deaths. Dose-related diarrhea, salivation, and emesis at ≥13.3 mg/kg. In addition, ataxia at 26.7 and 33.3 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings. (ACC)	745-01731	1.16	292
Dog (beagle) 4M + 4F, 40 7-8 Months	IV Bolus (2.0 mL/kg)[bb] 2 Weeks	SAL VC[g] 10 20 33.3	No deaths. Hypoactivity, emesis, excessive salivation, and ataxia at 20 and 33.3 mg/kg. In addition, tremors at 33.3 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings. (IRDC)	745-01733	1.17	001
Dog (beagle) 4M + 4 F, 24 10-12 Months	IV Bolus (0.67 mL/kg)[cc] 4 Weeks[dd]	VC[g] 10 20 33.3	No deaths. Dose-related incidence of emesis at ≥10 mg/kg and transient salivation, ataxia, and erythema of gums at ≥20 mg/kg. Tremors and hypoactivity at 33.3 mg/kg. Increased ALP at 33.3 mg/kg at Weeks 4 and 8. Increased salivary gland weights in both sexes at 33.3 mg/kg and females at 20 mg/kg at Week 4. Increased liver:body weight in males at 20 and 33.3 mg/kg; reversible at 20 mg/kg. Hypertrophy of salivary glands in males at 33.3 mg/kg at Weeks 4 and 8. (AA)	745-01970	1.18	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[aa] Fosphenytoin dosing solution concentrations ranged from 5.0 to 25 mg/mL.

[bb] Fosphenytoin dosing solution concentrations ranged from 7.5 to 25 mg/mL.

[cc] Fosphenytoin dosing solution concentrations ranged from 22.4 to 75.0 mg/mL.

[dd] One animal per sex per group was euthanatized after a 4-week withdrawal period (Week 8).

Tabular Summary of Toxicology Studies
(Page 10 of 19)

Species (Strain) Sex/Group, Total Age	Route (Dose Volume) Duration	Daily Dose[a] (mg/kg)	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Multidose Toxicity Studies (continued)						
Dog (beagle) 2M + 2F, 24 9-10 Months	IM (0.2-1.0 mL/kg)[x] 2 Weeks	SAL 10 20 33.3 40 50	No deaths. Dose-related incidence of emesis and ataxia at ≥33.3 mg/kg. Sporadic convulsions, diarrhea, and/or tonic stance at 40 and 50 mg/kg. In addition, prostration and excessive salivation at 50 mg/kg. No significant changes in clinical laboratory parameters. No pathologic findings. (DCC)	745-01739	1.18	311
Dog (beagle) 4M + 4F, 40 7-9 Months	IM (0.2-0.8 mL/kg)[x] 13 Weeks	SAL PHT[xx] 10 20 40	No deaths. Emesis and excessive salivation at all doses. In addition, ataxia, hypoactivity, diarrhea, increased ALP, increased liver weights, and intracytoplasmic hepatocellular vacuolation with fosphenytoin at 40 mg/kg. Similar findings were noted with phenytoin. Local irritation with fosphenytoin at 20 and 40 mg/kg and with phenytoin. (IRDC)	745-01740	1.19	001

Abbreviations are defined on Page 19 of the Tabular Summary

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[x] Fosphenytoin dosing solution concentration = 75 mg/mL.

[xx] Phenytoin Sodium Injection, USP, administered at 40 mg/kg, dosing solution concentration = 50 mg/mL.

Tabular Summary of Toxicology Studies
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Test Species (Strain) Sex/Group, Total	Study Design[ff]	Results (Laboratory)	Study Report		
			RR Number	NDA Location Volume	Page
Special Toxicity Studies					
Venous and Perivascular Irritation[zz] Rabbits (NZW) 6 M, 66	**Dosing:** Single 30-minute IV infusion or SC injection FOS(mg/mL):VC[e], 10, 25, 50, 75 PHT[b](mg/mL):VC, 6.7, 16.9, 33.7, 50 **Observation:** 24 hours ***Parameters:*** *Gross and microscopic examinations*	No significant differences in perivascular or venous irritation between fosphenytoin and saline controls. Significant venous and perivascular irritation and high incidence of thrombus formation with phenytoin. (ACC)	745-01724	1.20	001
Intramuscular Irritation[zz] Rabbits (NZW) 12 M, 12	**Dosing:** Single IM injection FOS(mg/mL):VC[g], 25, 50, 75, 100 PHT[b](mg/mL):VC, 50 **Observation:** 24 hours **Parameters:** Gross and microscopic examinations	Fosphenytoin less irritating than saline or phenytoin. Trace to mild hemorrhage, acute inflammation and necrosis with saline, phenytoin vehicle, and phenytoin. (ACC)	745-01737	1.20	055
Rabbits (NZW) 4 M, 28	**Dosing:** 5 daily IM injections FOS(mg/mL):VC[g], 50, 75, 100 PHT[b](mg/mL):VC, 50 **Observation:** 5 days **Parameters:** Serum CPK, gross and microscopic examinations	Hemorrhage in all control and treatment groups. Necrosis with phenytoin; less severe with fosphenytoin at 75 and 100 mg/mL. Increased CPK with phenytoin vehicle, phenytoin, and fosphenytoin. (ACC)	745-01741	1.20	094

Abbreviations are defined on Page 19 of the Tabular Summary.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[e] Vehicle = l-arginine HCl, pH adjusted to 8.8.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[ff] All in vivo studies included saline (0.9% NaCl) control group.

[zz] *Concentrations based on the weight of the sodium salt of fosphenytoin or phenytoin.*

Tabular Summary of Toxicology Studies
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Test Species (Strain) Sex/Group, Total	Study Design[ff]	Results (Laboratory)	Study Report		
			RR Number	NDA Location	
				Volume	Page
Special Toxicity Studies (continued)					
Glucosuria[a] Rats (SD) 10 M, 30	**Dosing:** Single 30-minute IV infusion **POS[g](mg/kg):** 100 **PHT[b](mg/kg):** 100 **Dose Volume:** 10 mL/kg[hh] **Observation:** 48 hours **Parameters:** Clinical signs, serum and urine glucose concentrations	Similar increases in serum and urinary glucose concentrations with fosphenytoin and phenytoin. (DCC)	745-01734	1.20	140
CNS Safety Screen[a] Mice (CD-1) 6 M, 90	**Dosing:** Single IP injection **POS(mg/kg):** VC[ii], 33.3, 66.7, 133, 333, 667 **PHT[b](mg/kg):** VC[ii], 33, 69, 134, 337, 675 **Dose Volume:** 20 mL/kg[jj] **Observation:** Approximately 4 hours **Parameters:** Clinical signs and behavioral changes	Deaths at 333 and 667 mg/kg fosphenytoin and 337 and 675 mg/kg phenytoin. Similar incidence and severity of CNS effects observed with fosphenytoin and phenytoin. (ACC)	745-01736	1.20	170

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[g] Vehicle = Tris buffer, pH adjusted to 8.8.

[ff] All in vivo studies included saline (0.9% NaCl) control group.

[hh] Fosphenytoin dosing solution concentration = 15 mg/mL. Phenytoin dosing solution concentration = 10 mg/mL.

[ii] Vehicle was tested in 3 groups of animals at 100% or diluted to 66% or 32% with saline (0.9% NaCl).

[jj] Fosphenytoin dosing solution concentrations ranged from 2.5 to 50 mg/mL. Phenytoin dosing solution concentrations ranged from 1.65 to 33.75 mg/mL.

Tabular Summary of Toxicology Studies
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Test Species (Strain) Sex/Group, Total	Study Design[ff]	Results (Laboratory)	Study Report		
			RR Number	NDA Location	
				Volume	Page
Special Toxicity Studies (continued)					
Cardiovascular Safety Screen[a] Dogs (Beagle) 4 F, 20	**Dosing:** Single IV injection **FOS(mg/kg):** VC[c], 18 **PHT**[b]**(mg/kg):** VC, 18 **Dose Volume:** 1 mL/kg[kk] **Observation:** 60 minutes **Parameters:** Cardiovascular, blood drug concentrations	No deaths. Gradual decrease in HR, LVdP/dt, and MABP with fosphenytoin and immediate decreases in these parameters with phenytoin. Significant increase in LVEDP with phenytoin. Maximum plasma phenytoin concentrations were 22.1 µg/mL 5 minutes postdose and 49.4 µg/mL 30 seconds postdose following administration of fosphenytoin and phenytoin, respectively. (ACC)	745-01735	1.20	193
Human Blood Compatibility[gg] In Vitro	**Concentrations:** **FOS(mg/mL):** 0.15 to 75 **PHT**[b]**(mg/mL):** 0.10 to 50 **Parameters:** Hemolysis, plasma protein flocculation	No hemolysis or plasma protein flocculation with fosphenytoin. Hemolysis at 5.0 to 7.0 mg/mL and mild plasma protein flocculation with phenytoin at 20 mg/mL. (DCC)	745-01746	1.20	279

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dose expressed as milligram/kilogram phenytoin equivalents. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

[b] Phenytoin Sodium Injection, USP; vehicle = 40% propylene glycol and 10% alcohol, pH adjusted to 12.

[c] Vehicle = Tris buffer, pH adjusted to 8.8.

[ff] All in vivo studies included saline (0.9% NaCl) control group

[gg] Concentrations based on the weight of the sodium salt of fosphenytoin or phenytoin.

[kk] Fosphenytoin dosing solution concentration = 27 mg/mL. Phenytoin dosing solution concentration = 18 mg/mL.

Tabular Summary of Toxicology Studies
(Page 14 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) (Dose Volume)	Dose[a] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Reproductive Toxicity Studies							
Fertility							
Male							
Rat (SD) 40, 200 12-13 Weeks	IM (Tris Buffer) [2 mL/kg]	UC VC 16.7 50 100	75 Days Prior to and through Mating	Paternal toxicity at 50 and 100 mg/kg. No effects on fertility or reproduction. (AA)	745-02042	1.21-22	001
Female							
Rat (SD) 40, 200 15 Weeks	IM (Tris Buffer) [2 mL/kg]	UC VC 16.7 50 100	15 Days Prior to Mating through Lactation Day 21	Maternal and reproductive toxicity at 50 and 100 mg/kg. Developmental toxicity at all doses, including teratogenicity at 16.7 and 100 mg/kg. (AA)	745-02092	1.23-24	017
Teratology							
Exploratory							
Rat (SD) 3F, 9 NA	IV Bolus (Tris Buffer) [2,3,10 mL/kg]	100	10 Days	All animals euthanatized moribund by Day 4. No trauma at injection site. (AA)	745-01843	1.24	276

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Dosed expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

Tabular Summary of Toxicology Studies
(Page 15 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Dose[1] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Reproductive Toxicity Studies (continued)							
Teratology (continued)							
Dose Range-Finding							
Rat (SD) 5F, 35 20 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	VC 6.7 16.7 33.3 50 66.7	Gestation Days 7 through 17	Maternal toxicity at 16.7, 33.3, and 66.7 mg/kg. Developmental toxicity at 50 and 66.7 mg/kg. No adverse effects at 6.7 mg/kg. MTD = 66.7 mg/kg. (AA)	745-01859	1.25	001
Definitive							
Rat (SD) 40F, 200 12-13 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	UC VC 6.7 33.3 66.7	Gestation Days 7 through 17	Four deaths, decreased maternal body weight gain and food consumption, decreased birth and male offspring weights at Week 13 at 66.7 mg/kg. No teratogenicity or behavioral toxicity. (AA)	745-01973	1.25-26	124

Abbreviations are defined on Page 19 of the Tabular Summary.

[1] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

Tabular Summary of Toxicology Studies
(Page 16 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Dose[a] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report RR Number	NDA Location Volume	NDA Location Page
Reproductive Toxicity Studies (continued)							
Teratology (continued)							
Exploratory							
Rabbit (NZW) 3F, 6 NA	IV Bolus (Tris Buffer) [1,2 mL/kg]	33.3	13 days	No clinical signs or effects on body weight or food consumption. No trauma at injection site. (AA)	745-01844	1.27	014
Dose Range-Finding							
Rabbit (NZW) 5F, 35 7-8 Months	IV Bolus (Tris Buffer) [1-2 mL/kg]	VC 3.3 16.7 33.3 50 66.7	Gestation Day 6 through 18	Maternal toxicity at 33.3, 50, and 66.7 mg/kg. Developmental toxicity at 66.7 mg/kg. No adverse effects at 3.3 mg/kg. MTD = 33.3 mg/kg. (AA)	745-01871	1.27	021

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

Tabular Summary of Toxicology Studies
(Page 17 of 19)

Species (Strain) Sex/Group, Total Age	Route (Vehicle) [Dose Volume]	Dose[a] (mg/kg)	Treatment Regimen	Results (Laboratory)	Study Report RR Number	NDA Location Volume	Page
Reproductive Toxicity Studies (continued)							
Teratology (continued)							
Definitive							
Rabbit (NZW) 20F, 100 7-8 Months	IV Bolus (Tris Buffer) [1 mL/kg]	UC VC 6.7 16.7 33.3	Gestation Day 6 through 18	No deaths. Decreased body weight gain and food consumption at 33.3 mg/kg. No maternal reproductive or fetal toxicity, and no teratogenicity. (AA)	745-01931	1.27	155
PERINATAL-POSTNATAL TOXICITY							
Rat (SD) 25 F, 125 12 Weeks	IV Bolus (Tris Buffer) [2 mL/kg]	UC VC 16.7 33.3 66.7	Gestation Day 15 through Lactation Day 20	Maternal and perinatal-postnatal toxicity at 33.3 and 66.7 mg/kg. Subtle behavioral toxicity at 33.3 and 66.7 mg/kg. (AA)	745-02071	1.28-30	001

Abbreviations are defined on Page 19 of the Tabular Summary.

[a] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 75 mg/mL. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

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Tabular Summary of Toxicology Studies
(Page 18 of 19)

Test	Concentration Range or Dose	Results (Laboratory)	Study Report		
			RR Number	NDA Location	
				Volume	Page
Genetic Toxicity Studies					
Mutagenicity					
Mutagenesis in *Salmonella typhimurium*	312.5-5000 µg/plate[mm]	Nonmutagenic in the absence or presence of S9. (AA)	745-01958	1.31	016
Point mutation assay in V79 Chinese hamster lung cells	500-4000 µg/mL[mm]	No mutation at HGPRT locus in the absence or presence of S9. (AA)	745-01935	1.31	083
Clastogenicity					
Structural chromosome aberration assay in V79 Chinese hamster lung cells	500-4000 µg/mL[mm](-S9) 125-4000 µg/mL[mm](+S9)	Clastogenic at ≥3000 µg/mL only in the presence of S9. (AA)	745-02101	1.31	145
Micronucleus assay	33.3, 66.7, 133 mg/kg[aa]	No increase in micronucleus frequency. (AA)	745-01898	1.31	248

Abbreviations are defined on Page 19 of the Tabular Summary.

[mm] Concentrations based on the weight of fosphenytoin.

[aa] Doses expressed as milligram/kilogram phenytoin equivalents; fosphenytoin dosing solution concentrations ranged from 5 to 20 mg/mL; dose volume = 10 mL/kg. Approximate fosphenytoin dose can be derived by multiplying the phenytoin equivalent dose by 1.5.

U:\NDA\CI-982\REG332RA.EA2

Tabular Summary of Toxicology Studies
(Page 19 of 19)

ABBREVIATIONS:

AA	=	Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan
ACC	=	American Critical Care, McGaw Park, Illinois
ALP	=	alkaline phosphatase
ALT	=	alanine aminotransferase
AST	=	aspartate aminotransferase
BUN	=	blood urea nitrogen
CNS	=	central nervous system
CPK	=	creatine phosphokinase
DCC	=	Du Pont Critical Care, Waukegan, Illinois
F	=	female
FOS	=	fosphenytoin
HGPRT	=	hypoxanthine-guanine phosphoribosyltransferase
HR	=	heart rate
IM	=	intramuscular
IP	=	intraperitoneal
IRDC	=	International Research and Development Corporation, Mattawan, Michigan
IV	=	intravenous
LVEDP	=	left ventricular end diastolic pressure
LVdP/dt	=	left ventricular contractility
M	=	male
MABP	=	mean arterial blood pressure
MLD	=	median lethal dose
MNLD	=	maximum nonlethal dose
MTD	=	maximum tolerated dose
NA	=	not available
ND	=	not determined
NOED	=	no observed effect dose
NZW	=	New Zealand White
PHT	=	phenytoin
S9	=	postmitochondrial supernatant from livers of rats induced by Aroclor 1254
SAL	=	saline (0.9% NaCl) control
SC	=	subcutaneous
SD	=	Sprague-Dawley
SP	=	Parke-Davis Research Institute, Sheridan Park, Mississauga, Ontario, Canada
UC	=	untreated control
VC	=	vehicle control

9. Microbial Growth Inhibition

The Microbial Inhibitory Concentrations (MC) for Fosphenytoin Sodium

Species	Fosphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

The Microbial Inhibitory Concentrations (MC) for Phenytoin

Species	Fosphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

The Microbial Inhibitory Concentrations (MC) for Hydroxyphenytoin

Species	Hydroxyphenytoin MC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc	>1000

10. The Acute Toxicity Studies with *Daphnia magna*

Compound	EC_{50} (mg/L)	NOEC (mg/L)
Fosphenytoin Sodium	170	48
Phenytoin	39	23
Hydroxyphenytoin	28	28

EC_{50}: Concentration at which 50% of the organisms are affected.
NOEC: The no-observed effect concentration for 48 hours.

ATTACHMENT II

MATERIAL SAFETY DATA SHEET

THIS MATERIAL SAFETY DATA SHEET IS DIRECTED PRINCIPALLY TO PROCESSORS, FORMULATORS, AND USERS OF THIS MATERIAL. THE DESCRIPTION OF PHYSICAL, CHEMICAL AND TOXICOLOGICAL PROPERTRIES AS WELL AS THE ADVICE ON HANDLING IS BASED ON PAST EXPERIENCE AND CURRENTLY AVAILABLE INFORMATION. IF YOU HAVE ANY QUESTIONS REGARDING THE HAZARDS ASSOCIATED WITH THE USE OF THIS MATERIAL PLEASE CONTACT THE PERSON NAMED IN SECTION I.

1. MATERIAL IDENTIFICATION

Product Name: 5,5-DIPHENYL-3-PHOSPHONOOXYMETHYL 2,4-IMIDAZOLIDINEDIONE DISODIUM SALT

Formula: C16H13N2O6P Na2
Process #: CI-982
W.L. ID #: PD 135711-00153
NDC ID #: ND
UPC #: NA

MSDS #: ND
Date of Issue: 06/10/94
Supersedes: 03/18/93
Revision No: 3

Manufacturing Division:
Parke-Davis
188 Howard Avenue
Holland, MICHIGAN 49424
USA

PERSON TO CONTACT:

Chris Pfeiffer
(616)392-2375

NIOSH RTECS No: ND

Common Name: NA
Chemical Family: ND

Synonyms:
5,5-DIPHENYL-3-PHOSPHONOOXYMETHYL 2,4-IMIDAZOLIDINEDIONE DISODIUM SALT
FOSPHENYTOIN SODIUM
CI-982

Comments: none

2. INGREDIENTS AND EXPOSURE LIMITS

INGREDIENT NAME	CAS #	
5,5-DIPHENYL-3-PHOSPHONOOXYMETHYL 2, 4-IMIDAZOLIDINEDIONE DISODIUM SALT	ND	99

OSHA PEL: ND
ACGIH TLV: ND
Other Exposure: ND
Regulatory: ND
Cancer: No
Synonym/Common: ND
Vapor Pressure: NA
Lower Explosive Limit (LEL): NA
Comments: NONE

PRODUCT Exposure Limits: NONE

MATERIAL SAFETY DATA SHEET

Issued: 06/10/94 MSDS # ND

3. PHYSICAL DATA

Appearance: Crystalline solid.
Odor Threshold: ND
Characteristic Odor: ND

Physical State: Solid
Specific Gravity (H_2O = 1): ND
Acidity (pH) @ 25°C: ND
Boiling Point °C (760 mmHg): NA
Melting Point °C: 220 + Decomp.
Percent Volatile by volume: ND
Water Solubility: Yes
Other Solubility: NO
Vapor Pressure (@ 20°C): ND
Vapor Density (Air = 1): ND
Evaporation Rate (H_2O = 1): ND
Molecular Weight: 406.23

4. FIRE AND EXPLOSION DATA

FLAMMABLE LIMITS IN AIR
LEL: NA
UEL: NA

AUTOIGNITION TEMPERATURE
ND

Flash Point (Method): NA

Extinguishing Media: CO_2, Dry Chemical, Foam, Water Spray

Special Fire Fighting Procedures: Use approved self-contained breathing apparatus.

Unusual Fire Hazards: ND

Unusual Explosion Hazards: ND

Harmful Combustion Products: HCN & Nitrogen Oxides

5. REACTIVITY DATA

Stability: Stable
Hazardous Polymerization: No

Conditions to Avoid: NA
Conditions to Avoid: NA

Chemical Incompatibilities: ND

6. HEALTH HAZARD INFORMATION

TOXICITY INFORMATION: ND

EFFECTS OF OCCUPATIONAL OVEREXPOSURE: ND

MATERIAL SAFETY DATA SHEET

Issued: 06/10/94

MSDS # ND

7. FIRST AID PROCEDURES

THERAPEUTIC CLASS: NA

Eyes: Flush with water for 15 minutes.

Skin: Wash with soap and water until free of residue.

Inhalation: Remove from exposure. Seek medical attention.

Ingestion: Seek medical attention.

8. WORKPLACE PRECAUTIONS / CONTROLS

Handling/Storage Precautions: Store in a cool, dry location, isolated from oxidizing agents. If unusual exposures are expected, an Industrial Hygiene review of work practices and controls is recommended.

Ventilation: General ventilation; local exhaust ventilation.

PERSONAL PROTECTIVE EQUIPMENT

Respirator: Negative pressure, full face, dust filter.
Eye Protection: Safety glasses
Gloves: Coveralls, Gloves

Work Practices: The above personal protective equipment represents the minimum protection recommended. Use appropriate handling methods to minimize dust generation. Avoid skin contact or inhalation of dusts. Wash face, hands and forearms before leaving work area.

9. SPILL & LEAK / ENVIRONMENT / SHIPPING

Procedures for Spill or Leak: Wear self-contained breathing apparatus and appropriate protective clothing.
Collect and place in a suitable container for future disposal.

Waste Management/Disposal: Dispose of in accordance with local, state and federal regulations or the authority having jurisdiction. Incineration in a permitted incinerator is the preferred disposal method. (Advise incinerator of the presence of chlorine, bromine, fluorine, sulfur, heavy metals, etc.)

SHIPPING REQUIREMENTS AND LIMITATIONS

ID/UN No: ND

DOT Hazard Class: ND
DOT Shipping Name: ND
DOT Labels/Placards: ND

Packaging Group: ND
Marking: ND
Container Specifications: ND
Shipping Limitations: ND

Storage Area Temperature Requirements: No restrictions.

MATERIAL SAFETY DATA SHEET

Issued: 06/10/94 MSDS # ND

10. LABELS / SUPPLEMENTAL / OTHER REGULATORY

Hazard Communication Labels: Intermediate - No Toxicity Data

SARA Hazard Classification(s): None

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 2**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-95
AMENDMENT	21-JUL-95	24-JUL-95		16-AUG-95

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: **CEREBYX®**
Nonproprietary/Established/USAN: fosphenytoin sodium, injection OCT 13 1995
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

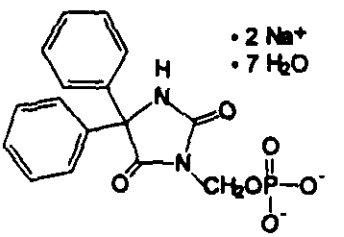
DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx __ OTC
SUPPORTING AND RELATED DOCUMENTS:

CONSULTS: Environmental Assessment: FONSI letter issued and signed by Dr. Jerussi 26-JUN-95
Microbiology / Sterilization Validation, sent to Dr. Cooney, HFD-160 13-APR-95.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt



$C_{16}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)

REMARKS/COMMENTS:

The 21-JUL-95 amendment was a response to 16-JUN-95 deficiency letter. A stability update for the drug product is included. CMC review issues are resolved, with the exception of Microbiology and DMF Inspections and methods validation are still outstanding.

CONCLUSIONS & RECOMMENDATIONS:

As inspections, Microbiology review are not yet completed and manufacturing deficiencies in DMF have not been corrected the application is Not Approvable for Chemistry at this time.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/16-AUG-95
HFD-120/RNighswender
HFD-120/SBlum/Init.: SMB 10/13/95

Martha R Heimann 8/16/95
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 3**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	-
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-95
AMENDMENT	21-JUL-95	24-JUL-95		16-AUG-95
AMENDMENT No. 15	27-SEP-95	28-SEP-95		02-FEB-96
AMENDMENT No. 17	27-OCT-95	30-OCT-95		02-FEB-96
AMENDMENT No. 18	27-OCT-95	30-OCT-95		02-FEB-96
AMENDMENT No. 22	04-JAN-96	05-JAN-96		02-FEB-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH

Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: **CEREBYX®**
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

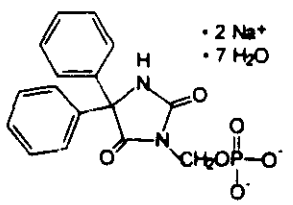
DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx ___ OTC
SUPPORTING AND RELATED DOCUMENTS:

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr. Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95. Minor deficiencies will be included in action letter to sponsor.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{15}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

Several minor amendments were submitted after completion of Review #2. Change in expiration date from 18 months to 24 months (01-JAN-96 amendment)will require adjustment of the post-approval stability protocol. Site inspections are complete and a copy of the EER is attached. DM[illegible] was revised on 18-SEP-95 and is satisfactory for use of phenytoin in synthesis of fosphenytoin. Methods Validation is not complete.

CONCLUSIONS & RECOMMENDATIONS:

Recommend APPROVABLE for Chemistry. The firm should increase stability sterility testing to ensure the product remains sterile through a 24 month expiration date [Draft letter attached] and correct microbiology deficiencies. Letter to sponsor should contain standard methods validation paragraph.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeima..n/02-FEB-96
HFD-120/RNighswander
HFD-120/SBlum/Init.: AMB 2/8/96

Martha R Heimann 2/2/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.003

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: # 4**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
ORIGINAL	14-JUL-94	15-JUL-94	04-AUG-94	N/A
RESUBMISSION	22-FEB-95	23-FEB-95	24-FEB-95	05-JUN-95
AMENDMENT	05-SEP-95	06-SEP-95		22-FEB-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: **CEREBYX®**
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (*drug substance*)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

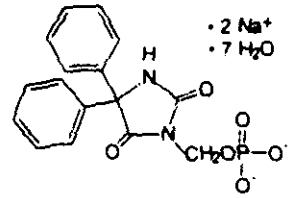
PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx __ OTC

SUPPORTING AND RELATED DOCUMENTS:

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr. Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95. Minor deficiencies will be included in action letter to sponsor.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{16}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

The 05-SEP-95 amendment contained additional copies of the sponsor's Methods Validation package and sample identification (lot #'s etc). Methods validation was performed by the DDA laboratory in St. Louis and by the Detroit District laboratory. Both analysts were able to reproduce the methods and found them generally satisfactory with some comments [see review notes].

CONCLUSIONS & RECOMMENDATIONS:

Methods validation is completed and methods validation paragraph in action letter is not necessary. The NDA remains APPROVABLE for Chemistry with minor deficiency noted in Review No. 3 (02-FEB-96).

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/22-FEB-96
HFD-120/RNeighswander
HFD-120/SBlum/Init.: SNB 2/22/96

Martha R Heimann 2/22/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-240.003

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: #5**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
New Correspondence	13-MAR-96	14-MAR-96		10-MAY-96
Amendment	12-APR-96	19-APR-96	15-APR-96	10-MAY-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road, Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: **CEREBYX®**
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

DESI / Patent Status: U. S. Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx __ OTC

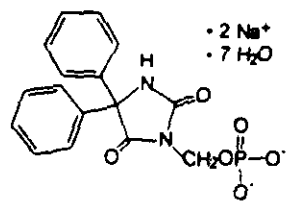
JUL 10 1996

SUPPORTING AND RELATED DOCUMENTS: DMF

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr. Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95 with deficiencies.
Microbiology portion of 13-MAR-96 response reviewed by Dr. Hussong, returned to HFD-120 on 19-APR-96 with approval recommendation.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{15}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

Two submissions dated 13-MAR-96 were a partial to the 23-FEB-96 approvable letter. The CMC and microbiology responses (with some typographical corrections to the microbiology section) are repeated in the 12-APR-96 amendment. All CMC issues have been resolved. Draft labeling expressing fosphenytoin content of the drug product as 'phenytoin equivalents' was submitted in response to the Agency's request [refer to review notes]

CONCLUSIONS & RECOMMENDATIONS:

Chemistry information is correct with minor revisions suggested Medical Reviewer's concurrence with Labeling is necessary.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/10-MAY-96
HFD-120/RNighswander
HFD-120/SBlum/Init: 5/10/96

Martha R. Heimann 5/10/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-450.005

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-450 **CHEMISTRY REVIEW: #6**

Submission Type	Document Date	CDER Date	Assigned Date	Date Reviewed
Amendment	14-MAR-96	15-MAR-96		18-JUL-96
Amendment	12-JUL-96	15-JUL-96	18-JUL-96	18-JUL-96

NAME AND ADDRESS OF APPLICANT: PARKE-DAVIS PHARMACEUTICAL RESEARCH
Division of Warner-Lambert Company
2800 Plymouth Road, Ann Arbor, MI 48105

DRUG PRODUCT NAME:

Proprietary: CEREBYX®
Nonproprietary/Established/USAN: fosphenytoin sodium, injection
Code Name/#: CI-982
Chem. Type/Therapeutic Class: 1S

DESI / Patent Status: U. S Patent 4,260,769, expiration date April 7, 1998 (drug substance)
U. S. Patent 4,925,860, expiration date May 15, 2007, (drug product)

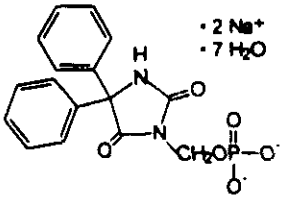
PHARMACOLOGICAL CATEGORY / INDICATION: Anti-epileptic
DOSAGE FORM: Injection
STRENGTHS: 75 mg/mL
ROUTE OF ADMINISTRATION: IV / IM
DISPENSED: XX Rx __ OTC

SUPPORTING AND RELATED DOCUMENTS: DMF

CONSULTS: Environmental Assessment: FONSI letter was signed by Dr. Jerussi on 26-JUN-95
Microbiology / Sterilization Validation: Reviewed by Dr. David Hussong, HFD-805, returned to HFD-120 on 29-DEC-95 with deficiencies.
Microbiology portion of 14-MAR-96 response reviewed by Dr. Hussong, returned to HFD-120 on 19-APR-96 with approval recommendation.

CHEMICAL NAME, STRUCTURAL FORMULA & MOLECULAR FORMULA:

5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt
$C_{16}H_{13}N_2O_6PNa_2 \cdot 7\ H_2O$ Mol. Weight: 406.24 (anhydrous)
532.35 (heptahydrate)



REMARKS/COMMENTS:

The 12-JUL-96 submission contains final printed labeling for the package insert, vials and cartons. At the request of the clinical review division, the labeling was revised to show both the actual weight of fosphenytoin contained and the equivalent weight of phenytoin sodium. The labeling is acceptable to chemistry and there are no CMC issues outstanding.

CONCLUSIONS & RECOMMENDATIONS:

Recommend Approval for Chemistry.

cc: Orig. NDA 20-450
HFD-120/Division File
HFD-120/MHeimann/18-JUL-96
HFD-120/RNighswander
HFD-120/SBlum/Init.: SWB 7/24/96

Martha R. Heimann 7/18/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-450.006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-450

SEP 12 1994

Parke-Davis Pharmaceutical Research
Division of the Warner-Lambert Company
Attention: Irwin G. Martin, Ph.D
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Dr. Martin:

Reference is made to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosphenytoin Sodium Injection (Cerebyx®).

On the basis of our initial review of your New Drug Application referred to above, received on July 15, 1994 and acknowledged on July 28, 1994, we have determined that the application is not acceptable for filing under 21 CFR 314.101 (d)(3).

The application is incomplete because it does not on its face contain information required under section 505(b) and 21 CFR 314.50(d)(5).

Clinical Safety Data:

1. Inadequate studies to show that the product will be safe for use under the conditions of use recommended in the proposed labeling.

   The application contains reports of only 4 patients with status epilepticus who have been treated with fosphenytoin at rates of infusion at or above 225 mg/min. Experience in normals at this dose and rate combination is also limited; although the application does not supply a precise number, preliminary review estimates that no more than 20 normals may have been so exposed.

   Accordingly, the information submitted is inadequate to permit a substantive assessment of whether or not fosphenytoin will be safe for use when administered under the conditions of use recommended in the Dosage and Administration Section of the proposed labeling which recommends, for the treatment of Status Epilepticus, that an intravenous dose of 22.5 to 30 mg/kg given *"At least 150 mg/min up to 225 mg/min"* be administered as a single dose. Additionally, the section recommends, for the treatment or prophylaxis of seizures, that an IM

or IV administration of 15 to 30 mg/kg fosphenytoin be given *"up to 225 mg/min"* as a single dose.

2. Lack of tests and/or reports on tests to show that the drug will be safe for use; a lack of information on the plasma concentrations of formaldehyde:

The application does not provide reports on the concentration of formaldehyde formed in plasma during the administration of your product when used as recommended in product labeling. Formaldehyde is a toxin and is formed during the conversion of fosphenytoin to phenytoin.

Your firm has been advised repeatedly for the need to provide this information, and has, nevertheless, failed to do so.

We note that your NDA SUMMARY;NDA Overview subsection (Item 2.2, page 106) discusses this and states that a complete discussion of this issue could be found under NDA Item 5, section 5.5.4.6, Tab 55. Our preliminary review of the cited reference to clinical data (RR 744-00024, Study 9653-86-01) reveals, however, that NO data regarding formate levels in human trials is included in the cited study report.

Environmental Assessment

Although not reasons for this Refuse to File Action, our environmental assessment staff has completed a preliminary review of your EA and has asked that the following comments be forwarded.

1. General issues:

a. The drug substance and drug product are incorrectly identified throughout the environmental assessment (e.g., the drug substance is identified as Fosphenytoin instead of the sodium salt). Please correct the environmental assessment (pages 3-28) to reflect the correct terminology.

b. The information in the Environmental Assessment is releasable under the Freedom of Information Act. Any proprietary information should be provided in Appendices and be clearly marked as confidential. Some of the information included in your environmental assessment may be confidential (e.g., the list of raw materials used in the synthesis of Fosphenytoin Sodium or the fifth year production estimates). If you wish you may move this information to an appendix and provide only summary information in the actual environmental assessment.

c. A flow diagram for the synthesis of the drug substance and the manufacturing process for the drug product was provided by FAX on August 22, 1994. Please provide an official copy to the file.

2. Please describe the locations where the drug product is expected to be used (Section IV).

3. What is the disposition of returned or expired drug product and rejected drug substance (Section IV)?

4. The Identification of Chemical Substance (Section V) should be revised to include:

a. The correct Chemical Name; i.e., the sodium salt;

b. An appropriate synonym (i.e., sodium salt) with a reference (IUPAC, USAN, etc.,);

c. A structural formula;

d. A list of the additives used or lack thereof; and

e A list of the impurities or lack thereof.

5. A Material Safety Data Sheet for Fosphenytoin Sodium should be provided (Section V).

6. Incomplete information (except for HEPA/air handling at Rochester) is provided regarding the introduction of substances in the environment, specifically the controls, effect of compliance with current emissions requirements, and estimate of the quantities and concentrations of substances expected to enter the environment (Section VI).

a. For air, liquid and solids emissions originating at both the Holland and Rochester facilities the following should be provided:

i. Emission permit numbers, authorizing Agencies and permit expiration dates;

ii. Applicable emission requirements (both qualitative and quantitative);

iii. An estimate, through use of calculations or direct measure, of the possible quantities and concentrations of substances expected to enter the environment (fifth year production estimates); and

iv. Effect of the quantities/concentrations (from 6.a.iii.) on meeting both the qualitative and quantitative emission requirements.

Inclusion of actual permits is not required. For ease of review it is preferred that this information be presented in a table format.

Any of the requested information that is not applicable to a specific permit/emission (e.g., permit expiration date, quantitative emission requirement) should be clearly indicated/explained.

If Warner Lambert does not have direct control (permits) over the waste disposal (e.g., solid waste), the contractors and/or facilities involved should be identified.

b. There are three air permits pending approval at the Holland facility for this product. Please update the status of these permits and indicate when approval is expected.

c. A discussion of the disposal of solid waste generated by the production of the material at the Holland facility should be included.

d. On pages 10 and 11 the expected environmental concentrations should be identified as "maximum" not "minimum".

7. Citation of and a statement of compliance with any appropriate Federal, State and Local occupational exposure requirements should be provided (Section VI).

8. The following are in regards to the fate of the emitted substances in the environment (Section VII)

a. The estimated percent excreted as phenytoin and hydroxyphenytoin should be provided if available.

b. No information was provided regarding hydrolytic stability or dissociation constants for the compounds of interest.

c. For the water solubility determination, a complete test report which includes information such as the methodology used, study site, temperature at which the solubility was determined and the HPLC method should be provided. If the HPLC method is the one included in the NDA it need only be referenced by number.

d. For the partition coefficient determination a complete test report which includes information such as the test methodology, the study site, concentrations at which the study was performed (Note: FDA methodology requires that 2 different concentrations be used) and the HPLC method should be provided. If the HPLC method is the one included in the NDA it need only be referenced by number.

e. The conclusion regarding the aquatic photolytic degradation of Fosphenytoin Sodium (page 17, last sentence in second paragraph) should be revised to indicate that photolysis is not a primary removal mechanism of Fosphenytoin from the environment.

f. You have indicated that aerobic aquatic biodegradation of Hydroxyphenytoin is rapid and that it has been proven/demonstrated to completely degrade to CO_2 (pages 17 and 21) The data provided does not support these conclusions. The appropriate statements should be revised to state that the data indicates that this biodegradation will occur, but that it is not rapid.

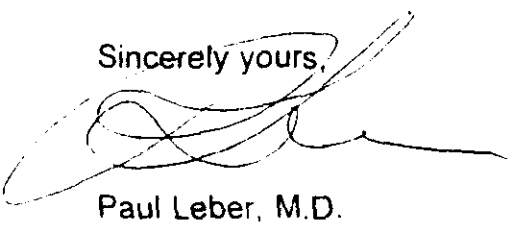
9. Please revise Section XI to state that based on the data you believe that there will be no impact on the environment (or similar wording).

10. You state that no consultants were used (Section XII), but have used the services of at least . Please revise as needed. The *Curricula vitae* cited were not included in Appendix 26.

Within 30 days of the date of this letter, you may request in writing an informal conference about FDA's refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

Should questions arise regarding this application, please contact Mr. Robbin Nighswander, Project Manager, at (301) 594-2777.

Sincerely yours,



Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEC 22 1995

REVIEW FOR HFD-120
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

DETIRM

DEC 2 > 1995

19 December 1995

A. 1. NDA 20-450

SPONSOR Parke-Davis Pharmaceutical Research
Division of Warner Lambert
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

2. PRODUCT NAMES: Cerebyx® (fosphenytoin sodium)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A sterile solution containing 75 mg/mL of 10 mL (in 10 mL vials) and 2 mL (in 3 mL vials), for injection

4. METHOD(S) OF STERILIZATION: Aseptic filling of filtered solution

5. PHARMACOLOGICAL CATEGORY: Neuropharmaceutical for treatment of epilepsy

6. DRUG PRIORITY CLASSIFICATION: 1S

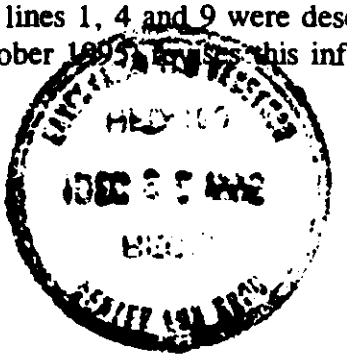
B. 1. DATE OF INITIAL SUBMISSION: 22 February 1995 (Subject of this review)

2. DATE OF AMENDMENT: 27 October 1995 (Also the subject of this review)

3. RELATED DOCUMENTS: DMF
DMF

4. ASSIGNED FOR REVIEW: 2 May 1995 (original) and 15 November 1995 (amendment)

C. REMARKS: The applicant provides a rather comprehensive sterility assurance document in the original submission. Originally, fill lines 1, 4 and 9 were described for this product's manufacture. The amendment (27 October 1995) revises this information, deleting fill line 9, and correcting minor details.



D. CONCLUSIONS: The application is not recommended for approval for reasons of sterility assurance. Specific comments are provided in section in the "Microbiologist's Draft of Letter to the Applicant". Stability information was not part of the consultative review package but was shown in the NDA index, so the review chemist should assure conformance of the testing schedule with Center policy. Labelling was not provided, and this product is not suitable for multiple dose use.

12-19-95

David Hussong, Ph.D.

12/22/95

cc:

HFD-850/Consult File
HFD-120/CSO
HFD-120/M. Heimann
HFD-805/Consult File
HFD-805/D. Hussong

Drafted by: D. Hussong, 12/19/95
R/D initialed by: P. Cooney, 12/ /95

Filename, c:\d\nda\20-450.rv1

MAY 15 1996

REVIEW FOR HFD-120
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #3 OF NDA

9 May 1996

RETURN

MAY 16 1996

A. 1. NDA 20-450

SPONSOR Parke-Davis Pharmaceutical Research
Division of Warner Lambert
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

2. PRODUCT NAMES: Cerebyx® (fosphenytoin sodium)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A sterile solution containing 75 mg/mL of 10 mL (in 10 mL vials) and 2 mL (in 3 mL vials), for injection

4. METHOD(S) OF STERILIZATION: Aseptic filling of filtered solution

5. PHARMACOLOGICAL CATEGORY: Neuropharmaceutical for treatment of epilepsy

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: 22 February 1995 (subject of Microbiologist's Review #1, 19 December 1995)

2. DATE OF AMENDMENTS: 27 October 1995 (also the subject of Microbiologist's Review #1, 19 December 1995); 14 March 1996 (subject of Microbiologist's Review #2, 9 April 1996); and 12 April 1996 (subject of this review)

3. RELATED DOCUMENTS: DMF
DMF

4. ASSIGNED FOR REVIEW: 22 April 1996

C. REMARKS: The applicant provided a rather comprehensive sterility assurance document in the original submission, and addressed 5 deficiency items in the 14 March 1996 amendment. These were acceptable in Microbiologist's Review #2, but some typographical errors were detected. The applicant chose to correct these errors by resubmitting the information from the 14 March 1996 amendment. The typographical

errors were annotated and corrected in this submission. No deficiencies were offered in Microbiologist's Review #2, and no further review is provided here.

D. CONCLUSIONS: The application is recommended for approval for reasons of sterility assurance.

5-9-96
David Hussong, Ph.D.
5/14/96

cc:

HFD-850/Consult File
HFD-120/CSO
HFD-120/M. Heimann
HFD-805/Consult File
HFD-805/D. Hussong

Drafted by: D. Hussong, 05/09/96
R/D initialed by: P. Cooney, 05/ /96

Filename, c:\d\nda\20-450.rv3

NDA 20450 S008

NDA 20460

5008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-460/S-008

DEC 12 1997

Roche Global Development
Palo Alto
Attn: Barbara S.T. Reynolds, Ph.D.
Regulatory Program Director
3401 Hillview Avenue
Palo Alto, CA 94304

Dear Dr. Reynolds:

Please refer to your June 2, 1997, supplemental New Drug Application (NDA) submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Cytovene® (ganciclovir) 500mg capsules.

We acknowledge receipt of your amendments dated:

September 30, 1997	November 17,1997	November 25,1997
October 16, 1997	November 20,1997	

This supplemental application provides for a 500mg strength of Cytovene (ganciclovir capsules).

We have completed our review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the November 25, 1997 draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed label (FPL) must be identical to the November 25, 1997 draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved NDA 20-460/S-008." Approval of this labeling is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Terrie L. Crescenzi, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

Debra Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Concurrence:
HFD530/ADepDir/Dempsey 12/12/97
HFD-530/MTL/Behrman 12/11/97
HFD-530/MO/Martin 12/11/97
HFD-530/ChemTL/Miller 12/11/97
HFD-530/Chem/Lo 12/4/97
HFD-530/BiopharmTL/Jenkins 12/11/97
HFD-530/Biopharm/Sekar 12/11/97
HFD-530/SCSO/ADeCicco 12-11-97
HFD-530/CSO/Crescenzi 12/10/97

cc:
HFD-530/Original NDA 20-460/S-008
HFD-530/Division File
HF-2/MedWatch (with draft/final labeling)
HFD-2/Lumpkin
HFD-80
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
HFD-735 (with draft/final labeling)
District Office
HFD-222/New Drug Chemistry Division Director
HFD-530/Behrman
HFD-530/Martin
HFD-530/Crescenzi
HFD-530/Lo
HFD-530/Sekar

Approval Date:

Approval (AP)

DEBARMENT CERTIFICATION

Syntex (USA) Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 306(a) and (b), in connection with this application.

PATENT INFORMATION FOR SUPPLEMENT TO NDA NO. 20-460

1)	Active Ingredient(s):	ganciclovir
2)	Strength(s):	500 mg capsules
3)	Trade Name:	CYTOVENE
4)	Dosage Form and Route of Administration:	capsule; oral
5)	Applicant (Firm) Name:	Syntex (U.S.A.) Inc
6)	NDA Supplement Number:	S-008
7)	First Approval Date of original NDA:	12/22/94
	First Approval Date of Supplemental NDA:	Not yet approved*
8)	Exclusivity:	Not applicable
9)	Patent Information:	See Attachment

CONFIDENTIAL INFORMATION

*Since the New Drug Application Supplement has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 U.S.C. 552). It is requested that this submission not be published until the New Drug Application Supplement has been approved.

Rev 12/97

ATTACHMENT

First U.S. Patent Number: 4,355,032

Expiration Date: June 23, 2003

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	X Y	N
2.	Drug Product (Composition/Formulation)	X Y	N
3.	Method of Use	X Y	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent: treatment of cytomegalovirus .

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number **4,355,032** covers the composition, formulation and/or method of use of ganciclovir This product is:

__X__ currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

__X__ the subject of this application for which approval is being sought)

Second U.S. Patent Number: 4,423,050

Expiration Date: May 21, 2001

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	___Y	____ N
2.	Drug Product (Composition/Formulation)	___Y	____ N
3.	Method of Use	X__Y	____ N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent: treatment of cytomegalovirus .

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number **4,423,050** covers the composition, formulation and/or method of use of ganciclovir. This product is:

__X__ currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

__X__ the subject of this application for which approval is being sought)

Third U.S. Patent Number: 4,507,305

Expiration Date: May 21, 2001

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	___Y	____ N
2.	*Drug Product (Composition/Formulation)*	___Y	____ N
3.	Method of Use	X_ Y	____ N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that are covered by patent: treatment of cytomegalovirus .

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number **4,507,305** covers the composition, formulation and/or method of use of ganciclovir This product is:

__X__ currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

__X__ the subject of this application for which approval is being sought.)

Fourth U.S. Patent Number: 4,642,346

Expiration Date: June 24, 2005

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	X Y	___ N
2.	Drug Product (Composition/Formulation)	___ Y	___ N
3.	Method of Use	___ Y	___ N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that are covered by patent .

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____. This product is:

___ currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

___ the subject of this application for which approval is being sought)

Signed: George W Johnston

Date: December 11, 1997

Title: Chief Patent Counsel, Hoffmann-La Roche Inc

Telephone Number: (973) 235-3656

A copy of the above information should be submitted with the NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit that information within 30 days of the date of issuance of the patent.

Trade Name
Applicant Nam
Approval Date

PART I IS AN

1. An exclusivit
Complete PART
following questi

a) Is it an or

b) Is it an ef

If yes, wha

c) Did it requ
to safety?

If your answer is
exclusivity, EXP
arguments made

_____

_____

If it is a supplem
change or claim

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes", how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /___/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one-never-before-approved active moiety and one previously approved active moiety, answer "yes". (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved).

YES /__/ NO /__/

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES", GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant". This section should be completed only if the answer to PART II, Question 1 or 2 was "yes".

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies). If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes", then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__/ NO /__/

IF "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying in that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /__/

If "no", state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /__/

(1) If the answer to 2(b) is "yes", do you personally know of any reason to disagree with the applicant's conclusion?

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no", are you aware of published studies not conducted or sponsored by the applicant or other publicly available date that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no", identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval", has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no").

Investigation #1 YES /__/ NO /__/

Investigation #2 YES /__/ NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /__/ NO /__/

Investigation #2 YES /__/ NO /__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are "no", identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /__/ NO /__/ Explain: _____

_____

Investigation #2

IND # _____ YES /__/ NO /__/ Explain: _____

_____

b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____ _____

Investigation #2

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

(c) Not withstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest)

YES /__/ NO /__/

If yes, explain: _____

_____

_____ 10 Dec 97

Signature of Project Manager — Date

_____ _____

Signature of Acting Division Director — Date

cc: Orig NDA Div File HFD-85

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-460 Supplement # 008 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: Cytovene (ganciclovir capsules) Action: AP AE NA

Applicant Syntex (U.S.A.), Inc. Therapeutic Class _____

Indication(s) previously approved CMV disease prevention in solid organ transplant recipients and immunosuppressed patients, and treatment of CMV disease in organ transplant recipients and immunosuppressed patients.
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Indication in this application Provides for a 500mg strength of Cytovene (ganciclovir capsules) (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** *Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.*

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. *A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.*

___ b. *A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.*

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** *The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.*

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[signature] 11 Dec 97

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-460/S-008
Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

DRAFT

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-530	2. NDA NUMBER 20-460

3. NAME AND ADDRESS OF APPLICANT *(City and State)*	4. AF NUMBER	
Syntex (U.S.A.) Inc. 3401 Hillview Avenue, M/S S1-200 Palo Alto, CA 94304	5. SUPPLEMENT(S)	
	NUMBER(S)	DATE(S)
	SE2-008	6/2/97

6. NAME OF DRUG	7. NONPROPRIETARY NAME
CYTOVENE®	Ganciclovir

8. SUPPLEMENT(S) PROVIDES FOR:	9. AMENDMENTS AND OTHER *(Reports, etc)* DATES
A 500 mg strength of CYTOVENE (ganciclovir capsules)	10/16/97, 11/20/97, 11/25/97

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Antiviral	|X| Rx | | OTC	NDA 20-460 Original

13. DOSAGE FORM (S)	14. POTENCY(IES)
Capsules	500 mg

15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS
9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine	*Current* | | Yes | | No *Reviewed* | | Yes | | No

17. COMMENTS

NDA 20-460/SE2-008 provides for a 500 mg strength of CYTOVENE (ganciclovir capsules) . The 500 mg capsules is identical in composition to the marketed 250 mg capsules, except for capsule shell size, color, and final fill weight, and is a direct scale-up of the 250 mg capsules.

This submission contains the following information:

1. CMC information for the 500 mg capsules
2. Bioequivalence studies to compare the bioavailability of the 250 mg and 500 mg capsules.
3. Labeling (package insert, and container and carton labels)

18. CONCLUSIONS AND RECOMMENDATIONS

The chemistry section of this supplement is approved.

19. REVIEWER		
NAME	SIGNATURE	DATE COMPLETED
Ko-Yu Lo, Ph.D.	Ko-Yu Lo	12/5/97

20. CONCURRENCE: HFD-530/SMiller

DISTRIBUTION						
	X	Original Jacket	X	Division File	X	KLo
	X	TCrescenzi	X	JMartin		

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20460 (008)
DRUG: Cytovene® (ganciclovir)
APPLICANT: Syntex Research
TYPE: Supplement
VOLUME(S): 1, 8 - 13

REVIEWER: Vanitha J. Sekar, Ph.D.
FORMULATION: 500 mg capsules
SUBMISSION DATE: June 5, 1997
LOGGED IN: June 16, 1997
FINAL REVIEW: December 5, 1997

TABLE OF CONTENTS

SYNOPSIS:

Background: Ganciclovir is a synthetic nucleoside analog that inhibits replication of human herpes viruses. Intravenous ganciclovir is approved for the treatment of CMV retinitis in AIDS patients and for the prevention of CMV disease in transplant patients. The oral formulation is indicated as an alternative to the intravenous formulation for maintenance therapy of CMV retinitis in immunocompromised patients, including patients with AIDS, in whom retinitis is stable following appropriate induction therapy and for whom the risk of a more rapid progression is balanced by the benefit associated with avoiding daily infusions. The maintenance dose for oral ganciclovir is 1000 mg t.i.d. with food. Alternatively, a regimen of 500 mg q3h 6 times a day with food, while awake, may be used.

The absolute bioavailability of ganciclovir after oral administration is low (~5% to 9%). Plasma protein binding for ganciclovir is low (1 to 2%). Approximately 90% of an orally administered dose of ganciclovir is excreted unchanged in urine and feces within 5 days of administration. When administered orally, ganciclovir exhibits linear pharmacokinetics up to a total daily dose of 4g/day. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. The average half life following intravenous and oral ganciclovir is approximately 3.5 and 5 hours, respectively.

Summary: This document contains reviews of two bioequivalence studies submitted as a supplement to NDA 20460. The current formulation for oral ganciclovir, which has been approved by the U.S. Food and Drug Administration, is a 250 mg hard gelatin capsule. In order to increase the convenience of dosing with oral ganciclovir, a 500 mg capsule formulation has been developed. Both formulations contain the same ingredients in the same proportions and use the same type of hard gelatin capsule. The only differences between the

formulations are the fill weights, capsule sizes, and capsule colors.

Composition of Ganciclovir 500 mg Capsules

Ingredient	Wt. Per capsule (mg)	% w/w	Function
Ganciclovir	500		Active Ingredient
Povidone			
Croscarmellose sodium NF			
Magnesium Stearate			
Purified water			
Total fill weight (theoretical)			

Study GANS2638 was a pivotal study conducted to determine the bioequivalence under steady state conditions of the 500 mg capsule formulation (at a dose of 1000 mg q8h) of ganciclovir to the 250 mg capsule formulation (at a dose of 1000 mg q8h). This was a single center, open label, randomized, two way crossover study in 14 HIV-positive male subjects. Assessment of bioequivalence was done using 90% confidence limits for the pharmacokinetic parameters $AUC_{0\text{-}8}$ and C_{max}. $AUC_{0\text{-}8}$ and C_{max} passed the criteria for bioequivalence. The statistical analysis indicated that the T_{max} for the reference (250 mg capsule) was significantly longer than for the test (500 mg capsule).

Ganciclovir Computed Parameter 90% Confidence Intervals (Study GAN2638)

Computed Parameter	Ratio (B/A)	Lower Limit	Upper Limit
$\ln AUC_{0\text{-}8}$	98.2%		
$\ln C_{max}$	102.1%		

Study GANS2686 was initiated as a result of the discovery of a new crystal form of ganciclovir in both the 250 mg and 500 mg capsules. The discovery was made after the approval of the 250 mg capsule NDA. Some capsule lots for which the hydrated Phase II crystal form of ganciclovir converts to the Phase III crystal form over time show a decrease in dissolution rate under ambient storage conditions. The trend of dissolution slowing under ambient storage conditions has not been observed for lots without the Phase III crystal form. The study was conducted to determine the bioequivalence of four treatments (A, B, C and D) of oral ganciclovir having different dissolution characteristics, storage conditions and crystal form compositions. Treatment A was the reference and B, C and D were the test treatments. The study was performed under steady state conditions, at a dose of 1000 mg q8h. This was a single center, open label, randomized, four way crossover study in 24 HIV-positive subjects. Assessment of bioequivalence was done using 90% confidence limits for the pharmacokinetic parameters, $AUC_{0\text{-}8}$, and C_{max}. The 90% confidence intervals showed that $AUC_{0\text{-}8}$ and C_{max} passed the criteria for bioequivalence for treatments B and C. For treatment D, $AUC_{0\text{-}8}$ passed

the criteria for bioequivalence, but C_{max} did not. The statistical analysis indicated that the T_{max} for the test treatment (D) was significantly longer than for the reference (A).

GANS 2686 Study Treatments, Storage Conditions, *In-Vitro* Dissolution and Crystal Composition.

Treatment	Dosage strength	Storage Conditions		Mean ±SD (% Dissolved at 45 min)		Polymorph composition (% Phase Crystals)		
		°C/%RH	Months	Water	0.1 N HCL	I	II	III
A (Reference)	250 mg	25/Ambient	18	102±1.16	102±0.937	52	48	0
B (Test)	500 mg	25/60	9	83.6±4.62	99.4±1.08	0	24	76
C (Test)	500 mg	30/60	8.5	62.0±4.70	88.7±3.08	0	Trace	100
D (Test)	500 mg	40/75	8.5	39.8±11.2	25.0±3.10	Trace	Trace	100

Ganciclovir Computed Parameter 90% Confidence Intervals (Study GAN2686)

Comparison of B vs A

Computed Parameter	Ratio (B/A)	Lower Limit	Upper Limit
$lnAUC_{0-t}$	94.2%		
lnC_{max}	89.5%		

Comparison of C vs A

Computed Parameter	Ratio (C/A)	Lower Limit	Upper Limit
$lnAUC_{0-t}$	96.0%		
lnC_{max}	90.6%		

Comparison of D vs A

Computed Parameter	Ratio (C/A)	Lower Limit	Upper Limit
$lnAUC_{0-t}$	86.4%		
lnC_{max}	78.5%		

Dissolution Method and Specification for Ganciclovir 500 mg Capsules: The recommended dissolution method for the ganciclovir 500 mg capsules utilizes

This method is the same as that for the approved 250 mg capsule. The proposed specification for ganciclovir 500 mg is Q= dissolved in 45 minutes. The specification proposed is than the current specification for the 250 mg capsule of Q= dissolved in 45 minutes.

The applicant has based this specification (Q= in 45 minutes) primarily on results from bioequivalence study GANS 2686 which showed that 500 mg capsules with dissolution rate o n 45 minutes were bioequivalent to the currently marketed 250 mg capsules. However, review of the dissolution data for the lots used in the bioavailability studies and for

the stability lots suggest that Q= in 45 minutes would be appropriate.

Conclusions: For the pivotal bioequivalence study, GANS2638, the test treatment (500 mg) passed the criteria for bioequivalence. For GANS2686, test treatments B and C passed the criteria for bioequivalence, however, treatment D did not. (For treatment D, AUC_{0-8} passed the criteria for bioequivalence, but C_{max} did not). Treatment D also exhibited the slowest dissolution characteristics. The storage conditions (elevated temperature and high relative humidity) and the predominance of Phase III crystals for Treatment D may be a reason for the poor dissolution characteristics for this treatment. The test product in the pivotal study GANS 2638 was from the same batch as the test product for Treatment D in GAN2686. In the pivotal study GANS 2638, the capsules were stored at 25°C and ambient RH (as opposed to study GANS 2686 where the storage conditions were 40°C and 75% RH). In the pivotal study GANS 2638, both C_{max} and AUC_{0-8} for the test product met the bioequivalence criteria. The results from this study suggest that the 500 mg ganciclovir capsules should not be stored at conditions greater than that of ambient temperature and relative humidity (this conclusion was also made by the chemistry reviewer).

Labeling: The proposed labeling revisions are acceptable.

Note: An Intra-division CPB briefing was held on October 31, 1997.

Attendees: Dr. John Lazor, Dr. Janice Jenkins, Dr. Dennis Bashaw, Dr. Frank Pelsor, Dr. Funmi Ajayi, Ms. Terrie Cresenzi

Based on the discussions at the briefing, the following comments were addressed to the applicant.

COMMENTS TO APPLICANT:

1. Based on the dissolution data (release data) for the 500 mg capsule lots used in the two bioavailability studies (GANS 2638 and GANS 2686) and the data for the stability lots (12514-1, 12516-1. 1195001, 1195051, 1195091), we feel that a dissolution specification of Q= in 45 minutes would be appropriate for the 500 mg ganciclovir capsules. (This specification is also the current interim dissolution specification for the 250 mg ganciclovir capsules).

2. The dissolution data for the 3 registration batches (1500571, 1500581, 1500591) stored at ambient conditions with and without desiccant suggest that the presence of desiccant in the container prevents slowing of the dissolution profile (which is observed under conditions where no desiccant is present). We feel that the dissolution data for batches stored with desiccant meet the requirements of Q= in 45 minutes (even after storage for 12 months).

3. Treatments C and D (from Study GANS 2686) have similar polymorphic composition (predominantly Phase III crystals). Therefore, the presence of Phase III crystals does not

explain the slowing of dissolution for treatment D. We feel that the slowing of dissolution may be associated with the hard gelatin shell of the capsules, and we would like you to study the dissolution profiles for the four study treatments from Study GANS 2686, in particular treatment D with and without enzymes (two-tier dissolution testing). Since your initial test medium is water, we would like for you to perform the two-tier dissolution test in water. Also, we would like you to perform the two-tier dissolution test using another medium such as 0.1N HCl/pepsin or pH 6.8 buffer/pancreatin.

Note: A teleconference was held with applicant on November 20, 1997 to discuss the above issues (as well as other issues related to CMC). There was agreement between the applicant and the agency regarding setting the dissolution specification for the 500 mg ganciclovir capsules at Q= dissolved in 45 minutes. Following the teleconference, the applicant submitted dissolution data for capsules from treatments C and D (from Study GANS 2686) using two-tier dissolution testing with 0.1N HCl/pepsin as the medium. These data (attached as Appendix 4) were generated to investigate how much of the dissolution is due to capsule fill versus capsule shell effects. These data suggest that for treatment C, the dissolution is faster in 0.1N HCl/pepsin compared to water or 0.1N HCL alone suggesting that in this case the dissolution slowing was primarily due to the capsule shell effects. For treatment C, the proposed dissolution specification of Q= in 45 minutes is met when dissolution is performed in simulated gastric fluid medium. However, for treatment D, the dissolution rate in simulated gastric fluid is moderately faster than in 0.1N HCL, but about the same as it is in water. For treatment D, the proposed dissolution specification of Q= in 45 minutes is not met even when dissolution is performed in simulated gastric fluid medium. This suggests that the dissolution slowing in this case may be attributable to capsule fill effects.

Recommendation: The applicant has adequately addressed the requirements of the Division of Pharmaceutical Evaluation III for approval of the 500 mg ganciclovir capsules as an additional dosage form.

APPEARS THIS WAY
ON ORIGINAL

Vanitha Jayanthan Sekar 12/5/97

Vanitha J. Sekar, Ph.D.
Reviewer, Antiviral Drugs Section, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Janice Barnett Jenkins 12/10/97
Janice B. Jenkins, Ph.D.
Team Leader, Antiviral Drugs Section, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

cc:

	HFD-530	NDA 20460 (SE2-008) /MO/J.Martin /CSO/T.Crescenzi /Biopharm/V.Sekar /TL Biopharm/J.Jenkins
	HFD-340	/Viswanathan
✓	HFD-880	/DPEIII
✓	CDR	(Attn: Barbara Murphy)

NDA20-460/SE2-008

Date submitted: 2 Jun 97
Date received: 5 Jun 97
Date assigned: 6 Jun 97
MOR completed: 18 Nov 97

Medical Officer Review of Supplemental NDA

Applicant: Syntex (USA) Inc
3401 Hillview Ave
Palo Alto, CA 94304-1397

Drug:
Chemical: 9-(1,3-dihydroxy-2-propoxymethyl) guanine
Generic: ganciclovir
Trade: Cytovene®

Route: Oral

Dosage form: 500 mg capsule

Purpose: To support approval of a new dosage strength

Supplement Contents: The supplement contains: (a) proposed labelling changes; (b) chemistry section; and (c) PK section. The PK section includes 2 PK studies: (i) GANS 2636- A phase I study to evaluate the bioequivalence of two formulations of oral ganciclovir (500 mg capsule and 250 mg capsule) in HIV positive subjects, and (ii) GANS 2686 - A phase I bioequivalence study of oral ganciclovir capsules in HIV- and CMV-seropositive subjects.

Related INDs, NDAs:

Resume The supplement contains 2 PK studies intended to support approval of a new dosage strength of ganciclovir.

Other Reviews

Chemistry: Please see Dr. Ko-Yu Lo's review

Pharmacokinetics: Please see Dr. Vanitha Sekar's review.

Proposed Labelling Changes

Clinical Studies:

A. GANS2636: A phase I study to evaluate the bioequivalence of two formulations of oral ganciclovir (500 mg capsule and 250 mg capsule) in HIV positive subjects.

A. Objective: To determine the bioequivalence under steady-state conditions of the 500 mg capsule formulation compared with the 250 mg capsule formulation at a dose of 1000 mg Q8H following a meal or snack, as assessed by the AUC_{0-8} and observed C_{max} in HIV + subjects.

B. Study Design: Single center, open label, randomized two-way crossover study of 15-21 days duration. Subjects were randomized to either the 250 mg or 500 mg capsule regimen, followed the next week by the other regimen. On Days 1-4 and 8-11, subjects received GCV, 1000 mg Q8H. A washout period (Days 5-7) separated the two regimens.

C. Study Population: A total of 14 subjects, all males were enrolled, mean age 36 yrs (range: 25-51 yrs). These subjects were sercpositive for HIV and CMV, but asymptomatic for AIDS.

D. Conduct of the Study

Enrollment: All 14 enrolled subjects completed the trial.

Withdrawals: none

E. Safety results: *Deaths.* None. *Serious Adverse Events.* None.

Adverse Events: Similar numbers of adverse events were observed in each of the treatment groups. A single hemic/lymphatic event, lymphadenopathy, was observed in each treatment group. Fluctuations in ANC in individual patients were minor and not evidently related to treatment group.

Comment: This study raises no formulation-related or other safety concerns.

F. Pharmacokinetics results: The study report concludes that "the 250 gm and 500 mg capsule formulations of oral ganciclovir were bioequivalent for AUC_{0-8} and C_{max}." Please see Dr. Sekar's review.

B. GANS 2686: A phase I bioequivalence study of oral ganciclovir capsules in HIV- and CMV-seropositive subjects.

A. Objective: to determine bioeqivalence of oral ganciclovir capsules having different dissolution characteristics and crystal form compositions under steady state conditions at a dose of 1000 mg Q8H.

B. Study Design: open-label, randomized, four-way crossover design. Four regimens in random order, all administered 1000 mg Q8H for 10 doses (Days 1-4, 8-11, 15-18, 22-25) are compared:

Regimen A (ref.), oral GCV, 250 mg caps, storage: 25°C, ambient RH x 18 mo (Lot955731)
Regimen B, oral GCV, 500 mg caps, storage: 25°C/60%RH x 9 mo (Lot 1450021)
Regimen C, oral GCV, 500 mg caps, storage: 30°C/60%Rh x 8.5 mo (Lot 1446461)
Regimen D, oral GCV, 500 mg caps, storage: 40°C/70%RH x 8.5 mo (Lot 1446481)

C. Study Population: Twenty-four subjects (23 M, 1 F), aged 22-51 yrs, were randomized.

D. Conduct of the Study

Enrollment: Of 24 subjects enrolled, 21 completed the study.

Protocol violations: Entry criteria were met by all subjects.

Withdrawals: Three subjects terminated the study early, 2 for adverse events (facial swelling-see Premature Terminations, below) and 1 for personal reasons.

E. Safety results

Deaths. There were no deaths.

Serious Adverse Events. There were no serious adverse events.

Premature terminations. Two subjects are described as having had severe facial swelling, each after receiving 2 of the 4 regimens. Because of concern that facial swelling might relate to study drug, the Principle Investigator prematurely terminated both subjects from the study.

In both instances, facial swelling was identified during evaluation prior to dosing at the third dosing period. One subject had received Regimens B and C, and the other, Regimens A and B during the first two dosing periods.

> **Comment:** In controlled trials, facial swelling is not an event that has been found to relate to GCV therapy. In this study, the GCV treatment in Period 2 in both cases involved the 500 mg capsule dosing form; the capsules were, however, from a different drug lot in each case. Facial swelling was not reported in these subjects while on GCV therapy, but after 3 days following the last GCV dose in the previous dosing period. Thus, facial swelling, if related to GCV therapy in this case, would presumably relate specifically to the 500 mg dosing form, and is a relatively delayed event.
>
> The Applicant was asked to provide additional information and to comment on facial swelling in these two subjects. The Applicant notes that Subject 833 had had a history of facial rashes and dry skin, and that facial swelling was accompanied by rash in this instance. A causative relationship to study drug was not established or ruled out, and a rechallenge was not attempted. Subject 844 had unilateral facial swelling, with a raised area on the buccal mucosa; four days later following the application of warm compresses, "oral drainage (pus)" was reported for this subject.
>
> It seems unlikely that facial swelling in these subjects is related to GCV treatment.

F. Pharmacokinetics results. Please see Dr. Sekar's review.

Labelling Comments: Please see Chemistry and Biopharmaceutics reviews for comments. No modifications to the propose labelling need to be made based on the clinical review of the Application.

Conclusions: In Study GANS 2686, two subjects who had received the 500 mg dosage form of GCV were discontinued from the study because of severe facial swelling. No such adverse event was described in Study GANS 2636. It is considered unlikely that facial swelling is related to treatment with the 500 mg dosage form of GCV. No other safety concerns were identified.

Recommendation: It is recommended that this Supplemental Application be approved.

John R. Martin, M.D.
Medical Officer

concurrences:
HFD-530/ActDivDir/DBirnkrant DB 12-12-97
HFD-530/TL/RBehrman ESO 12-10-97

cc: NDA
HFD-530
HFD-530/ActDivDir/DBirnkrant
HFD-530/TL/RBehrman
HFD-530/CSO/TCrescenzi
HFD-530/Chem/KYLo
HFD-530/Biopharm/VSekar
HFD-530/MO/JMartin

REQUEST FOR CATEGORICAL EXCLUSION FROM AN ENVIRONMENTAL ASSESSMENT FOR GANCICLOVIR CAPSULES, 500 MG (SUPPLEMENT TO NDA 20-460)

Pursuant to Title 21 CFR 25.24(c)(2), Syntex (U.S.A.) Inc., 3401 Hillview Ave., Palo Alto, California, 94304 requests a categorical exclusion from the requirement for the preparation of an environmental assessment for Ganciclovir Capsules, 500 mg. Under 21 CFR § 25.24(c)(2), a supplement to an NDA may be categorically excluded from the preparation of an Environmental Assessment "if the drug product will not be administered at higher dosage levels, for longer duration, of for different indications than were previously in effect and if data available to the agency do not establish that, at the expected levels of exposure, the substance may be toxic to organisms in the environment."

A 250 mg capsule formulation for oral administration of ganciclovir is currently approved (NDA 20-460) in the United States under the name Cytovene® (ganciclovir capsules). It was originally indicated for prevention of CMV disease in individuals with advanced HIV infection at risk of developing CMV disease, and also as an alternative to the IV formulation for maintenance treatment of CMV retinitis in immunocompromised individuals, including individuals with AIDS. A supplement to NDA 20-460 for the additional indication of the prevention of CMV disease in solid organ transplant recipients was approved by the FDA in November 1996 (Supplement #SE1-006).

This Request for Categorical Exclusion from an Environmental Assessment Report is submitted in support of a supplement to NDA 20-460 for Ganciclovir Capsules, 500 mg. In this supplement, the only changes are increasing the ganciclovir capsule dosage strength from 250 mg to 500 mg, and the size and color of the gelatin capsule. The proposed capsule is a #0 two–piece hard gelatin capsule consisting of an opaque green body and yellow cap. It contains FD&C Blue #2, Yellow Iron Oxide, Titanium Oxide, and Gelatin (the same ingredients as are found in the 250 mg capsule). Although the dosage strength of the proposed 500 mg capsules is greater than the approved 250 mg capsules, the daily dosage of ganciclovir will not increase as fewer capsules will be administered; nor will the drug be administered for longer durations or for different indications than already approved. Thus, the proposed action is not expected to result in an increase of production of ganciclovir and is therefore not expected to increase the amount of ganciclovir and its metabolites entering the environment through product use.