N 20312

UNIVASC


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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR ! 9 1995

NDA 20-312

Schwarz Pharma
Kremers Urban Company
Attention: Mr. Steven Pollock
P.O. Box 2038
Milwaukee, WI 53201

Dear Mr. Pollock:

Please refer to your December 18, 1992 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Univasc (moexipril hydrochloride) 7.5 and 15 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated May 25, July 11, August 9 and 18, September 13, November 11, December 1, 8, 26, 27, 28 (two) and 30, 1994; January 5 and 17, March 2, 3, and 16, 1995.

This new drug application provides for the use of Univasc (moexipril hydrochloride) in the treatment of hypertension.

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 enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed 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 fifteen 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 20-312. Approval of this labeling by FDA 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.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

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:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

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

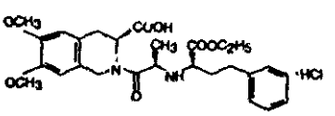
UNIVASC™ (moexipril hydrochloride)
Tablets

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, UNIVASC should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

UNIVASC (moexipril hydrochloride), the hydrochloride salt of moexipril, has the empirical formula $C_{27}H_{34}N_2O_7 \cdot HCl$ and a molecular weight of 535.04. It is chemically described as [3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride. It is a non-sulfhydryl containing precursor of the active angiotensin-converting enzyme (ACE) inhibitor moexiprilat and its structural formula is:



Moexipril hydrochloride is a fine white to off-white powder. It is soluble (about 10% weight-to-volume) in distilled water at room temperature.

UNIVASC is supplied as scored, coated tablets containing 7.5 mg and 15 mg of moexipril hydrochloride for oral administration. In addition to the active ingredient, moexipril hydrochloride, the tablet core contains the following inactive ingredients: lactose, magnesium oxide, crospovidone, magnesium stearate and gelatin. The film coating contains hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol 8000, magnesium stearate, titanium dioxide, and ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Moexipril hydrochloride is a prodrug for moexiprilat, which inhibits angiotensin-converting enzyme in humans and animals. The mechanism through which moexiprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes the conversion of the inactive decapeptide angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor that also stimulates aldosterone secretion by the adrenal cortex and provides negative feedback on renin secretion. ACE is identical to kininase II, an enzyme that degrades bradykinin, an endothelium-dependent vasodilator. Moexiprilat is about 1000 times as potent as moexipril in inhibiting ACE and kininase II. Inhibition of ACE results in decreased angiotensin II formation, leading to decreased vasoconstriction, increased plasma renin activity, and decreased aldosterone secretion. The latter results in diuresis and natriuresis and a small increase in serum β-fraction concentration (mean increase of about 0.25 mEq/L were noted when moexipril was used alone, see PRECAUTIONS).

Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of moexipril remains to be elucidated. Although the principal mechanism of moexipril in blood pressure reduction is believed to be through the renin-angiotensin-aldosterone system, ACE inhibitors have some effect on blood pressure even in apparent low-renin hypertension. As is the case with other ACE inhibitors, however, the antihypertensive effect of moexipril is considerably smaller in black patients, a predominantly low renin population, than in non-black hypertensive patients.

Pharmacokinetics and Metabolism

Pharmacokinetics: Moexipril's antihypertensive activity is almost entirely due to its deesterified metabolite, moexiprilat. Bioavailability of oral moexipril is about 13% compared to intravenous (I.V.) moexiprilat (both measuring the metabolite moexiprilat), and is markedly affected by food, which reduces the peak plasma level (C_{max}) and AUC (see Absorption). Moexipril should therefore be taken in a fasting state. The time of peak plasma concentration (T_{max}) of moexiprilat is about 1½ hours and elimination half-life ($t_{1/2}$) is estimated at 2 to 9 hours in various studies, the variability reflecting a complex elimination pattern that is not simply exponential. Like all ACE inhibitors, moexiprilat has a prolonged terminal elimination phase, presumably reflecting slow release of drug bound to the ACE. Accumulation of moexiprilat with repeated dosing is minimal, about 30%, compatible with a functional elimination half-life of about 12 hours. Over the dose range of 7.5 to 30 mg, pharmacokinetics are approximately dose proportional.

Absorption: Moexipril is incompletely absorbed, with bioavailability as moexiprilat of about 13%. Bioavailability varies with formulation and food intake which reduces peak plasma level (C_{max}) and AUC by about 79% and 46% respectively after the ingestion of a low-fat breakfast or by 86% and 68% respectively after the ingestion of a high-fat breakfast.

Distribution: The clearance (CL) for moexipril is 441 mL/min and for moexiprilat 232 mL/min with a $t_{1/2}$ of 1.3 and 9.8 hours, respectively. Moexiprilat is about 50% protein bound. The volume of distribution of moexiprilat is about 183 liters.

Metabolism and Excretion: Moexipril is relatively rapidly converted to its active metabolite moexiprilat, but remains longer than some other ACE inhibitor prodrugs, such that its half-life is over one hour and it has a significant AUC. Both moexipril and moexiprilat are converted to diketopiperazine derivatives and unidentified metabolites. After I.V. administration of moexipril, about 40% of the dose appears in urine as moexiprilat, about 25% as moexipril, with small amounts of the metabolites; about 20% of the I.V. dose appears in feces, principally as moexiprilat. After oral administration, only about 7% of the dose appears in urine as moexiprilat, about 1% as moexipril, with about 5% as other metabolites. Fifty-two percent of the dose is recovered in feces as moexiprilat and 1% as moexipril.

Special Populations:
Decreased Renal Function: The effective elimination half-lives and AUC of both moexipril and moexiprilat are increased with decreasing renal function. There is insufficient information available to characterize this relationship fully, but at creatinine clearances in the range of 10 to 40 ml/min, the half-life of moexiprilat is increased by a factor of 3 to 4.

Decreased Hepatic Function: In patients with mild to moderate cirrhosis given single 15 mg doses of moexipril, the C_{max} of moexiprilat was increased by about 50% and the AUC increased by about 120%, while the C_{max} for moexiprilat was decreased by about 80% and the AUC increased by almost 300%.

Elderly Patients: In elderly male subjects (65-80 years old) with otherwise normal renal and hepatic function, the AUC and C_{max} of moexiprilat is about 39% greater than those of younger subjects (18-42 years old).

Pharmacokinetic Interactions With Other Drugs:
No clinically important pharmacokinetic interactions occurred when UNIVASC was administered concomitantly with hydrochlorothiazide, digoxin, or cimetidine.

Pharmacodynamics and Clinical Effect

[redacted] Single and multiple doses of 15 mg or more of Univasc give a sustained inhibition of plasma ACE activity of 80-90%, beginning within 2 hours and lasting 24 hours (80%)

In controlled trials, the peak effects of orally administered moexipril increased with the dose administered over a dose range of 7.5 to 60 mg, given once a day. Antihypertensive effects were first detectable about 1 hour after dosing, with a peak effect between 3 and 6 hours after dosing. Just before dosing (i.e., at trough), the antihypertensive effects were less prominently related to dose and the antihypertensive effect tended to diminish during the 24-hour dosing interval when the drug was administered once a day.

In multiple dose studies in the dose range of 7.5 to 30 mg once daily, UNIVASC lowered sitting diastolic and systolic blood pressure effects at trough by 3 to 6 mmHg and 4 to 11 mmHg, more than placebo, respectively. There was a tendency toward increased response with higher doses over this range. These effects are typical of ACE inhibitors but, to date, there are no trials of adequate size comparing moexipril with other antihypertensive agents.

The trough diastolic blood pressure effects of moexipril were approximately 4 to 6 mmHg in various studies. Generally, higher doses of moexipril have a greater fraction of the peak blood pressure effect still present at trough. During dose titration, any decision as to the adequacy of a dosing regimen should be based on trough blood pressure measurements. If diastolic blood pressure control is not adequate at the end of the dosing interval, the dose can be increased or given as a divided (BID) regimen.

During chronic therapy, the antihypertensive effect of any dose of UNIVASC is generally evident within 2 weeks of treatment, with maximal reductions after 4 weeks. The antihypertensive effects of UNIVASC have been proven to continue during therapy for up to 24 months.

UNIVASC, like other ACE inhibitors, is less effective in decreasing trough blood pressures in blacks than in non-blacks. Placebo-corrected trough group mean diastolic blood pressure effects in blacks in the proposed dose range varied between +1 to -3 mmHg compared with responses in non-blacks of -4 to -6 mmHg.

The effectiveness of UNIVASC was not significantly influenced by patient age, gender, or weight. UNIVASC has been shown to have antihypertensive activity in both pre and postmenopausal women who have participated in placebo-controlled clinical trials.

Formal interaction studies with moexipril have not been carried out with antihypertensive agents other than thiazide diuretics. In these studies, the added effect of moexipril was similar to its effect as monotherapy. In general, ACE inhibitors have less than additive effects with beta-adrenergic blockers, presumably because both work by inhibiting the renin-angiotensin system.

INDICATIONS AND USAGE
UNIVASC is indicated for treatment of patients with hypertension. It may be used alone or in combination with thiazide diuretics.

In using UNIVASC, consideration should be given to the fact that another ACE inhibitor (captopril) has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that UNIVASC does not have a similar risk (see WARNINGS).

In considering use of UNIVASC, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in blacks than in non-black patients (see WARNINGS, Angioedema).

CONTRAINDICATIONS
UNIVASC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS
Anaphylactoid and Possibly Related Reactions:
Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including UNIVASC) may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema involving the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including UNIVASC. Symptoms suggestive of angioedema or facial edema occurred in <0.5% of moexipril-treated patients in placebo-controlled trials. None of the cases were considered life-threatening and all resolved either without treatment or with medication (antihistamines or glucocorticoids). One patient treated with hydrochlorothiazide alone experienced laryngeal edema. No instances of angioedema were reported in placebo-treated patients.

In cases of angioedema, treatment should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with involvement of the tongue, glottis, or larynx, may be fatal due to airway obstruction. Appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) and/or measures to ensure a patent airway, should be promptly provided (see ADVERSE REACTIONS).

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

Hypotension

UNIVASC can cause symptomatic hypotension, although, as with other ACE inhibitors, this is unusual in uncomplicated hypertensive patients treated with UNIVASC alone. Symptomatic hypotension was seen in 0.3% of patients given moexipril and led to discontinuation of therapy in about 0.25%. Symptomatic hypotension is most likely to occur in patients who have been salt- and volume-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and salt-depletion should be corrected and, in general, diuretics stopped, before initiating therapy with UNIVASC (see PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS).

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or progressive azotemia, and rarely, with acute renal failure and death. In these patients, UNIVASC therapy should be started under close medical supervision, and patients should be followed closely for the first two weeks of treatment and whenever the dose of moexipril or an accompanying diuretic is increased. Care in avoiding hypotension should also be taken in patients with ischemic heart disease, aortic stenosis, or cerebrovascular disease, in whom an excessive decrease in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with an intravenous infusion of normal saline. UNIVASC treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow suppression, rarely in patients with uncomplicated hypertension, but more frequently in hypertensive patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Although there were no instances of severe neutropenia (absolute neutrophil count <500/mm³) among patients given UNIVASC, as with other ACE inhibitors, monitoring of white blood cell counts should be considered for patients who have collagen-vascular disease, especially if the disease is associated with impaired renal function. Available data from clinical trials of UNIVASC are insufficient to show that UNIVASC does not cause agranulocytosis at rates similar to captopril.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these were caused by the ACE inhibitor exposure.

Fetal and neonatal morbidity do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester. Mothers who have used ACE inhibitors only during the first trimester should be informed of this. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of moexipril as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, moexipril should be discontinued unless it is considered life-saving to the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be detected until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Theoretically, the ACE inhibitor could be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

No embryotoxic, fetotoxic, or teratogenic effects were seen in rats or in rabbits treated with up to 90.9 and 0.7 times, respectively, the maximum recommended human dose (MRHD) on a mg/m² basis.

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Hepatic Failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. There is no clinical experience of UNIVASC in the treatment of hypertension in patients with renal failure.

In hypertensive patients with no apparent preexisting renal vascular disease, have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when UNIVASC has been given concomitantly with a thiazide diuretic. This is more likely to occur in patients with preexisting renal impairment. There may be a need for dose adjustment of UNIVASC and/or the discontinuation of the thiazide diuretic.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hypertensive Patients With Congestive Heart Failure: In hypertensive patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including UNIVASC, may be associated with oliguria and/or progressive azotemia and, rarely, acute renal failure and/or death.

Hypertensive Patients With Renal Artery Stenosis: In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Hyperkalemia: In clinical trials, persistent hyperkalemia (serum potassium above 5.4 mEq/L) occurred in approximately 1.3% of hypertensive patients receiving UNIVASC. Risk factors for the development of hyperkalemia with ACE inhibitors include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with UNIVASC (see PRECAUTIONS, Drug Interactions).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, moexipril may block the effects of compensatory renin release. If hypotension occurs in this setting and is considered to be due to this mechanism, it can be corrected by volume expansion.

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials with moexipril, cough was present in 4.1% of moexipril patients and 2.2% of patients given placebo.

Information for Patient

Food: Patients should be advised to take moexipril one hour before meals (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Angioedema: Angioedema, including laryngeal edema, may occur with treatment with ACE inhibitors, usually occurring early in therapy (within the first month). Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of the face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more UNIVASC until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur with UNIVASC, especially during the first few days of therapy. If fainting occurs, the patient should stop taking UNIVASC and consult the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult their physician if they develop these conditions.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) that could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors and should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Diuretics: Excessive reductions in blood pressure may occur in patients on diuretic therapy when ACE inhibitors are started. The possibility of hypotensive effects with UNIVASC can be minimized by discontinuing diuretic therapy for several days or cautiously increasing salt intake before initiation of treatment with UNIVASC. If this is not possible, the starting dose of moexipril should be reduced. (See WARNINGS and DOSAGE AND ADMINISTRATION).

Potassium Supplements and Potassium-Sparing Diuretics: UNIVASC can increase serum potassium because it decreases aldosterone secretion. Use of potassium-sparing diuretics (spironolactone, triamterene, amiloride) or potassium supplements concomitantly with ACE inhibitors can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored.

Oral Anticoagulant: Interaction studies with warfarin failed to identify any clinically important effect on the serum concentrations of the anticoagulant or on its anticoagulant effect.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other Agents: No clinically important pharmacokinetic interactions occurred when UNIVASC was administered concomitantly with hydrochlorothiazide, digoxin, or cimetidine.

UNIVASC has been used in clinical trials concomitantly with calcium-channel-blocking agents, diuretics, H_2 blockers, digoxin, oral hypoglycemic agents, and cholesterol-lowering agents. There was no evidence of clinically important adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

[redacted] No evidence of carcinogenicity was detected in long-term studies in mice and rats at doses up to 14 or 27.3 times the maximum recommended human dose (MRHD) on a mg/m² basis.

No mutagenicity was detected in the Ames test and microbial reverse mutation assay, with and without metabolic activation, or in an *in vivo* nucleus anomaly test. However, increased chromosomal aberration frequency in Chinese Hamster Ovary cells was detected under metabolic activation conditions at a 20-hour harvest time.

[redacted] Reproduction studies have been performed in rabbits at oral doses up to 0.7 times the MRHD on a mg/m² basis, and in rats up to 90.9 times the MRHD on a mg/m² basis. No indication of impaired fertility, reproductive toxicity, or teratogenicity was observed.

Pregnancy

Pregnancy Categories C (for 1st trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether UNIVASC is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when UNIVASC is given to a nursing mother.

Geriatric Use

Of the patients who received UNIVASC in controlled clinical studies, 33% were 65 years of age or older. No overall differences in effectiveness or safety were observed between these patients and younger patients. In elderly patients receiving UNIVASC, plasma levels of drug are slightly higher and renal clearance is reduced when compared to younger patients, but this did not have detectable consequences.

Pediatric Use

Safety and effectiveness of UNIVASC in pediatric patients have not been established.

ADVERSE REACTIONS

UNIVASC has been evaluated for safety in more than 2500 patients with hypertension; more than 250 of these patients were treated for approximately one year. The overall incidence of reported adverse events was only slightly greater in patients treated with UNIVASC than patients treated with placebo.

Reported adverse experiences were usually mild and transient, and there were no differences in adverse reaction rates related to gender, race, age, duration of therapy, or total daily dosage within the range of 3.75 mg to 60 mg. Discontinuation of therapy because of adverse experiences was required in 3.4% of patients treated with UNIVASC and in 1.8% of patients treated with placebo. The most common reasons for discontinuation in patients treated with UNIVASC were cough (0.7%) and dizziness (0.4%).

All adverse experiences considered at least possibly related to treatment that occurred at any dose in placebo-controlled trials of once-daily dosing in more than 1% of patients treated with UNIVASC alone and that were at least as frequent in the UNIVASC group as in the placebo group are shown in the following table:

ADVERSE EVENTS IN PLACEBO-CONTROLLED STUDIES

ADVERSE EVENT	UNIVASC (N=674)	PLACEBO (N=226)
	N (%)	N (%)
Cough Increased	41 (6.1)	5 (2.2)
Dizziness	29 (4.3)	5 (2.2)
MI Pain	21 (3.1)	5 (2.2)
Flu Syndrome	21 (3.1)	0 (0)
HCope	16 (2.4)	4 (1.8)
Pharyngitis	12 (1.8)	2 (0.9)
Vomiting	11 (1.6)	0 (0)
Rash	11 (1.6)	2 (0.9)
Myalgia	9 (1.3)	0 (0)

Other adverse events occurring in more than 1% of patients on UNIVASC that were at least as frequent on placebo include: headache, upper respiratory infection, pain, rhinitis, dyspepsia, nausea, peripheral edema, diarrhea, chest pain, and urinary frequency. See WARNINGS and PRECAUTIONS for discussion of anaphylactoid reactions, angioedema, hypotension, neutropenia/agranulocytosis, second and third trimester fetal/neonatal mortality and morbidity, hyperkalemia, and cough.

Other potentially important adverse experiences reported in controlled or uncontrolled clinical trials in less than 1% of moexipril patients or that have been attributed to other ACE inhibitors include the following:

Cardiovascular: Symptomatic hypotension, postural hypotension, or syncope were seen in 9/1759 (0.51%) patients; these reactions led to discontinuation of therapy in controlled trials in 3/1254 (0.24%) patients who had received UNIVASC monotherapy and in 1/344 (0.3%) patients who had received UNIVASC with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other adverse events included angina/myocardial infarction, palpitations, rhythm disturbances, and cerebrovascular accident.

Renal: Of hypertensive patients with no apparent preexisting renal disease, 1% of patients receiving UNIVASC alone and 2% of patients receiving UNIVASC with hydrochlorothiazide experienced increases in serum creatinine to at least 140% of their baseline values (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Gastrointestinal: Abdominal pain, constipation, vomiting, appetite/weight change, dry mouth, pancreatitis, hepatitis.

Respiratory: Bronchospasm, dyspnea.

Urogenital: Renal insufficiency, oliguria.

Dermatologic: Apparent hypersensitivity reactions manifested by rashes, itch, pruritus, photosensitivity.

Musculoskeletal and Psychiatric: Drowsiness, sleep disturbances, nervousness, mood changes, anxiety.

Other: Angioedema (see WARNINGS), taste disturbances, tinnitus, sweating, malaise, arthralgia, hemolytic anemia.

Clinical Laboratory Test Findings

Proteinuria and Blood Urea Nitrogen: As with other ACE inhibitors, minor increases in blood urea nitrogen or serum creatinine, reversible upon discontinuation of therapy, were observed in approximately 1% of patients with essential hypertension who were treated with UNIVASC monotherapy and more likely to occur in patients receiving concomitant diuretics and in patients with compromised renal function (see PRECAUTIONS, General).

Other (cause and/or relationship unknown): Clinically important changes in standard laboratory tests were rarely associated with UNIVASC administration.

Elevations of liver enzymes and uric acid have been reported. In trials, less than 1% of moexipril-treated patients discontinued UNIVASC treatment because of laboratory abnormalities. The incidence of abnormal laboratory values with moexipril was similar to that in the placebo-treated group.

OVERDOSAGE

Human overdosage of moexipril have not been reported. In case reports of overdosage with other ACE inhibitors, hypotension has been the principal adverse effect noted. Single oral doses of 2 g/kg moexipril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 2 g/kg.

No data are available to suggest that physiological maneuvers (e.g., maintenance to change the pH of the urine) would accelerate elimination of moexipril and its metabolites. The dialyzability of moexipril is not known.

Angiotensin II would presumably serve as a specific antagonist-antidote in the setting of moexipril overdose, but angiotensin II is essentially unavailable outside of research facilities. Because the hypotensive effect of moexipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat moexipril overdose by infusion of normal saline solution. In addition, renal function and serum potassium should be monitored.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended initial dose of UNIVASC in patients not receiving diuretics is 7.5 mg, one hour prior to meals, once daily. Dosage should be adjusted according to blood pressure response. The antihypertensive effect of UNIVASC may diminish towards the end of the dosing interval. Blood pressure should, therefore, be measured just prior to dosing to determine whether satisfactory blood pressure control is obtained. If control is not adequate, increased dose or divided dosing can be tried. The recommended dose range is 7.5 to 30 mg daily, administered in one or two divided doses one hour before meals. Total daily doses above 60 mg a day have not been studied in hypertensive patients.

In patients who are currently being treated with a diuretic, symptomatic hypotension may occasionally occur following the initial dose of UNIVASC. The diuretic should, if possible, be discontinued for 2 to 3 days before therapy with UNIVASC is begun, to reduce the likelihood of hypotension (see WARNINGS). If the patient's blood pressure is not controlled with UNIVASC alone, diuretic therapy may then be instituted. If diuretic therapy cannot be discontinued, an initial dose of 3.75 mg of UNIVASC should be used with medical supervision until blood pressure has stabilized (see WARNINGS and PRECAUTIONS, Drug Interactions).

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance ≤40 mL/min/1.73 m², an initial dose of 3.75 mg once daily should be given cautiously. Dosage may be titrated upward to a maximum daily dose of 15 mg.

HOW SUPPLIED

UNIVASC (moexipril hydrochloride) 7.5 mg tablets are pink colored, biconvex, film-coated and scored with engraved code 707 on the uncored side and SP above and 7.5 below the score. They are supplied as follows:

Bottles of 90 (Unit-of-Use)	NDC 0091-3707-09
Bottles of 100	NDC 0091-3707-01

UNIVASC (moexipril hydrochloride) 15 mg tablets are salmon colored, biconvex, film-coated, and scored with engraved code 715 on the uncored side and SP above and 15 below the score. They are supplied as follows:

Bottles of 90 (Unit-of-Use)	NDC 0091-3715-09
Bottles of 100	NDC 0091-3715-01

[redacted] Store, tightly closed, at controlled room temperature. Protect from excessive moisture.

[redacted] Dispense in a tight container, if product package is subdivided.

[redacted] **Caution:** Federal law prohibits dispensing without prescription.

Mfd by:
SCHWARZ PHARMA AG
Monheim, Germany
For:
SCHWARZ PHARMA
Kremers Urban Company
Milwaukee, WI 53201

PC15[illegible]9 10/94

AE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-312

MAY 26 1994

G.H. Besselaar Associates
Agent for Schwarz Pharma A.G.
Attention: Gregory M. Hockel, Ph.D.
Princeton Forrestal Center
103 College Road East
Princeton, NJ 08540-6681

Dear Dr. Hockel:

Please refer to your December 18, 1992 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Fempres (moexipril hydrochloride) 7.5 and 15 mg Tablets.

We also acknowledge receipt of your amendments and correspondence dated January 25, February 24, March 8 and 19, April 26 and 30, May 3 and 17, June 4 (two), 22 (two), 23, 28 and 29, July 7, 12 (two), 20 and 29, August 5, September 7 and 22, October 4, 6, 8 and 18, and November 11, 16 (two), and 19, December 1, 7 (two), and 28, 1993 and January 10, February 2, March 7, April 15, and May 9, 1994.

We have received your amendment dated April 22, 1994. We note that the updated primary stability data and statistical analysis supporting the expiration dating period contained in this amendment are currently under review.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling for the drug. The labeling should be identical in content to the enclosed marked-up draft and should include the trade name, Fempres, for moexipril hydrochloride tablets. The container labels must indicate that the drug product is manufactured in Germany, either by stating "Made in Germany" or "Manufactured by Schwarz Pharma, Monheim, Germany." If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and two copies, along with two copies of the package insert, directly to:

Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane, Room 17B17
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.

We remind you that satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) and evaluation of your Environmental Assessment are required before the application may be approved.

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:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

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

Enclosure

cc: Schwarz Pharma
Attention: Dr. E. Fritschi
Alfred Nobel Strasse 10
4019 Manheim, Germany

cc:
Original NDA
HFC-130/JAllen
~~HFD-110~~
HFD-110/CSO
HFD-240 (with draft labeling)
HFD-85
HFD-100/Dr. Temple
HF-2 (with labeling)
HFD-735/Baresh (with labeling)
HFD-110/KBongiovanni;12/17/93;1/25/94
sb/11/22/93;2/1/94
R/D: RWolters/12/17/93;1/26/94
ADeFelice/12/17/93
AKarkowsky/12/17/93
NMorgenstern/1/31/94

APPROVABLE

MOEXIPRIL

PROPOSED LABELING

TRADENAME
moexipril hydrochloride
Tablets

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE Inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, TRADENAME should be discontinued as soon as possible. See WARNINGS: Fetal/neonatal morbidity and mortality.

DESCRIPTION

TRADENAME, moexipril hydrochloride, the hydrochloride salt of moexipril, has the empirical formula $C_{27}H_{35}N_2O_7Cl$ and a molecular weight of 535.04. It is chemically described as 2-[2-[[(1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxypropyl]-6, 7- dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, hydrochloride (S,S,S). It is a non-sulfhydryl containing pre-cursor of the active angiotensin converting enzyme (ACE) inhibitor moexiprilat and its structural formula is:

Moexipril hydrochloride is a fine white to off-white powder. It is soluble (about 10% weight-to-volume) in distilled water at room temperature.

TRADENAME is supplied as coated tablets containing 7.5 mg and 15 mg of moexipril hydrochloride for oral administration. In addition to the active ingredient, moexipril hydrochloride, the tablet core contains the

following inactive ingredients: lactose, magnesium oxide, crospovidone, magnesium stearate, and gelatin.*

CLINICAL PHARMACOLOGY

Mechanism of Action

Moexipril is a prodrug for moexiprilat, which inhibits angiotensin-converting enzyme in humans and animals. The mechanism through which moexiprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes the conversion of the inactive decapeptide angiotensin I to the vasoconstrictor substance angiotensin II. Augiotensin II is a potent peripheral vasoconstrictor that also stimulates aldosterone secretion by the adrenal cortex and provides negative feedback on renin secretion. ACE is identical to kininase II, an enzyme that degrades bradykinin, an endothelium-dependent vasodilator. Moexiprilat is about 1000 times as potent as moexiprilat in inhibiting ACE and kininase II. Inhibition of ACE results in decreased angiotensin II

*(Please include inactive ingredients in coating; please add colors)

formation, leading to decreased vasoconstriction, increased plasma renin activity and decreased aldosterone secretion. The latter results in diuresis and natriuresis and a small increase in serum potassium concentration (mean increases of about 0.25 mEq/L were seen when moexipril was used alone.) (see PRECAUTIONS)

Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the theraputic effects of moexipril is unknown. Although the principal mechanism of moexipril in blood pressure reduction is believed to be through the renin-angiotensin-aldosterone system, ACE inhibitors have some effect on blood pressure even in apparent low renin hypertension. As is the case with other ACE inhibitors, however, the antihypertensive effect of moexipril is considerably smaller in black patients, a predominently low-renin population, than in non-black hypertensive patients.

Pharmacokinetics and Metabolism

Pharmacokinetics

Moexipril's antihypertensive activity is almost entirely due to its deesterified metabolite, moexiprilat. Bioavailability of moexipril as moexiprilat is low, about 20%, and is markedly affected by food, with peak plasma level (Cmax) and AUC reduced by more than 50%. Moexpril should therefore be taken in the fasting state. The time of peak plasma concentration (Tmax) of moexiprilat is about 1-1/2 hours and elimination half-life is estimated at from 2-9 hours in various studies, the variability reflecting a complex elimination pattern not linear over time. Like all ACE inhibitors, moexiprilat has a prolonged terminal elimination phase, presumably reflecting slow release of drug bound to the ACE. Accumulation of moexiprilat with repeated dosing is minimal, about 30%, compatible with a functional elimination half-life of about 12 hours. Over the dose range of 7.5 - 30mg, pharmacokinectics are approximately dose proportional.

Absorption

Moexipril is poorly absorbed, with bioavailability of about 20%. This appears to reflect substantial presystemic deesterification with subsequent fecal excretion[b] of moexiprilat. Bioavailability varies with formulation and food intake, falling by more than 50% with the marketed formulation after ingestion of a relatively high-fat breakfast.

Distribution

The volume of distribution of moexiprilat is not known. It is about 50% protein bound.

Metabolism and Excretion

Moexipril is relatively rapidly converted to its active metabolite moexiprilat, but persists longer than some other ACE inhibitor prodrugs, such that its half-life is over one hour and it has a significant AUC. Both moexipril and moexiprilat are converted to diketopiperazine derivatives and unidentified metabolites. After IV administration of moexipril, about 40% of the dose appears in urine as

[b] Comment: The data doesn't allow a differentiation between gut hydrolysis with poor absorption or hepatic hydrolysis with efficient biliary excretion.

moexiprilat, about 20% as moexipril, with small amounts of the metabolites; about 20% of the IV dose appears in feces, principally as moexiprilat. After oral administration, only about 7% of the dose appears in urine as moexiprilat, about 1% as moexipril, with about 5% as other metabolites. Fifty-two percent of the dose is recovered in feces as moexiprilat and 1% as moexipril.

Special Populations:

Decreased Renal Function

The effective elimination half-lives and AUC of both moexipril and moexiprilat are increased with decreasing renal function, ~~with increased AUC for both.~~ There is insufficient information available to characterize this relationship fully, but at creatinine clearances in the range of 10 to 40 mL/min, the half-life of moexiprilat is increased by a factor of 3 to 4.

Decreased Hepatic Function

In patients with mild to moderate cirrhosis the C_{max} of moexipril was increased by ~~up to 56%~~ about 50% and the AUC increased by ~~110%, for moexiprilat~~ about 120% while the C_{max} for moexiprilat was decreased

given single 15 mg doses of moexipril,

by ~~up to 55%~~ about 50% and the AUC ~~was increased by up to 280%, in patients with mild to moderate cirrhosis after single 15mg doses of moexipril.~~ almost 300%.

Elderly Patients

In elderly male subjects (65-80 years old) with clinically normal renal and hepatic function, the AUC and C_{max} of moexiprilat is about 30% greater than those of younger subjects (19-42 years old).

PK Interactions with other Drugs : No clinically important pharmacokinetic interactions occurred when TRADENAME was administered concomitantly with hydrochlorothiazide, digoxin or cimetidine.

Pharmacodynamics and Clinical Effect

Single and multiple doses of 15 mg or more of TRADENAME caused a sustained inhibition of plasma ACE activity of 60% to 90% for at least 48 hours after dosing.[c]

In controlled trials the peak effects of orally administered moexipril ~~were related to~~ increased with the dose administered over a dose range of 7.5 mg to 60 mg, given once a day. Antihypertensive effects were first detectable at about 1 hour

---

[c] Describe effects of ACE inhibition and angiotensin I inhibition by dose and with actual numbers. Source of moexipril (extent and time course)

after dosing, with a peak effect between 3 and 6 hours after dosing. Just before dosing (i.e., at trough), the antihypertensive effects were less prominently related to dose and the antihypertensive effect tended to diminish during the 24 hour dosing interval when the drug was administered once a day.

In multiple dose studies in the dose range of 7.5 to 30 mg once daily, TRADENAME lowered sitting diastolic and systolic blood pressure effects at trough by 3 to 6 mm Hg and 4 to 11 mm Hg, more than placebo, respectively. There was a tendency toward increased response with higher doses over this range. ~~[In studies of modest size the blood pressure-lowering effect was similar to HCTZ (12.5mg/day), verapamil (180-240mg/day), and captopril (50-100mg/day)] (*see note in memo).~~

These effects are typical of ACE inhibitors but to date there are no trials of moexipril with other antihypertensive agents adequate size compari

Dr Kerkvliet's

The trough diastolic blood pressure effects of moexipril were approximately 3 to 6 mmHg in various studies. Generally, higher doses of moexipril leave a greater fraction of the peak blood pressure effect still present at trough. During dose titration, any decision as to the

adequacy of a dosing regimen should be based on trough blood pressure measurements.

If diastolic blood pressure control is not adequate at the end of the dosing interval, the dose can be increased or given as a divided (bid) regimen.

During chronic therapy, the antihypertensive effect of TRADENAME of any dose is generally evident within 2 weeks of treatment, with maximal reduction after 4 weeks. The antihypertensive effects of TRADENAME have continued during therapy for up to 24 months.

TRADENAME, like other ACE inhibitors, is less effective in decreasing trough blood pressures in blacks than in non-blacks. Placebo-corrected trough group mean diastolic blood pressure effects in blacks in the proposed dose range varied between +1 to -3 mm Hg compared with responses in non-blacks of -4 to -6 mm Hg.

The effectiveness of TRADENAME was not significantly influenced by patient age, gender, or weight. TRADENAME has been shown to have antihypertensive activity in both pre- and post-menopausal women who have participated in placebo-controlled clinical trials.

Formal interaction studies with moexipril have not been carried out with antihypertensive agents other than thiazide diuretics. In these studies the added effect of moexipril was similar to its effect as monotherapy. In general ACE inhibitors have less than additive effects with beta-adrenergic blockers, presumably because both work by ~~through~~ inhibiting the renin-angiotensin system.

INDICATIONS AND USAGE

TRADENAME is indicated for treatment of patients with hypertension. It may be used alone or in combination with thiazide diuretics.

c. Sponsor to examine possible lower response in wo

In using TRADENAME, consideration should be given to the fact that another ACE inhibitor (captopril) has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that TRADENAME does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

TRADENAME is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE

inhibitors (including TRADENAME) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema involving the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including TRADENAME. Symptoms suggestive of angioedema or facial edema occurred in <0.5% of moexipril-treated patients in placebo-controlled trials. None of the cases were considered life-threatening and all resolved either without treatment or with medication (antihistamines or glucocorticoids). One patient treated with hydrochlorothiazide alone experienced laryngeal edema. No instances of angioedema were reported in placebo-treated patients.

In cases of angioedema, treatment should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with involvement of the tongue, glottis, or larynx, may be fatal due to airway obstruction. Appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway, should be promptly provided (see ADVERSE REACTIONS).

Anaphylactoid Reactions During Desensitization:

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

Hypotension

TRADENAME can cause symptomatic hypotension, although, as with other ACE inhibitors, this is unusual in uncomplicated hypertensive patients treated with TRADENAME alone.[d] Symptomatic hypotension is most likely to occur in patients who have been salt- and volume-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and salt-depletion should be corrected and, in general, diuretics stopped, before initiating therapy with TRADENAME (see PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS).

was seen in 0.5% of patients given moexipril and led to discontinuation of therapy about 0.25%. Symptomatic hypotension

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or progressive azotemia, and rarely, with acute renal failure and death. In these patients, TRADENAME therapy should be started under close medical supervision,

[d] There was no symptomatic hypotension in the moexipril trials. Dr.S. Chun

and patients should be followed closely for the first two weeks of treatment and whenever the dose of moexipril or an accompanying diuretic is increased. Care in avoiding hypotension should also be taken in patients with ischemic heart disease, aortic stenosis, or cerebrovascular disease, in whom an excessive decrease in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with an intravenous infusion of normal saline. TRADENAME treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in patients with uncomplicated hypertension, but more frequently in hypertensive patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Although there were

no instances of severe neutropenia (absolute neutrophil count <500/mm^3) among patients given TRADENAME, as with other ACE inhibitors, monitoring of white blood cell counts should be considered for patients who have collagen-vascular disease, especially if the disease is associated with impaired renal function. Available data from clinical trials of TRADENAME are insufficient to show that TRADENAME does not cause agranulocytosis at rates similar to captopril.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has caused fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably

resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosis have also been reported, although it is not clear whether these were caused by the ACE-inhibitor exposure.

Fetal and neonatal morbidity do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester. Mothers who have used ACE inhibitors only during the first trimester should be informed of this. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of moexipril as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, moexipril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be detected until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Theoretically, the ACE inhibitor could be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

No embryotoxic, fetotoxic, or teratogenic effects were seen in rats treated with moexipril up to 250 mg/kg/day or in rabbits treated with up to 1.0 mg/kg/day. On a mg/kg basis, these multiples are 500 times and 2 times, respectively, the maximum recommended human dose (or 95.7 times and 0.7 times on a mg/m^2 basis).

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of ACE inhibitor inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. There is no clinical experience of TRADENAME in the treatment of hypertension in patients with renal failure.

→ (from next page)

Hypertensive Patients with Congestive Heart Failure:

In hypertensive patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including TRADENAME, may be associated with oliguria and/or progressive azotemia and, rarely, acute renal failure and/or death.

← Hypertensive patients with Renal Artery Stenosis:

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum

creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when TRADENAME has been given concomitantly with a thiazide diuretic. This is more likely to occur in patients with preexisting renal impairment. There may be a need for dose adjustment of TRADENAME and/or the discontinuation of the thiazide diuretic.

move to p 21

Evaluation of hypertensive patients should always include assessment of renal function. (see DOSAGE AND ADMINISTRATION)

Hyperkalemia: In clinical trials, persistant hyperkalemia (serum potassium above 5.4 mEq/L) occurred in approximately 1.3% of hypertensive patients receiving

TRADENAME. Risk factors for the development of hyperkalemia with ACE inhibitors include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with TRADENAME (see PRECAUTIONS, Drug Interactions).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, moexipril may block the effects of compensatory renin release. If hypotension occurs in this setting and is considered to be due to this mechanism, it can be corrected by volume expansion.

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials with moexipril, cough was present

in 6.1% of moexipril patients and 2.2% of patients given placebo.

Information for Patients

Patients should be advised to take moexipril one hour before meals (see CLINICAL PHARMACOLOGY and DOSE and ADMINISTRATION).

Angioedema: Angioedema, including laryngeal edema, may occur with treatment with ACE inhibitors, ~~especially following the first dose~~ usually occurring early in therapy (in the first month). Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of the face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more TRADENAME until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur with TRADENAME, especially during the first few days of therapy. If fainting occurs, the patient should stop taking TRADENAME ~~until he/she has consulted with~~ and consult the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult their physician if they develop these conditions.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) that could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and ~~they~~ should also be

told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Diuretics: Excessive reductions in blood pressure may occur in patients on diuretic therapy when ACE inhibitors are started. The possibility of hypotensive effects with TRADENAME can be minimized by discontinuing diuretic or cautiously increasing salt intake therapy for several days before initiation of treatment with TRADENAME. If this is not possible, the starting dose of moexipril should be reduced. (See WARNINGS and DOSAGE AND ADMINISTRATION).

Potassium Supplements and Potassium-Sparing Diuretics: TRADENAME can increase serum potassium because it decreases aldosterone secretion. Use of potassium-sparing diuretics (spironolactone, triamterene, amiloride) or potassium supplements[d] ~~or other drugs that can increase serum potassium (indomethacin, heparin,~~

d. The "other drugs" statement is based on another ACE inhibitor labeling. We are looking into its basis.

~~cyclosporine and others~~) concomitantly with ACE inhibitors can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored.

Oral Anticoagulants: Interaction studies with warfarin failed to identify any clinically important effect on the serum concentrations of the anticoagulant or on its anticoagulant effect.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other Agents: No clinically important pharmacokinetic interactions occurred when TRADENAME

was administered concomitantly with hydrochlorothiazide, digoxin, or cimetidine.

TRADENAME has been used in clinical trials concomitantly with calcium-channel-blocking agents, diuretics, H_2 blockers, digoxin, oral hypoglycemic agents, and cholesterol-lowering agents. There was no evidence of clinically important adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was detected in long-term studies in mice and rats at doses up to 75 mg/kg/day, which is 300-times the Maximum Recommended Human Dose (MRHD) on a mg/kg basis and 24 or 33 times MRHD on a mg/m^2 basis.

No mutagenicity was detected in the Ames test and microbial reverse mutation assay, with and without metabolic activation, or in an in vivo nucleus anomaly test. However, increased chromosomal aberration frequency in Chinese

Hamster Ovary cells was detected under metabolic activation conditions and at the highest tested ~~dose~~ concentration (5100 µg/ml) at a 20 hour harvest time.

Reproduction studies have been performed in rabbits at oral doses up to 1 mg/kg (4 times the MRHD on a mg/kg basis and 1.3 times the MRHD on a mg/m^2 basis) and in rats at up to 75 mg/kg (300 times the MRHD on a mg/kg basis and 52.7 times the MRHD on a mg/m^2 basis). No indication of impaired fertility, reproductive toxicity or teratogenicity was observed.

Pregnancy Category C (first trimester); Category D (second and third trimesters)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether TRADENAME is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when TRADENAME is given to a nursing mother.

Geriatric Use

Of the of patients who received TRADENAME in controlled clinical studies, 33% were 65 years of age or older. No overall differences in effectiveness or safety were observed between these patients and younger patients. In elderly patients receiving TRADENAME, plasma levels of drug are slightly higher and renal clearance is reduced when compared to younger patients, but this did not have detectable consequences.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

TRADENAME has been evaluated for safety in more than 2500 patients with hypertension; more than 250 of these patients were treated for approximately one year. The overall

incidence of reported adverse events was only slightly greater in patients treated with TRADENAME than patients treated with placebo.

Reported adverse experiences were usually mild and transient, and there were no differences in adverse reaction rates related to gender, race, age, duration of therapy, or total daily dosage within the range of 3.75 mg to 60 mg. Discontinuation of therapy because of adverse experiences was required in 3.4% of patients treated with TRADENAME and in 1.8% of patients treated with placebo. The most common reasons for discontinuation in patients treated with TRADENAME were cough (0.7%) and dizziness (0.4%).

All ~~side effects (including those~~ considered ~~or probably~~ possibly related that occurred ~~in all dosing groups once daily dosing,~~ in placebo-controlled trials in more than 1% of patients treated with TRADENAME alone and at least as frequent in the TRADENAME group as on placebo are shown in the following table:

ADVERSE EVENTS IN PLACEBO-CONTROLLED STUDIES

	TRADENAME (N=674)	PLACEBO (N=226)
	N (%)	N (%)
Cough Increased	41 (6.1)	5 (2.2)
Dizziness	29 (4.3)	5 (2.2)
Diarrhea	21 (3.1)	5 (2.2)
Flu Syndrome	21 (3.1)	0 (0)
Fatigue	16 (2.4)	4 (1.8)
Pharyngitis	12 (1.8)	2 (0.9)
Flushing	11 (1.6)	0 (0)
Rash	11 (1.6)	2 (0.9)
Myalgia	9 (1.3)	0 (0)

Other adverse events occurring in more than 1% of patients on moexipril, but at least as frequently on placebo include: headache, upper respiratory infection, rhinitis, dyspepsia,

nausea, peripheral edema, sinusitis, chest pain, and urinary frequency. See Warnings and Precautions for discussion of anaphylactoid reactions, angioedema, hypotension, neutropenia/agranulocytosis, second and third trimester fetal/neonatal mortality and morbidity, hyperkalemia, and cough.

Other potentially important adverse experiences reported in controlled or uncontrolled clinical trials ~~occurring~~ in less than 1% of moexipril patients ~~and less frequent clinically significant events which~~ or that have been attributed to other ACE inhibitors include the following:

Cardiovascular: Symptomatic hypotension, postural hypotension, or syncope were seen in 9/1750 (0.51%) of patients; these reactions led to discontinuation of therapy in controlled trials in 3/1254 (0.24%) patients who had received TRADENAME monotherapy and in 1/344 (0.3%)patient who had received TRADENAME with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other adverse events included angina/myocardial infarction, palpitations, rhythm disturbances, and cerebrovascular accident.

Renal: Of hypertensive patients with no apparent preexisting renal disease, 1% of patients receiving

TRADENAME alone and 2% of patients receiving TRADENAME with hydrochlorothiazide experienced increases in serum creatinine to at least 140% of their baseline values (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Gastrointestinal: Abdominal pain, constipation, vomiting, appetite/weight change, dry mouth, pancreatitis, hepatitis.

Respiratory: Bronchospasm, dyspnea.

Urogenital: Renal insufficiency, oliguria.

Dermatologic: Apparent hypersensitivity reactions manifested by urticaria, rash, pruritus, photosensitivity.

Neurological and Psychiatric: Drowsiness, sleep disturbances, nervousness, mood changes, anxiety.

(see Warnings),

Other: Angioedema, taste disturbances, tinnitus, sweating, malaise, arthralgia, hemolytic anemia.

Clinical Laboratory Test Findings

Creatinine and Blood Urea Nitrogen: As with other ACE inhibitors, minor increases in blood urea nitrogen or serum creatinine, reversible upon discontinuation of therapy, were observed in approximately 1% of patients with essential hypertension who were treated with TRADENAME. Increases are more likely to occur in patients receiving concomitant diuretics than in those on TRADENAME alone, and in patients with compromised renal function (see PRECAUTIONS, General).

Other (causal relationship unknown): Clinically important changes in standard laboratory tests were rarely associated with TRADENAME administration. Elevations of liver enzymes and uric acid have been reported. In trials, less than 1% of moexipril-treated patients discontinued TRADENAME treatment because of laboratory abnormalities. The incidence of abnormal lab values with moexipril was similar to that in the placebo-treated group.

~~See table in edited edition.~~

29 April 1994

No
~~Do you want table ? I~~ ~~can go either way~~

OVERDOSAGE

Human overdoses of moexipril have not been reported. In case reports of ~~other ACE inhibitor~~ overdose with other ACE-inhibitors, hypotension has been the principal adverse effect noted. Single oral doses of 2 g/kg moexipril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 3 g/kg. One male and one female beagle dog each tolerated up to 900 mg/kg moexipril with no significant drug-related changes in their clinical condition or gross or microscopic pathology.

No data are available to suggest that physiological maneuvers (e.g., maneuvers to change the pH of the urine) ~~might~~ would accelerate elimination of moexipril and its metabolites. The dialyzability of moexipril is not known.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of moexipril overdose, but angiotensin II is essentially unavailable outside of research

facilities. Because the hypotensive effect of moexipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat moexipril overdose by infusion of normal saline solution. In addition, renal function and serum potassium should be monitored.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended initial dose of TRADENAME in patients not receiving diuretics is 7.5 mg, one hour prior to meals, once daily. Dosage should be adjusted according to blood pressure response. The antihypertensive effect of TRADENAME may diminish towards the end of the dosing interval. Blood pressure should, therefore, be measured just prior to dosing to determine whether satisfactory blood pressure control is obtained. If control is not adequate, increased dose or divided dosing can be tried. The recommended dose range is 7.5 to 30 mg daily, administered in one or two divided doses one hour before meals. Total

daily doses above 60 mg a day have not been studied in hypertensive patients.

In patients who are currently being treated with a diuretic, symptomatic hypotension may occasionally occur following the initial dose of TRADENAME. The diuretic should, if possible, be discontinued for 2 days to 3 days before therapy with TRADENAME is begun, to reduce the likelihood of hypotension (see WARNINGS). If the patient's blood pressure is not controlled with TRADENAME alone, diuretic therapy may then be reinstituted. If diuretic therapy cannot be discontinued, an initial dose of 3.75 mg of TRADENAME should be used with medical supervision until blood pressure has stabilized (see WARNINGS and PRECAUTIONS; Drug Interactions).

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance $\leq$ 40 mL/min/1.73 m^2, an initial dose of 3.75 mg once daily should be given cautiously. Doses may be titrated upward to a maximum daily dose of 15 mg,

HOW SUPPLIED

TRADENAME (moexipril HCL) **7.5 mg tablets** are pink, round, scored, and engraved with **"M"** and **"7.5"** on one side and **"SP"** on the other. They are available as follows:

Unit-of-Use Bottles of 30 Tablets	NDC 0091-3707-30
Unit-of-Use Bottles of 90 Tablets	NDC 0091-3707-09
Bottles of 100 Tablets	NDC 0091-3707-01
Bottles of 500 Tablets	NDC 0091-3707-05
Unit Dose Blister, 100 Units	NDC 0091-3707-11

TRADENAME (moexipril HCL) **15 mg tablets** are red, round, scored, and engraved with **"M"** and **"15"** on one side and **"SP"** on the other. They are available as follows:

Unit-of-Use Bottles of 30 Tablets	NDC 0091-3715-30
Unit-of-Use Bottles of 90 Tablets	NDC 0091-3715-09
Bottles of 100 Tablets	NDC 0091-3715-01
Bottles of 500 Tablets	NDC 0091-3715-05
Unit Dose Blister, 100 Units	NDC 0091-3715-11

STORAGE

Store at controlled room temperature between 15°C and 30°C (59°F and 86°F). Protect from excessive moisture.

Dispense in a tight container, if product package is subdivided.

CAUTION: Federal law prohibits dispensing without prescription.

SCHWARZ PHARMA
Kremers Urban Company
Milwaukee, Wisconsin 53201

DIVISION DIRECTOR & OFFICE DIRECTORS MEMOS

M E M O R A N D U M

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

DATE: APR 20 1995

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Moexipril, NDA 20-312

TO: Dr. Raymond Lipicky, HFD-110

At long last moexipril. I have just a few labeling comments.

1. Clin Pharm

Although we asked for a section on the extent and time course of ACE inhibition and angiotensin 1 inhibition, the new labeling has only the former (although it does say it twice). Under Pharmacodynamics and Clinical Effect, the second and third sentences repeat the first and the fourth and fifth are unnecessary. It should be revised to say:

> Single and multiple doses of 15 mg or more of UNIVASC give a sustained inhibition of plasma ACE activity if 80-90%, beginning within 2 hours and lasting 24 hours (80%). Inhibition of angiotensin I pressor effect was 100% within 2 hours and was still 80% at 24 hours.

2. Is the latest Indications section the same as our most recent other efforts (spirapril, I guess)?

3. Dr. DeGeorge has asked that the Carcinogenis section be revised to:

   a. Delete the mg/kg comparisons "..doses up to 75 mg/kg/day (14 and 27 times the MRHD on a mg/m^2 basis".

   b. Delete concentration data from the mutagenicity section.

   c. Delete mg/kg comparisons from the repro studies paragraph, as in a. above.

The application can be approved with these requested modifications. Note that we need to fill in two percentage figures in #1. The labeling seems identical in critical respects to other recent labeling but I

haven't done a direct comparison this time (I did with approvable). Please be sure any revisions of concept in the last year are incorporated (I realize the angioedema data are different from spirapril).

Robert Temple, M.D.

Bongiovanni

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: MAY 19 1994

FROM: Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 20-312 Fempres (moexipril HCl) Tablets, Besselaar for Schwarz Pharma

TO: Director, Office of Drug Evaluation I

We are returning the package for moexipril with the approvable letter. We have no problem with your revisions to the labeling. On page 36 of the draft labeling, you asked whether we want to include a table, and the answer is no.

Raymond J. Lipicky, M.D.

cc:
NDA 20-312
HFD-110
HFD-111/KBongiovanni
kb/5/19/94.

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
MAY - 2 1994 CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:
FROM: Dr. Abraham Karkowsky, Supervisory Reviewer HFD-110

TO. Dr. Robert Temple Director, Office of Drug Evaluation I, HFD-100
THROUGH: Dr. Raymond Lipicky, Director, Division of Cardio-Renal Drug Products

SUBJECT: Responses to Moexipril Memo dated April 21, 1994.

Under the section labeled a Moexipril seems typical etc.
No comments:

Under the section labeled as: Apart From That:
It is not clear to me if positive controlled data is warranted in labeling. Since the net effect at this dosing range for moexipril (placebo-subtracted) is 3-5 mm Hg, it is difficult to assert equivalence since in each of the positive controlled studies the effect of comparator was superior to moexipril.

Let me first summarize the data (this was taken from Dr. Rodin's review, I have not independently reviewed these studies).

•re captopril- Study # 648 contains the only data I saw . Captopril was administered at doses of 50-100 mg/day (?divided). There was no placebo group. Moexipril effect was less than captopril.
Moexipril effect - 11.8 mm Hg Captopril effect - 12.2 mm Hg.

•re verapamil- study # 647 was on background of 25 mg HCTZ. Verapamil was administered 180-240 mg/day)(?divided). Moexipril was administered at 7.5-15 mg/day. Verapamil was superior:
Moexipril effect -10.7 mm Hg Verapamil -11.2 mm Hg

Study # 645 was a positive controlled study- with no placebo group. Verapamil was given at 180-240 mg/day)(?divided). moexipril was given at 7.5-15 mg/day. Verapamil was superior

Moexipril effect -9.7 mm Hg Verapamil effect -10.6 mm Hg

Point estimates for verapamil suggest a 0.5-0.9 mm Hg superiority of verapamil relative to moexipril.

•re HCTZ: I could only find a single study with 12.5 mg HCTZ . This was a factorial design study #638 with one limb having 12.5 mg HCTZ alone. Moexipril effect at highest doses was -2.8 mm Hg for HCTZ it was -2.6 mm Hg.

The data you have requested are included in the marked-up labeling.

NB: I spoke with Kathleen, of the ACE inhibitors only Accupril has some positive controlled data included in labeling. I do not, however, know what data supported the inclusion of such data.

Your comment no 3. Re renal function:

In considering poor renal function-Item #3. The studies were rather small and really underpowered to see any effect. Trends towards increasing AUC, both for moexipril and moexiprillat, may be occurring even in the Group III renal dysfunction patients (Creatinine Cl 41-65 ml/min). Any effect was small but since the study was only single dose and modest in size I could see adding precautionary concerns even in this range of creatinine clearances. The mean maximal blood pressure changes in the severe and moderate renal dysfunction patients is shown below. The systolic BP drops were substantial.

	Degree of Renal Dysfunction			
	none Ccr ≥90	mild (Ccr 66-90)	moderate (Ccr 41-65)	severe (Ccr < 40)
Average Maximum BP Change	-16/-14	-23/-20	-31/-15	-30/-19

Your comment re hepatic dysfunction.

Again this is single dose study. My assessment is that these subjects had only mild hepatic compromise. Nevertheless, across-study comparisons shows a 2-4 fold increase in AUC for moexiprillat among those with hepatic dysfunction compared with normals (see Table 15.2 Phase I-II studies). I've written in the % change in the labeling. See Table below

PK constants in cirrhotics and normals (normalized to 1 mg dose)

	Moexipril		Moexiprillat	
	C max	AUC	C max	AUC
Cirrhotic	10.3	21.6	1.08	15.2
Normals*	6.6-8.5	10.0-14.6	1.19-2.36	3.9-7.5

*Data derived from several different studies which were not concurrently performed with cirrhotic patients.

Under section Labeled as: There Are a Few Areas...
Re. Subgroup analyses by demographics for safety: Dr. Chun has appended sponsor's tabulated subgroup analyses as Appendix A.

Re Table (Karkowsky review p. 6): Upon editing the table both this column was shifted over and the next line of tabulated blood pressures (see your comment #3)was deleted. The corrected table is appended as Appendix B.

Re: Subgroup analysis from P. 42 of Dr. Rodin's review:
Dr. Rodin has asked the sponsor put together this data for females

no, we don't know the answer now. This should not hold up approvable.
R L 5/2/94

versus males and for less than and greater than 65 years old.

Re questions directed to Dr. Chun's review:

a. The PK study # 637 the adverse events in healthy elderly were 2/12 and 0/12 in the younger group (18-45 years old). There was a typographical error in the last line of the statement. The corrected statement should read:

" The incidence of common AEs in pooled data below did not show a trend to increases in AEs in the elderly population".

b. With respect to persistence of effect- The same effect seems to be evident at weeks 0 and at week 8 (see Appendix C)

c. Much depends on whether you consider placebo subtracted data (the preferable analysis) or raw data. Since the placebo group had disparate effects at trough. At week 0 the placebo effect relative to baseline was negative. At week 8 the placebo effect was highly positive, it does not seem to make much out of the peak and trough data given the variability of the placebo data and the small sample size.

d. The table indeed seems funny. Dr. Chun has contacted the sponsor.

Under section; Labeling:

Re Metabolites: The only data on metabolites of moexipril are shown in Tables 1.2-1.4 of the Phase I-II study Review. Diketomoexiprillat was a prominent plasma metabolite after oral administration. At 1 and 2 hours post dose on day 6 of therapy (this time span is near T max) diketomoexiprillat was approximately 19-30 % of the observed plasma radioactivity. Diketomoexiprillat excreted as percent of dose on day 6 (a surrogate for steady state) was approximately 7% (combining urine and faecal excretions).

cc: NDA 20-312
HFD-110
HFD 110 / Akerman / Skoda / Schnaa / Rapp
(HFD 111 / Bongiorni
HFD 713 / Ghai

Appendix A

CSL

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA# 20-312

Name of Drug: Moexpril

Sponsor: G. H. Resselaar Assoc.

Type of Submission: Original NDA

Date of Review: 4/21/94

Reviewer: Sughok K. Chun. M.D. HFD-110 S.K. Chun 4/22/94

A. Resume:

This is an addendum to the original safety review done 8/02/93 for the subgroup analysis of safety data. The incidence of adverse experiences (AEs) in subgroups of pts defined by age, sex, and race in the placebo controlled studies (GHBA-638, -642, -643, -644, -651 and -623) are evaluated on Moex and placebo treatments for comparison. Moex +HCTZ or HCTZ alone groups are not included in this comparison. The distribution and pts evaluated for the drug safety is shown Table A.

AGE AND SEX DISTRIBUTION OF PATIENTS IN THE EVALUATION OF DRUG SAFETY (POOLED DATA BASE)

	Moexipril (N=897)			Moexipril + HCTZ (N=238)			HCTZ Alone (N=197)			Placebo Alone (N=322)		
Age Interval (years)	M	F	T	M	F	T	M	F	T	M	F	T
Less Than 65	421	204	625	146	84	230	66	42	108	152	63	215
65 and Over	157	115	272	27	29	56	51	38	89	68	39	107
Total Patients	578	319	897	173	113	286	117	80	197	220	102	322
Mean Age (years)	55.0	58.7	56.3	58.4	58.5	58.4	58.3	61.7	59.7	58.5	59.3	58.7
Minimum Age (years)												
Maximum Age												

Source Data: Appendix B, Table 3A.
[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623.
M = Male; F = Female; T = Total

by Age

Of the 897 Moex treated pts in the pooled data base, 625 (70%) were < 65 yrs and 272 (30%) were ≥ 65 yrs. Among the 322 placebo-treated pts, 215 (67%) < 65 yrs old, and 107 (33%) were ≥ 65 years. Table B shows the incidence by age subgroup of the most frequently occurring (1% or more) AEs by decreasing order of frequency in the total Moex population.

Table B shows that moexipril treatment did not adversely affect the subgroup of patients who were 65 years of age or older.

AEs by Sex

Of the 897 pts in the pooled data base treated with Moex, 578 (64%) were men, and 319 (36%) were women. For the 322 patients treated with placebo, 220 (68%) were men, and 102 (32%) were women. Table C shows the incidence of the most frequently occurring (1% or more) AEs by decreasing order of frequency.

Table C shows that Moex treatment, when compared with placebo, did not adversely affect the subgroup of pts who were women.

AEs by Race

Of the 897 pts in the pooled data base treated with Moex, 741 (83%) were non-black (including Hispanic and Oriental), and 156 (17%) were black. For the 322 pts treated with placebo, 278 (86%) were non-black, and 44 (14%) were black. Table D shows the incidence by racial subgroup of the most frequently occurring (1% or more) AEs. Thus, Moex treatment, when compared with placebo, did not adversely affect the black subgroup of pts.

AEs by Dose

AEs by Moex monotherapy dose (3.75 mg, 7.5 mg, 15 mg, 30 mg, and 60 mg) were examined for Moex-treated pts in the pooled safety data base. Table E shows the distribution of dose regimens for the seven placebo-controlled studies in the pooled safety data base.

Table E does not show an appreciable dose effect with Moex.

SUMMARY

Moexipril treatment does not adversely affect demographic subgroups of pts defined by age, sex, or race and does not appear to have a clinically important dose effect.

cc.
Orig
HFD-110
✓ HFD-110/CSO
HFD-100/R Temple
HFD-110/R Lipicky
HFD-110/R Fenichel
HFD-110/S Chun
vl/4-22-94

TABLE B
NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY AGE (POOLED DATA BASE[a])

	Number (%) of Patients				
		< 65 Years		≥ 65 Years	
Adverse Experience	Total Moexipril (N=897)	Moexipril (N=625)	Placebo (N=215)	Moexipril (N=272)	Placebo (N=107)
Total Number With Adverse Experiences	479 (53)	344 (55)	100 (47)	135 (50)	49 (46)
Headache	89 (10)	69 (11)	19 (9)	20 (7)	12 (11)
Upper Respiratory Infection	73 (8)	55 (9)	16 (7)	18 (7)	7 (7)
Cough Increased	63 (7)	43 (7)	4 (2)	20 (7)	6 (6)
Flu Syndrome	44 (5)	30 (5)	1 (<1)	14 (5)	1 (1)
Dizziness	43 (5)	31 (5)	5 (2)	12 (4)	3 (3)
Rhinitis	34 (4)	30 (5)	7 (3)	4 (1)	3 (3)
Diarrhea	33 (4)	25 (4)	2 (1)	8 (3)	3 (3)
Pain	33 (4)	23 (4)	11 (5)	10 (4)	2 (2)
Fatigue	24 (3)	20 (3)	4 (2)	4 (1)	0 (0)
Sinusitis	20 (2)	16 (3)	7 (3)	4 (1)	1 (1)
Back Pain	19 (2)	16 (3)	3 (2)	3 (1)	5 (5)
Pharyngitis	19 (2)	14 (2)	1 (<1)	5 (2)	2 (2)
Injury	16 (2)	12 (2)	4 (2)	4 (1)	0 (0)
Rash	16 (2)	8 (1)	2 (1)	8 (3)	1 (1)
Dyspepsia	15 (2)	6 (1)	4 (2)	9 (3)	1 (1)
Nausea	15 (2)	11 (2)	2 (1)	4 (1)	2 (2)
Myalgia	14 (2)	10 (2)	0 (0)	4 (1)	0 (0)
Peripheral Edema	14 (2)	11 (2)	5 (2)	3 (1)	1 (1)
Bronchitis	13 (1)	10 (2)	3 (1)	3 (1)	1 (1)
Chest Pain	12 (1)	9 (1)	4 (2)	3 (1)	1 (1)
Flushing	11 (1)	10 (2)	1 (<1)	1 (<1)	0 (0)
Hypertonia	10 (1)	8 (1)	0 (0)	2 (1)	0 (0)
Abdominal Pain	9 (1)	5 (1)	1 (<1)	4 (1)	1 (1)
Hyperkalemia	9 (1)	7 (1)	0 (0)	2 (1)	0 (0)
Nervousness	9 (1)	5 (1)	2 (1)	4 (1)	0 (0)
Paresthesia	9 (1)	9 (1)	1 (<1)	0 (0)	0 (0)
Somnolence	9 (1)	6 (1)	0 (0)	3 (1)	1 (1)
Urinary Frequency	9 (1)	8 (1)	4 (2)	1 (<1)	1 (1)
Electrocardiogram Abnormal	8 (1)	8 (1)	1 (<1)	0 (0)	0 (0)
Vomiting	8 (1)	6 (1)	0 (0)	2 (1)	2 (2)
Arthritis	7 (1)	4 (1)	0 (0)	3 (1)	1 (1)
Asthenia	7 (1)	4 (1)	0 (0)	3 (1)	0 (0)
Hypesthesia	7 (1)	7 (1)	1 (<1)	0 (0)	1 (1)
Insomnia	7 (1)	5 (1)	0 (0)	2 (1)	1 (1)
Tenosynovitis	7 (1)	7 (1)	1 (<1)	0 (0)	0 (0)
Tinnitus	7 (1)	6 (1)	0 (0)	1 (<1)	0 (0)
Urinary Tract Infection	7 (1)	4 (1)	1 (<1)	3 (1)	0 (0)
Ecchymosis	6 (1)	3 (<1)	2 (1)	3 (1)	0 (0)
Fever	6 (1)	5 (1)	0 (0)	1 (<1)	0 (0)
Infection	6 (1)	6 (1)	0 (0)	0 (0)	2 (2)
SGPT Increased	6 (1)	4 (1)	3 (1)	2 (1)	0 (0)
Cardiovascular Disorder	5 (1)	5 (1)	1 (<1)	0 (0)	0 (0)
Constipation	5 (1)	4 (1)	1 (<1)	1 (<1)	0 (0)

Source Data: Appendix B, Tables 6A, 9A, and 9B.

[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623. Data for GHBA-644 are not presented in this table.

TABLE C
NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY SEX (POOLED DATA BASE[a])

	Number (%) of Patients				
		Male		Female	
Adverse Experience	Total Moexipril (N=897)	Moexipril (N=578)	Placebo N=220)	Moexipril (N=319)	Placebo (N=102)
Total Number With Adverse Experiences	479 (53)	294 (51)	95 (43)	185 (58)	54 (53)
Headache	89 (10)	44 (8)	17 (8)	45 (14)	14 (14)
Upper Respiratory Infection	73 (8)	47 (8)	15 (7)	26 (8)	8 (8)
Cough Increased	63 (7)	34 (6)	4 (2)	29 (9)	6 (6)
Flu Syndrome	44 (5)	28 (5)	0 (0)	16 (5)	2 (2)
Dizziness	43 (5)	31 (5)	4 (2)	12 (4)	4 (4)
Rhinitis	34 (4)	25 (4)	6 (3)	9 (3)	4 (4)
Diarrhea	33 (4)	21 (4)	3 (1)	12 (4)	2 (2)
Pain	33 (4)	23 (4)	8 (4)	10 (3)	5 (5)
Fatigue	24 (3)	14 (2)	1 (<1)	10 (3)	3 (3)
Sinusitis	20 (2)	9 (2)	5 (2)	11 (3)	3 (3)
Back Pain	19 (2)	11 (2)	3 (1)	8 (3)	7 (7)
Pharyngitis	19 (2)	13 (2)	2 (1)	6 (2)	1 (1)
Injury	16 (2)	9 (2)	3 (1)	7 (2)	1 (1)
Rash	16 (2)	10 (2)	1 (<1)	6 (2)	2 (2)
Dyspepsia	15 (2)	10 (2)	3 (1)	5 (2)	2 (2)
Nausea	15 (2)	7 (1)	2 (1)	8 (3)	2 (2)
Myalgia	14 (2)	9 (2)	0 (0)	5 (2)	0 (0)
Peripheral Edema	14 (2)	6 (1)	3 (1)	8 (3)	3 (3)
Bronchitis	13 (1)	7 (1)	0 (0)	6 (2)	4 (4)
Chest Pain	12 (1)	4 (1)	5 (2)	8 (3)	0 (0)
Flushing	11 (1)	6 (1)	1 (<1)	5 (2)	0 (0)
Hypertonia	10 (1)	9 (2)	0 (0)	1 (<1)	0 (0)
Abdominal Pain	9 (1)	5 (1)	1 (<1)	4 (1)	1 (1)
Hyperkalemia	9 (1)	6 (1)	0 (0)	3 (1)	0 (0)
Nervousness	9 (1)	3 (1)	2 (1)	6 (2)	0 (0)
Paresthesia	9 (1)	6 (1)	1 (<1)	3 (1)	0 (0)
Somnolence	9 (1)	3 (1)	0 (0)	6 (2)	1 (1)
Urinary Frequency	9 (1)	8 (1)	2 (1)	1 (<1)	3 (3)
Electrocardiogram Abnormal	8 (1)	6 (1)	1 (<1)	2 (1)	0 (0)
Vomiting	8 (1)	7 (1)	0 (0)	1 (<1)	2 (2)
Arthritis	7 (1)	4 (1)	1 (<1)	3 (1)	0 (0)
Asthenia	7 (1)	2 (<1)	0 (0)	5 (2)	0 (0)
Hypesthesia	7 (1)	4 (1)	1 (<1)	2 (1)	1 (1)
Insomnia	7 (1)	4 (1)	1 (<1)	2 (1)	0 (0)
Tenosynovitis	7 (1)	3 (1)	1 (<1)	4 (1)	0 (0)
Tinnitus	7 (1)	4 (1)	0 (0)	3 (1)	0 (0)
Urinary Tract Infection	7 (1)	2 (<1)	0 (0)	5 (2)	1 (1)
Ecchymosis	6 (1)	1 (<1)	0 (0)	5 (2)	2 (2)
Fever	6 (1)	6 (1)	0 (0)	0 (0)	0 (0)
Infection	6 (1)	3 (1)	0 (0)	3 (1)	2 (2)
SGPT Increased	6 (1)	3 (1)	2 (1)	3 (1)	1 (1)
Cardiovascular Disorder	5 (1)	3 (1)	0 (0)	2 (1)	1 (1)
Constipation	5 (1)	3 (1)	1 (<1)	2 (1)	0 (0)

Source Data: Appendix B, Tables 6A, 9C, and 9D.

[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623.

TABLE D
NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY RACE (POOLED DATA BASE[a])

	Number (%) of Patients				
		Non-Black		Black	
Adverse Experience	Total Moexipril (N=897)	Moexipril (N=741)	Placebo (N=278)	Moexipril (N=156)	Placebo (N=44)
Total Number With Adverse Experiences	479 (53)	409 (55)	131 (47)	70 (45)	18 (41)
Headache	89 (10)	77 (10)	24 (9)	12 (8)	7 (16)
Upper Respiratory Infection	73 (8)	65 (9)	21 (8)	8 (5)	2 (5)
Cough Increased	63 (7)	57 (8)	8 (3)	6 (4)	2 (5)
Flu Syndrome	44 (5)	38 (5)	1 (<1)	6 (4)	1 (2)
Dizziness	43 (5)	34 (5)	7 (3)	9 (6)	1 (2)
Rhinitis	34 (4)	30 (4)	7 (3)	4 (3)	3 (7)
Diarrhea	33 (4)	29 (4)	5 (2)	4 (3)	0 (0)
Pain	33 (4)	27 (4)	11 (4)	6 (4)	2 (5)
Fatigue	24 (3)	22 (3)	4 (1)	2 (1)	0 (0)
Sinusitis	20 (2)	15 (2)	8 (3)	5 (3)	0 (0)
Back Pain	19 (2)	16 (2)	9 (3)	3 (2)	1 (2)
Pharyngitis	19 (2)	18 (2)	2 (1)	1 (1)	1 (2)
Injury	16 (2)	13 (2)	2 (1)	3 (2)	2 (5)
Rash	16 (2)	14 (2)	3 (1)	2 (1)	0 (0)
Dyspepsia	15 (2)	14 (2)	5 (2)	1 (1)	0 (0)
Nausea	15 (2)	14 (2)	4 (1)	1 (1)	0 (0)
Myalgia	14 (2)	14 (2)	0 (0)	0 (0)	0 (0)
Peripheral Edema	14 (2)	10 (1)	5 (2)	4 (3)	1 (2)
Bronchitis	13 (1)	12 (2)	4 (1)	1 (1)	0 (0)
Chest Pain	12 (1)	10 (1)	4 (1)	2 (1)	1 (2)
Flushing	11 (1)	11 (1)	1 (<1)	0 (0)	0 (0)
Hypertonia	10 (1)	9 (1)	0 (0)	1 (1)	0 (0)
Abdominal Pain	9 (1)	7 (1)	4 (1)	2 (1)	0 (0)
Hyperkalemia	9 (1)	9 (1)	0 (0)	0 (0)	0 (0)
Nervousness	9 (1)	8 (1)	1 (<1)	1 (1)	1 (2)
Paresthesia	9 (1)	9 (1)	1 (<1)	0 (0)	0 (0)
Somnolence	9 (1)	7 (1)	1 (<1)	2 (1)	0 (0)
Urinary Frequency	9 (1)	9 (1)	4 (1)	0 (0)	1 (2)
Electrocardiogram Abnormal	8 (1)	7 (1)	1 (<1)	1 (1)	0 (0)
Vomiting	8 (1)	7 (1)	2 (1)	1 (1)	0 (0)
Arthritis	7 (1)	6 (1)	1 (<1)	1 (1)	0 (0)
Asthenia	7 (1)	7 (1)	0 (0)	0 (0)	0 (0)
Hypesthesia	7 (1)	7 (1)	1 (<1)	0 (0)	1 (2)
Insomnia	7 (1)	5 (1)	1 (<1)	2 (1)	0 (0)
Tenosynovitis	7 (1)	6 (1)	1 (<1)	1 (1)	0 (0)
Tinnitus	7 (1)	7 (1)	0 (0)	0 (0)	0 (0)
Urinary Tract Infection	7 (1)	6 (1)	0 (0)	1 (1)	1 (2)
Ecchymosis	6 (1)	6 (1)	2 (1)	0 (0)	0 (0)
Fever	6 (1)	5 (1)	0 (0)	1 (1)	0 (0)
Infection	6 (1)	6 (1)	2 (1)	0 (0)	0 (0)

Source Data: Appendix B, Tables 6A, 9E, and 9F.
[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623.

TABLE E

NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY DOSE (POOLED DATA BASE[a])

	Number (%) of Patients					
Adverse Experience (AE)	Total N=897	3.75 mg N=49	7.5 mg N=336	15 mg N=341	30 mg N=110	60 mg N=61
Headache	89 (10)	5 (10)	31 (9)	35 (10)	13 (12)	5 (8)
Upper Resp Infection	73 (8)	2 (4)	25 (7)	39 (11)	4 (4)	3 (5)
Cough Increased	60 (7)	3 (6)	24 (7)	23 (7)	8 (7)	5 (8)
Flu Syndrome	44 (5)	0 (0)	22 (7)	17 (5)	3 (3)	2 (3)
Dizziness	43 (5)	2 (4)	19 (6)	15 (4)	3 (3)	4 (7)
Rhinitis	34 (4)	3 (6)	16 (5)	9 (3)	3 (3)	3 (5)
Diarrhea	33 (4)	1 (2)	17 (5)	13 (4)	1 (1)	1 (2)
Pain	33 (4)	3 (6)	11 (4)	11 (3)	5 (5)	3 (5)
Fatigue	24 (3)	1 (2)	11 (3)	7 (2)	3 (3)	2 (3)
Sinusitis	20 (2)	0 (0)	10 (3)	7 (2)	3 (3)	0 (0)
Back Pain	19 (2)	1 (2)	9 (3)	6 (2)	0 (0)	3 (5)
Pharyngitis	19 (2)	0 (0)	10 (3)	6 (2)	2 (2)	1 (2)
Injury	16 (2)	1 (2)	7 (2)	8 (2)	0 (0)	0 (0)
Rash	16 (2)	0 (0)	9 (3)	5 (1)	1 (1)	1 (2)
Dyspepsia	15 (2)	0 (0)	5 (1)	5 (1)	2 (2)	3 (5)
Nausea	15 (2)	0 (0)	8 (2)	6 (2)	1 (1)	0 (0)
Myalgia	14 (2)	1 (2)	4 (1)	6 (2)	1 (1)	2 (3)
Peripheral Edema	14 (2)	1 (2)	5 (1)	6 (2)	1 (1)	1 (2)
Bronchitis	13 (1)	0 (0)	4 (1)	7 (2)	2 (2)	0 (0)
Chest Pain	12 (1)	0 (0)	7 (2)	3 (1)	1 (1)	1 (2)
Flushing	11 (1)	0 (0)	4 (1)	3 (1)	2 (2)	2 (3)
Hypertonia	10 (1)	0 (0)	6 (2)	4 (1)	0 (0)	0 (0)

Source Data: Appendix B, Table 10A.

[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 622. Data for GHBA-644 are not presented in this table.

Appendix B

Table 2. Sitting Blood Pressure Response (Systolic/Diastolic) in mm Hg. Placebo Corrected. Bold Italicized Values Are Significantly Different From Placebo

Trial Number	Description	No. of Subjects/Tx	Formulation/ Dose	3.75 mg	7.5 mg	15 mg	30 mg	60 mg
#642	12-Week, PBO-C, DB, II Study- Endpoint ITT Analysis- Trough	47-51	Once Daily Dose Formulations C2 =7.5 mg C3= 15 mg		***-7.1/ -4.8***	***-10.7/ -5.2***		
#638	8-week, PBO-C, DB, II Study With and W/O 12.5 mg HCTZ- ITT Analysis- Trough	42-49	Once Daily Dose Formulations C1= 3.75 C2 =7.5 mg C3= 15 mg C4= 30 mg No HCTZ	-0.6/ -1.1	***-4.0/ -3.2***	***-4.4/ -3.1***	***-5.3/ -3.4***	
	ITT Analysis Trough- With HCTZ Alone Subtracted	39-48	Formulations Are as Above With 12.5 mg HCTZ-	-5.1/ ***-3.6***	-5.3/ ***-4.1***	***-6.6/*** 2.4		
#643	12-Week,PBO-C, Withdrawal Study, Trough Analysis of Withdrawal- ITT	46-48	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg		-2.6/ ***-4.5***	***-11.4/ -4.7***		
#640	8-Week, PBO-C DB, II, Also HCTZ (25 mg), In Elderly (65 -80 Years Old). ITT Analysis Endpoint Trough	49-51	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg		-1.0/ ***-4.8***	-5.6/ ***-6.2***		
#651	8-week, PBO-C, DB, II Study, Ambulatory as Well as Office BP Measurements- Endpoint ITT Trough-Ambulatory measurements	16-18	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg		-0.2/ +6.0	-7.9/ +3.0		
	As above but Ambulatory Data- Trough	13-15	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg		+5.1/ +2.7	-6.9/ -2.7		
#623	6-week, PBO-C, DB, II study- Endpoint ITT Analysis Trough	60-65	Capsule Formulations-First 40 Patient's Formulations Contained No Vegetable Oil- After That Formulations Contained Vegetable Oil		-4.6/ -2.4	***-8.0/ -4.1***	***-10.0/ -6.2***	***-7.1/ -3.7***
#644	8-week, PBO-C, DB, II study, with HCTZ 25 mg Daily	49-52	Once Daily Dose Formulations C1= 3.75; C2 =7.5 mg; C3= 15 mg	***-10.3/ -3.8***	***-11.4/ -4.2***	***-11.1/ -4.3***		
#622	PBO-C , DB, II study Three phases to study. Phase 1- dosing of 0-15 mg BID; 1 week Phase 2- BID dosing 0-30 mg; 5 weeks Phase 3- down-titration phase -0-15 mg BID ; 2 weeks ITT of Phase 2.	36-40	Uncharacterized formulations -relative to the to-be marketed formulation		-1.0/ -1.4	-6.1/ -2.9	***-11.4/*** -2.3	-5.3/ -5.2

Abbreviations: PBO-C = placebo controlled; DB= Double Blind; II = parallel; HCTZ= hydrochlorothiazide; ITT= intention to treat; DR= Dose Response Tx=Treatment Group

Appendix C

Table 6: ADJUSTED@ MEAN CHANGE (S.E.) FROM BASELINE & BY WEEK AND TWO-HOUR INTERVALS AMBULATORY SYSTOLIC BLOOD PRESSURE (mmHg) COMPARISON OF MoexIPRIL TO PLACEBO Study #651

WEEK 0 (DAY 1. First Dose)

Baseline N	Placebo	Moex 7.5 mg	Moex 15 mg
Hour	14	16	17
0 Sitting	149.3	160.6	156.7
Immed. Stand	148.6	162.4	154.1
2 min. Stand	148.9	161.6	153.1
2	-7.5 (3.95)	1.4 (3.84)	-7.8 (3.72)
2-4	-4.8 (3.42)	2.4 (3.44)	-14.5* (3.34)
4-6	-6.2 (3.14)	-5.8 (3.08)	-22.5*** (2.88)
6-8	-4.6 (3.79)	-8.5 (3.77)	-18.1* (3.62)
8-10	-6.3 (4.12)	-8.1 (3.56)	-19.5* (3.43)
10-12	0.5 (4.18)	-7.2 (4.22)	-13.1 (3.87)
12-14	-6.3 (4.12)	-2.0 (4.32)	-10.4 (4.07)
14-16	0.7 (3.75)	1.8 (3.89)	-7.6 (3.62)
16-18	-3.1 (3.69)	-4.3 (4.01)	-12.6 (3.56)
18-20	-0.3 (3.46)	-4.0 (3.66)	-15.5** (3.36)
20-22	2.0 (4.57)	-11.4 (4.94)	-15.3** (4.21)
22-24	-2.5 (3.39)	-3.8 (3.39)	-12.5 (3.11)

WEEK 8: CHANGE FROM PRE TO POST-LAST DOSE SYSTOLIC BP (mmHg) ADJUSTED@ MEAN CHANGE (S.E.) STUDY #651

Hour	N	Placebo 14	Moex 7.5 mg 16	Moex 15 mg 15
0	sitting	144.5	159.5	146.2
	immediate stand	141.5	158.7	145.6
	2 min. stand	142.7	161.7	146.0
1-2		-4.9 (3.86)	-3.4 (3.52)	-15.4 (3.65)
2-4		-6.2 (4.10)	-2.9 (3.80)	-22.2** (3.98)
4-6		-2.6 (4.74)	-12.8 (4.45)	-19.2* (4.48)
6-8		-2.5 (4.49)	-11.3 (4.22)	-15.7 (4.36)
8-10		-1.4 (5.04)	-7.1 (4.74)	-12.9 (4.92)
10-12		6.1 (5.44)	-3.4 (5.14)	-6.3 (5.09)
12-14		1.0 (5.05)	1.0 (5.07)	-3.0 (5.24)
14-16		7.8 (5.81)	6.6 (5.72)	-4.6 (5.79)
16-18		-4.2 (5.24)	-2.7 (5.43)	-8.3 (5.26)
18-20		4.1 (5.74)	-1.4 (6.10)	-5.6 (5.54)
20-22		-2.9 (3.67)	-3.9 (3.42)	-7.8 (3.30)
22-24		-4.2 (3.91)	0.9 (3.55)	-11.1 (3.79)

@ Mean change from baseline adjusted by analysis of covariance.
* p≤0.050, ** p≤0.010 *** p≤0.001 (significantly different from placebo mean change).

In Study #651 Moex 7.5 QD dosing has very little BP effect 4-10 hr post dose in chronic therapy and hypotensive effect is seen only with Moex 15 mg QD in this small sample of study (Table 7). Treatment with Moex 15 QD has wide peak/through ratio after the 1st dose and it became smaller with chronic dosing.

Antihypertensive effect may diminish toward the end of the 24h dosing interval in some pts specially with Moex 7.5 mg dose and such pts may be given as BID dosing.

M E M O R A N D U M

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

DATE: APR 21 1994

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Moexipril

TO: Dr. Raymond Lipicky, HFD-110
Director, Division of Cardio-Renal Drug Products

Moexipril seems typical of ACEIs with perhaps two unusual features.

1. Bioavailability is markedly decreased by meals; labeling should probably advise taking prior to meals.

2. We have better than usual data on first dose effect, an effect not usually attributed to ACEIs, although need for caution in volume-depleted patients (e g., anyone on a diuretic) has long been recognized.

Apart from that:

1. Effect size is typical; active control studies of fair size vs verapamil, HCTZ and captopril show no difference. Response to increased dose is pretty flat; there seems no reason to go past 30 mg.

2. Trough/peak ratios probably tend to increase at higher doses, although this is not wholly documented. This should lead to a recommendation to increase dose or go to b.i.d. if response of trough is not adequate. There is reasonable 24 hour effect on BP and ACE despite a relatively short $T_{\frac{1}{2}}$ (described as 4-9 hours in various places), presumably because of binding to ACE. The peak/trough differences seem perhaps wider than I recall with other drugs, but the data are sparse and persistence of ACE inhibition seems good.

3. There is a modest increase in AUC and Cmax in elderly and 3.75 mg seems to work well in them (but see #2 below). Poor renal function seems to have no significant effect to CCl below 40 ml/minute and poor hepatic function appears to have no effect.

There are a few areas that need a little more attention (post-approvable could be OK in many cases, if you think that's appropriate).

1. There is no by-gender, race, and age analysis of safety data (other than exposure) discussed. Such an analysis was done (Vol 1.192) but not reviewed.

2. Study 640 in the elderly studied either doses of 3.75 and 7.5 mg (Karkowsky) or 7.5 and 15 mg (Rodin). It's OK either way, but the difference could affect labeling. Older patients have an increase in Cmax and AUC and a starting dose of 3.75 might be reasonable (but not if it wasn't studied).

3. Dr. Karkowsky's review (p. 6) omits BP data on study 644. As the Table 3 on that page is a helpful summary, it would be good to amend/complete the table.

4. On the subgroup analyses (Rodin review, p. 42), significance vs placebo is shown, but there is no direct comparison of the subgroups. I realize this comparison might be statistically dubious but I think it should be considered any way. If n at each dose is too small; could pool the 7.5-30 mg groups. I agree that blacks clearly respond less well. Does it also appear as if women also respond less well? Have we seen that before? Is there a theoretical explanation? (Note that labeling and the integrated summary of effectiveness do not agree that there is a difference.)

5. I am inclined to like the interaction studies (see Karkowsky review, p. 58-9) more than Dr. Karkowsky, and believe they would have discovered sizable effects. I am therefore inclined to include them in labeling.

6. A few questions on Dr. Chun's review:

   a. P. 5 - The AE rate is said to trend toward an increase in the elderly. The table on p. 6 seems to show the opposite, or perhaps no difference.

b. P. 6 - The fraction of patients with a >30 mm Hg systolic fall in BP after 2 minutes of standing is quite striking and strikingly dose-related. Have we seen this before? And do we have data on longer-term therapy that shows this effect goes away? I note that captopril and nifedipine give similar rates to moexipril doses ≤30 mg.

c. The ambulatory BP study 651 (p. 8-9 Dr. Chun) seems to show little difference in peak/trough ratio from first day to week 8. If anything, the peak/trough difference is larger in week 8 (because trough values are lower). But Dr. Chun says the peak/trough ratio gets smaller with chronic dosing. Is this a typo?

d. Table 7 (p. 13) seems to have errors. For HCTZ monotherapy, the combined controlled/uncontrolled K goes up at endpoint, instead of down as it must (and does in the controlled trials).

5. Labeling: See comments on draft.

Also:

a. I have tried to redo the PK section but I think it needs further examination. (Please carefully check my changes for accuracy.) Because moexiprilat is 1000 times as potent an ACE inhibitor as moexipril, I have limited the discussion to it but data are confusing with half-life estimates varying from less than one to over 20 hours, with perhaps some tendency to decrease with dose. I suspect this has something to do with a fundamentally difficult decay curve and a long dose-independent fail due to ACE-binding, which is more prominent at low doses but it needs a further look. I would suggest a post-approvable meeting just to look at PK and get labeling right.

Also unclear are:

1. Metabolites other than moexiprilat

2. The basis for the surprisingly greater AUC for moexipril ($T_{1/2}$ about 9 hours), when moexipril becomes moexiprilat. The only explanation I can see is that quite a lot of moexipril, after absorption, is excreted or metabolized before de-esterification (but I don't see evidence of that).

3. Whether bioavailability is dose-proportional; it seems slightly less than dose proportional, probably because the long tail affects low doses more than high doses. In this case it may be helpful to compare AUC (0-24) rather than AUC (0-infinity).

Robert Temple, M.D.

Robert Temple, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — Public Health Service

Memorandum

DATE : DEC 17 1993

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval of NDA 20-312, Moexipril, (Kremers Urban) Schwarz Pharma AG, G.H. Besselar Associates are the NDA applicant.

TO : Director, Office of Drug Evaluation I, HFD-100

General Preamble

Moexipril will be manufactured by SIFA Ltd. in Ireland. Although the request for plant inspection has been made, the best estimate of when the (foreign) inspections will be able to made is sometime near the end of the first quarter of 1994. Although we can "approvable" this application now, final approval cannot occur until 1994.

Small Points

Although I agree that moexipril is approvable and that the Division unanimously recommends its approval, I have some additional thoughts to add to the considerations that are in the appended materials regarding, dose-response, interval between dose and labelling. I am adding these thoughts in the form of this memorandum, for the sake of conserving time. I do not think the following thoughts represent any major conceptual differences between myself and Drs. Karkowsky, Rodin, Chi or Nuri (of course, they will see this memorandum, so, if there are conceptual differences they can add to the written material).

The data that represent all of the diastolic blood pressure changes from baseline (placebo subtracted) that were measured in 9 randomized, double-blind, placebo controlled clinical trials as a function of the dose of moexipril are shown in Dr. Karkowsky's memorandum (Figure 1 of that memorandum) dated November 30, 1993. The sign of blood pressure change is minus if blood pressure decreased during the trial and plus if blood pressure increased during the trial. Indeed, the conglomerate of data is entirely consistent with (but a test for the probability has not been done) a greater effect as dose is increased. But as Dr. Karkowsky points out, the slope is shallow (flat). That there is a slope is, by inspection, pretty clear. I would venture to guess that if one included 0, 0 (zero change for zero dose), the hypothesis that there was zero slope would be rejected (with a pretty small p value), if such a calculation had been done (assuming a straight line).

In fact, Dr. Nuri did fit some models (a quadratic model, a logistic (log) model, an E_{Max} Model, as well as linear model) to the trough diastolic blood pressure data of studies of 623 and 638. On the basis of getting the smallest least-square residuals and having a biological basis (not an unreasonable reason for picking the best fit; more reasonable, perhaps would have been to include a third criterion, namely the smallest standard error of the parameter estimates), he came to the conclusion that the best model that fits the data (among those tested) was a logistic model, I choose to interpret that as meaning that dose does not enter linearly and, for simplistic reasons think that the logarithm of dose is justified. Indeed, that conclusion fits all of my biases (I chose that word from all others that I could have used, since up until starting work at FDA, I never plotted any data as a function of dose of any drug without having dose on log

scale). Dr. Nuri does give a quantitative estimate of the probability of the effect increasing as dose increases, presumably because he was confident the change in blood pressure was unquestionably due to moexipril and he was attempting to decide how best to describe the change quantitatively as a function of dose. After looking over the fitted data, I can certainly agree that the best fit is one that comes from expecting the effect seen to be a function of the log of the dose and find the overall data to be compelling. The effect is a function of dose, and although one fitted function was best of those tested, there is no reason to believe this function has physiological significance.

Why belabor this point ? No compelling reason, other than that I do not want the description of "flat" to be interpreted as conceivably meaning that there is no dose response relationship that has been demonstrated by the data. Moreover, if the log of the dose does "best" describe the relationship between effect and dose, the dose range of 3.75 to 60 (a factor of 16) is associated with a 3 to 5 mm Hg blood pressure change, so to see another 3 to 5 mm Hg additional effect would require dose ranges up to at least 900 mg to have been studied.

Of course, the above notions are predicated upon there being some mass-action drug-receptor phenomena underlying the description of the relationship of effect and dose. At trough, this seems unlikely to be the case. Although there must be some form of steady-state mass-action drug-receptor phenomenon that drives the whole system, the trough blood pressure, if related to that kind of phenomenon, is more a tortuous function of duration-of-action and dose that has as its basis a relation to mass-action but also to hysteresis and the effect of dose on duration-of-action. So, trough blood-pressure is a poor place to look for a dose-response description.

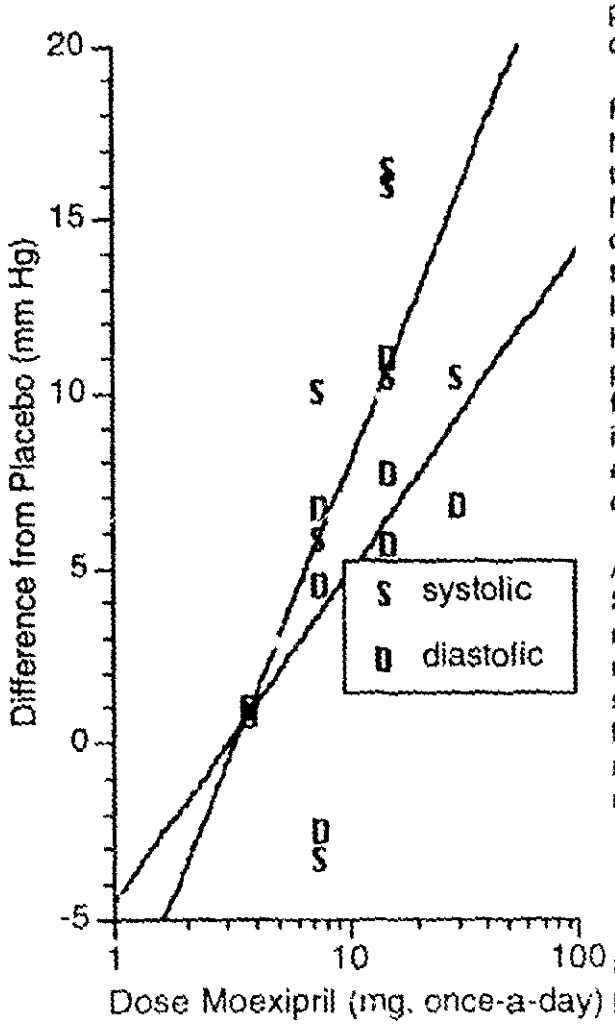

Figure 1 Peak Effect, Dose-Response.

Peak-effect is a more likely place to look, assuming no hysteresis. So I have done that and the plot follows (data taken from Dr. Karkowksy's memorandum dated November 30, 1993, Page 9) in Figure 1. The lines drawn are fits to the systolic and diastolic data assuming that the best model has effect varying as a function of the log of the dose. For this plot, I have departed from Dr. Karkowsky's convention. For the following Figure 1, a positive number means a decrease in blood pressure from baseline and a negative number means an increase in blood pressure from baseline. I have preserved the effect being defined as placebo subtracted, so, this is drug-effect.

As can be seen, the dose-response is not "flat" at peak. So, I am confident that there is a reasonably prominent relationship between dose and effect, even though I readily acknowledge that the measured peak effect was at some arbitrary time after dosing and that peak effect may be greater (it cannot be less), if the correct time to measure it was known (which it is not). The fit (using the natural logarithm) gave the following result:

Systolic Effect = 7.06 * ln(Dose) -8.3
Diastolic Effect = 4.05 * ln(Dose) -4.5.

So, at peak effect there is a 7 mm Hg change in systolic pressure for each 10 fold change in dose and a 4 mm Hg change in diastolic pressure for each 10 fold change in dose. The 1 mg dose extrapolation of -8.3 mm Hg and -

4.5 mm Hg (systolic and diastolic, respectively) give one reason to question the validity of model over the range of dose = 0 to dose = about 7.5 mg. Indeed, over the ranges of low doses and high doses (those that approach maximum effect) a log dose vs effect plot is usually not a straight line. But, the range of doses tested does not allow reasonable use of an E_{Max} model either, Dr. Nuri adequately demonstrated that.

Since the trough blood pressure measurements have a less steep slope (around 1 from the logistic model), the Trough/Peak ratios would be expected to be frequently less than 0.50, especially at low doses. As Dr. Karkowsky points out (page 9 of his memo), they were.

As has been a frequent finding with ACE inhibitors, even without resorting to an analysis of ambulatory blood pressure monitoring , one can conclude that the effects of a dose given once-a-day may not last throughout the dosing interval. So, what should one do about that? Dr. Karkowsky's suggestion is that one should look for a controlled clinical trial where the effects of a more frequent dosing regimen can be empirically examined and that the results of such a trial should be interpreted in a rigorous fashion. The null hypothesis should once again be tested and denied (e.g., one should once again determine if the ACE inhibitor has an antihypertensive effect, on the basis of a single trial, measuring blood pressure at trough), else the drug cannot be administered at a dosing interval other than the dosing interval that leads to denial of the null hypothesis. Moreover, Dr. Karkowsky asserts that the most reasonable interpretation of study 622, the only study (which incidentally randomized 203 patients) conducted that used a BID regimen (for all randomized patients; there was no once-a-day randomized comparison) is that moexipril when administered in a BID regimen is an ineffective therapy for hypertension because the adjusted mean change form baseline in supine diastolic blood pressure (with p values adjusted for multiple comparisons with placebo) did not meet the standard statistical significance criterion (even at the highest dose, end-point intent-to-treat-analysis it only had a p = 0.059).

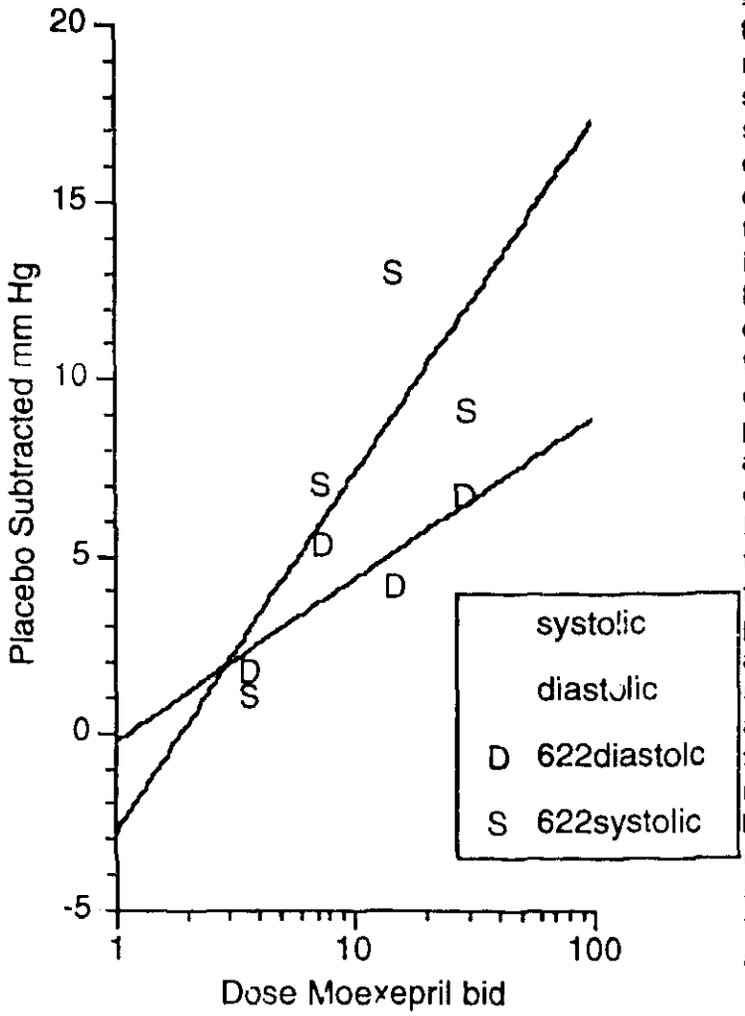

Figure 2 Trough, Study 622 Dose-Response

Other interpretations of the data are, I think, equally viable. The following (Figure 2) is a plot of the data obtained at week 4 (Placebo subtracted data, numbers taken from Dr. Rodin's review) for trough blood pressure measurements (week 6 data and end-point data would have less of a slope). As can be seen, there is relatively clear dose-response relationship (again a positive number means that there was a decrease in blood pressure from baseline) in study 622. The inferential statistics calculated by Dr. Nuri are sufficiently convincing, to conclude that the numbers coming from the study differ from those that would come from a table of random numbers and that the description of those numbers as a function of dose (Figure 2) are as reasonable a description as was the case for Figure 1 that described the peak effects as a function of once-a-day dosing. The fit (again using the natural logarithm) gave the following results:

Systolic Effect = 4.37 * ln(Dose) -2.8
Diastolic Effect = 1.99 * ln(Dose) -2.5.

Moreover, the results of study 622 are in keeping with all of the results of once-a-day dosing on peak blood Pressure Effect(see Figure 3, below). So, I see no compelling reason to declare that the results of study 622 need to be interpreted as showing that moexipril should be considered ineffective when given in a BID regimen. To the contrary, I think the results of study 622, in conjunction with the results of all other studies, show that moexipril has antihypertensive activity when administered once-a-day or twice-a-day and being able to make such a statement is all that we require to approve an anti-hypertensive drug (clinically meaningful "effect" implied by lower blood pressure).

The lines drawn in Figure 3 (this page) are the ln fit to the same S and D data points shown in Figure 2. I once again, say that to my eye, the results of study 622 (trough blood pressure effects) are closer to the peak effects seen in studies 638, 640 and 651 (presumably the only studies where a peak effect was measured) than they are to the graph of trough blood pressure response shown in Figure 1 of Dr. Karkowsky's memorandum. Although there is a lack of definitive data (no QD and BID data in the same randomized population), I assert that it would be a greater error to declare BID an ineffective regimen than it would be to declare both BID and QD effective regimens. I do not deny that only the QD regimen has individual trial data that, by two point comparisons,meets conventional criteria for the 15, 30 and 60 mg doses. That is what qualifies moexipril as having been shown to have antihypertensive activity like that of the 8 ACE inhibitors that preceded it. That is also what allows, in my judgment, the freedom to extract the "best" description of its effects as a function of administered dose. The overall considerations then lead me to conclude that moexipril has antihypertensive activity when administered once-a-day or twice-a-day. I cannot conceive of the model that would predict that an ACE inhibitor that unequivocally has antihypertensive activity in a once-a-day regimen, loses antihypertensive activity (really loses potency) when given more frequently than once-a-day. Nor do I think the available data for moexipril require that one consider the applicability of a model that I cannot conceive.

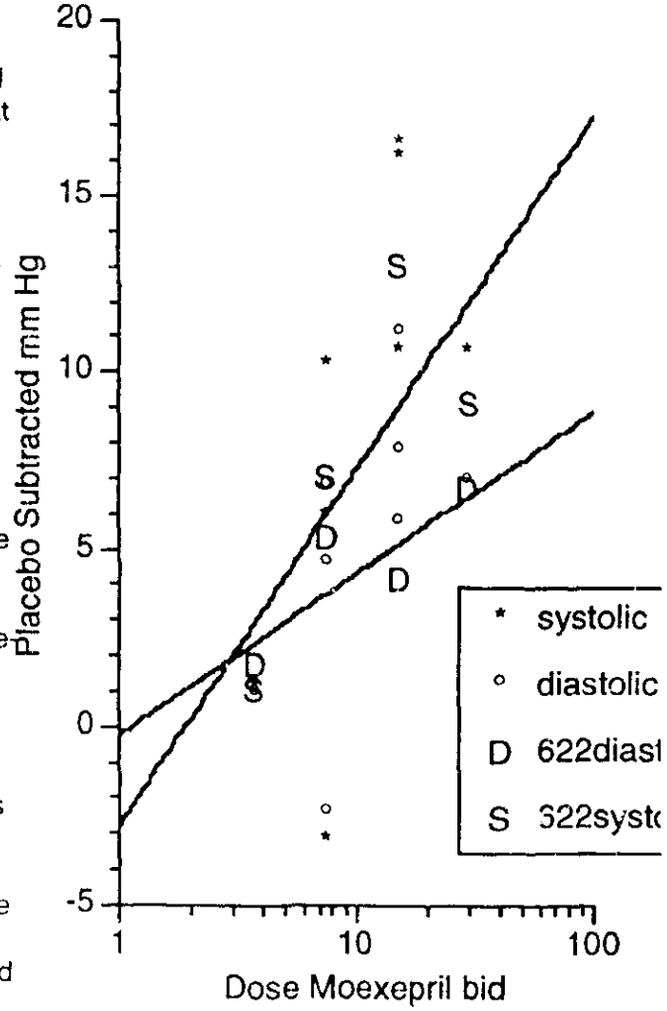

Figure 3 Peak Effect other studies and Study 622 trough effect, Dose-Response

So, all of the above for adding five words to the dosing and administration section of the package insert. Namely, to add "or two equally divided doses." Not a trivial addition. There is absolutely no reason to have moexipril join the ranks of ACE inhibitors that have a once-a-day claim. The data for moexipril do not support such a claim. Although once-a-day may be fine in some circumstances, twice-a-day could be necessary in other circumstances and there is every reason to think that such a regimen would be "better" in some patients when once-a-day would not suffice. Moexipril is not a once-a-day ACE inhibitor.

Although I am convinced that combination therapy is "appropriate," particularly when one can start with lower doses of two agents than is readily available, I think that it is not appropriate to recommend that one add another agent until one has explored the entire useful dosing regimen for a single agent. I think the entire useful dosing range for moexuipril is 7.5 to 60 mg, once -a-day or twice-a-day (in two equally divided doses. (Why take the second drug's non-dose dependent side effects unless the first drug has inadequate efficacy?). To propose that the entire useful dosing regimen for moexipril

excludes BID is not in keeping with all of the data available for moexipril and/or the results of other ACE inhibiotr antihypertensive trials

Raymond John Lipicky, M.D.

cc: Orig. NDA
HFD-110
HFD-110/CSO
HFD-110/RLipicky
ef:12/14/93

MEMORANDUM

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

DATE: 11/30/93
FROM: Dr. Abraham Karkowsky, Supervisory Reviewer HFD-110

TO Dr. Raymond Lipicky, Director , Division of Cardio-Renal Drug Products

SUBJECT: Approvability of NDA 20-312, Moexipril Hydrochloride (sponsor: G. H. Besselaar Associates).

This memorandum, based on the accompanying reviews, constitutes my, and should you agree the Division's, rationale for the approval of moexipril for the treatment of hypertension. A marked-up copy of labeling is included. The SBA, also included with the package, was only lightly edited. There is little doubt that moexipril through its de-esterified metabolite is an effective inhibitor of angiotensin converting enzyme. There is also little doubt that moexipril is useful as an antihypertensive. Several, issues, however are briefly outlined below and expanded upon later in the memo.

First, based on the totality of data in this submission, there is at best, only a modest relationship of blood pressure effect to dose. Moexipril, in this sense, is similar to already approved ACE inhibitors. Despite the nearly flat dose-response relationship, the dose range chosen by the sponsor, 7.5 to 30 mg once daily, seems reasonable. Doses as low as 3.75 mg daily, and perhaps even lower, may be effective with concurrent diuretic treatment.

There did not appear to be an appreciable increase in trough diastolic blood pressure response over the order of magnitude range of doses which were studied in moexipril's development program. It is, therefore, unlikely that any modest dose increases would translate into substantial additional blood pressure responses. Unless we are willing to push the dose up by more than an additional order of magnitude, it is unlikely that more convincing dose-response information will be available. It is my opinion that a 3-5 mm Hg effect consistently noted at trough, is sufficient to allow approval of this drug at these doses.

Second, there is no convincing data within this NDA that the blood pressure effects of moexipril are uniformly sustained throughout the interdosing interval. The treating physician should, therefore, be encouraged to make dosing recommendations based on trough blood pressure measurements.

What recommendation should be included for those individuals whose blood pressure is not adequately controlled at trough by maximum moexipril doses? Since there were two well-controlled studies which demonstrated an additional blood pressure response while on diuretic, I would recommend that concurrent diuretic therapy be considered. The alternative approach of dividing the total daily dose into two equal portions is not supported by the data within this submission. Only a single study was performed in which moexipril was administered in a BID regimen. Surprisingly, the study did not demonstrate convincing benefit of the BID regimen in

the proposed dosing range .

Lastly, although the sponsor seeks approval of the dosing range of 7.5 to 30 mg daily, legitimate concerns can be raised whether there is sufficient safety information for the highest dose (see issues under formulations). The 30 mg to-be-marketed dose (2 x 15 mg) differs in composition from the studied 30 mg dose. I have to admit that my recommendation for approval of even this high dose rests largely on the generally benign safety profile of moexipril. Furthermore, there is a reasonable empirical data base, a cohort of subjects treated with doses of up to 60 mg daily (again the formulation is not well characterized), in which nothing "terrible" happened. The safety data from this 60 mg cohort adds a factor of two to the safety cushion. Even though the 30 and 60 mg dosage forms studied in the clinical trials cannot directly be linked to the to-be-marketed formulation, it is unlikely that these formulations are so drastically different (based on the noted efficacy) as to constitute a safety concern.

Pharmacology:

Moexipril, through its active metabolite moexiprilat, seems to be another relatively benign non-sulfhydryl ACE-inhibitor. The only issue in the otherwise uncomplicated pharmacology profile of moexipril was raised by the statistical reviewer in the interpretation of the mouse carcinogenicity study. In that review, both the adequacy of the study as well as the possibility that moexipril was a tumorigen were raised. Neither of the issues raised by the statistical reviewer, I believe, is supportable by the data.

With respect to the adequacy of the study, the statistical reviewer sets criteria for duration of exposure in animals that would allow a "no carcinogenic effect" conclusion. The duration of survival for animals in the mouse study is shown below as Table 1 (derived from Dr. Rahman's review). Several criteria are noted in Dr. Rahman's review in order to demonstrate the adequacy of an individual study. One criterion[1] sets a minimum survival of 50% of the exposed animals at one year, to assure that there was adequate exposure to drug. Using this criterion, the mouse study appears adequate. Also cited by the statistical reviewer is a second criterion, that 50% of the initial group of animals in the high-dose group should survive through 80-90 weeks. This latter criterion stems from personal communication with Dr. Haseman of the National Toxicology Program and is much stricter in defining the adequacy of a dose within a study. Our Division is generally comfortable in accepting a carcinogenicity study as demonstrating adequate exposure of animals to drug if substantially fewer animals survive to 80-90 weeks (approximately 20% or greater survival in the high-dose group). Consequently, based on the published criterion as well as the criterion generally applied by our Division, the duration of exposure in the high-dose group in this study is adequate.

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[1] Chu, Cueto and Ward, Journal of Toxicology and Environmental Health 8: 251-280, 1981.

Table 1

Percent Survival, Mice Carcinogenicity Study Related to Duration of Exposure High Dose Group

Sex	End of 52 Weeks	End of 75 Weeks	End of Study (83 weeks)
Male	87	47	28
Female	75	35	23

With respect to tumorigenicity, there appears to be a positive trend in the mouse study, limited to axillary node lymphomas. In considering all lymphomas, no significantly positive trend is evident (trend test p value =0.17). Since there does not appear to be any biologic reason for the lymphomas to specifically affect axiliary nodes, this apparent positive finding is an artifact of *post-hoc* and multiple subgroup analyses and should not be considered meaningful. There is, consequently, no compelling evidence in either carcinogenicity study to suggest that moexipril is a carcinogen. In fact, the "no-effect" conclusion seems the appropriate based on this study.

Formulations:

During the evolution of the moexipril development program several formulations of moexipril were used in clinical trials. Table 2 is a summary of the pertinent formulations and their relationship to the to-be -marketed formulation. The to-be-marketed 15 mg formulation is designated as Formulation L. The to-be-marketed 7.5 mg formulation is proportionately equivalent in ingredients to Formulation L.

Formulation L was, in turn, found to be bioequivalent to formulation B (Study PHAKI-794). Formulation B is a capsule filled with a mixture of moexipril and excipients. Formulation C3, also a filled capsule, was the 15 mg capsule used in the clinical studies. Formulation C3 differed from formulation B only in that all components of the capsular mixture of C3 were present in a 5% proportional overage compared to Formulation B.

Formulations C2 and C4 are the 7.5 and 30 mg moexipril formulations which were used in the clinical studies. They are not proportionally equivalent in ingredients to C3 or to each other. There is, furthermore, no bioequivalence data directly linking formulations C2 and C4 to the 7.5 or 15 mg dose of Formulation L.

Table 2
Formulations of Moexipril and Their Relationship to the To-Be-Marketed Formulation

Dose Size	Formulation Description	Relationships:
15 mg	Formulation L-Tablet	To-be-marketed formulation. This formulation was studied also in PHAKI-796 the food-effect study.
7.5 mg	Formulation L-Tablet	To-be-marketed formulation of 7.5 mg. It is proportional in ingredients to 15 mg formulation L.
15 mg	Formulation B-capsule	It is bioequivalent to formulation L.
15 mg	Formulation C3-capsule	This was the 15 mg dose used in most of the clinical studies. It is equivalent in proportion to formulation B with the exception that formulation C3 contains a 5% overage of all ingredients.
7.5 mg	Formulation C2-capsule	This is the 7.5 mg dose used in most clinical trials- there is no *in vivo* or *in vitro* data that defines its relationship to either formulation L or formulation C3
30 mg	Formulation C4-capsule	This is the 30mg dose used in most clinical trials- there is no *in vivo* or *in vitro* data that defines its relationship to either formulation L or formulation C3

Unfortunately, the pharmacokinetics of moexipril is formulation dependent (see study GHBA 619). Furthermore, the absolute bioavailability estimates of moexipril are extremely low (18-22%). Thus, the potential for mischief which could result from unreliable formulations is large.

I do not, however, believe that the lack of equivalence of the 7.5 or 30 mg doses used in clinical studies is a matter of concern either from an efficacy or a safety standpoint.

With respect to efficacy, since the 15 mg to-be-marketed formulation of moexipril can be directly linked to the 15 mg formulations which demonstrated efficacy in clinical trials, there is little doubt that the recommended doses (7.5-30 mg) will be effective in the treatment of hypertension.

With respect to the safety of the "to-be-marketed" 30 mg dose of moexipril (2 x 15 mg ot

Formulation L), the data within the NDA supports its safety. First, there are only modest differences between the approved 7.5 and 30 mg dose and the formulations used in the clinical studies (Formulations C2 and C4). The differences are in the amount of microcrystalline cellulose (3-12 % higher for Formulation C3 relative to the other two formulations-C3 is bioequivalent to the to be marketed 15 mg dose) and lactose (4-13% lower for Formulation C3 relative to the other formulations). It is unlikely that the large differences in bioavailability noted in study GHBA 619 will be reproduced by these minor changes to the formulation. In study GHBA 619 there was a conscious attempt to retard moexipril's absorption. Second, there is a reasonable cohort of subjects treated with 60 mg daily of moexipril. The adverse event profile of subjects treated with 60 mg/ day was not particularly alarming. It is therefore highly unlikely that treatment with 30 mg of Formulation L will exceed the safety range of the 60 mg doses use. Consequently, the safety of doses of moexipril, up to 30 mg daily, is supported by the NDA.

Efficacy:

A total 8 of placebo-controlled, clinical trials support the approvability of moexipril (see Table 3). The studies include one placebo-withdrawal study (study #643) one study in the elderly (study #640), one study with superimposed hydrochlorothiazide (study #644) and one factorial-design study with and without low doses (12.5 mg/day) of hydrochlorothiazide (study # 638). All clinical trials, except for one, demonstrated a decrease in trough sitting diastolic blood pressure while subjects were treated with moexipril. In most studies this blood pressure effect was statistically significant at doses of 7.5 mg and greater, administered once daily. In most studies, once daily doses afford a 3-5 mm Hg decrease at trough. With concurrent hydrochlorothiazide therapy doses as low as 3.75 mg, and perhaps lower doses, might be useful.

The one anomalous study (#651) is substantially smaller than the other studies (n=16-18/group) and consequently, this study has less power to ascertain efficacy. The apparent lack of effect of the 7.5 mg dose in this study, although somewhat surprising, is not inconsistent with the trough blood pressure decreases noted in other studies in which this dose was administered. My own conclusion, supported by the vast majority of the data, is that moexipril given once daily at doses of 7.5-30 mg has a reasonable effect on trough blood pressure.

Table 3. Blood Pressure Response (Systolic/Diastolic) [illegible]g. Placebo Corrected. Bold Italicized Values Are Significant Different From Placebo

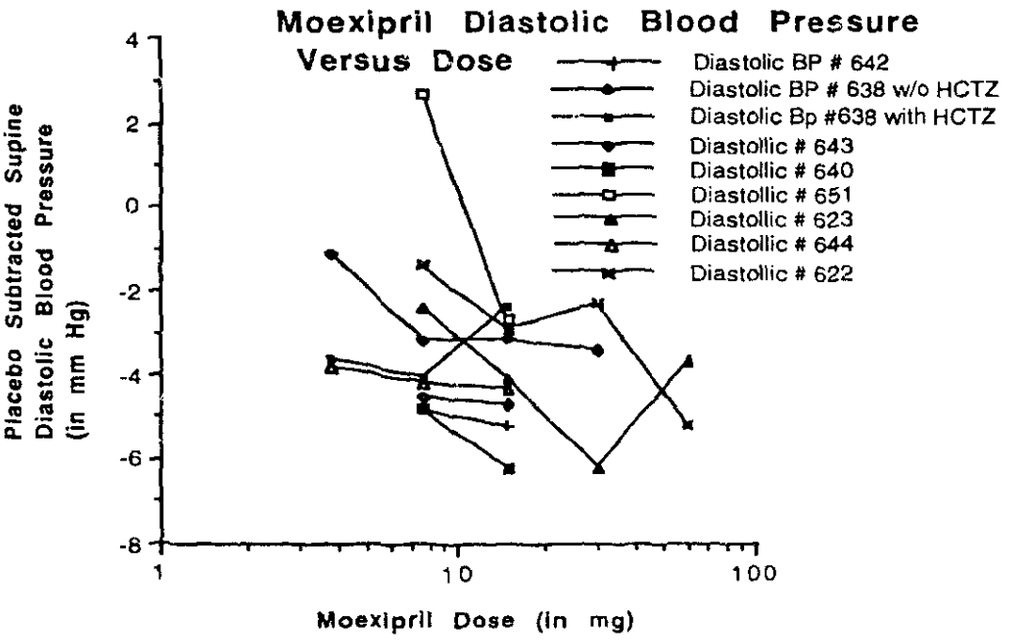
Trial Number	Description	No. of Subjects/ Treatment	Formulation/ Dose	3.75 mg	7.5 mg	15 mg	30 mg	60 mg
#642	12-Week, PBO-C, DB, II Study- Endpoint ITT Analysis- Trough	47-51	Once Daily Dose Formulations C2 =7.5 mg C3= 15 mg		***-7.1/*** ***-4.8***	***-10.7/*** ***-5.2***		
#638	8-week, PBO-C, DB, II Study With and W/O 12.5 mg HCTZ- ITT Analysis- Trough	42-49	Once Daily Dose Formulations C1= 3.75 C2 =7.5 mg C3= 15 mg C4= 30 mg No HCTZ	-0.5/ -1.1	***-4.0/*** ***-3.2***	***-4.4/*** ***-3.1***	***-5.3/*** ***-3.4***	
	ITT Analysis Trough- With HCTZ Alone Subtracted	39-48	Formulations Are as Above. With 12.5 mg HCTZ-	-5.1/ ***-3.6***	-5.3/ ***-4.1***	***-6.6/*** -2.4		
#643	12-Week,PBO-C, Withdrawal Study. Trough Analysis of Withdrawal- ITT	46-48	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg		-2.6/ ***-4.5***	***-11.4/*** ***-4.7***		
#640	8-Week, PBO-C DB, II, Also HCTZ (25 mg), In Elderly (65 -80 Years Old). ITT Analysis Endpoint Trough	49-51	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg	-1.0/ ***-4.8***	-5.8/ ***-5.2***			
#651	8-week, PBO-C, DB, II Study, Ambulatory as Well as Office BP Measurements- Endpoint ITT Trough-Ambulatory measurements	16-18	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg		-0.2/ +6.0	-7.9/ +3.0		
	As above but Ambulatory Data- Trough	13-15	Once Daily Oral Formulation: C2 = 7.5 mg C3= 15 mg		+5.1/ +2.7	-6.9/ -2.7		
#623	6-week, PBO-C, DB, II study- Endpoint ITT Analysis Trough	60-65	Capsule Formulations-First 40 Patient's Formulations Contained No Vegetable Oil- After That Formulations Contained Vegetable Oil		-4.6/ -2.4	***-8.0/*** ***-4.1***	***-10.0/*** ***-6.2***	***-7.1/*** ***-3.7***
#644	8-week, PBO-C, DB, II study, with HCTZ 25 mg Daily	49-52	Once Daily Dose Formulations C1= 3.75; C2 =7.5 mg; C3= 15 mg					
#622	PBO-C , DB, II study. Three phases to study. Phase 1- dosing of 0-15 mg BID; 1 week Phase 2- BID dosing 0-30 mg; 6 weeks Phase 3- down-titration phase -0-15 mg BID ; 2 weeks ITT of Phase 2.	38-40	Uncharacterized formulations -relative to the to-be marketed formulation		-1.0/ -1.4	-6.1/ -2.9	***-11.4/*** -2.3	-5.3/ -5.2

Abbreviations: PBO-C = placebo controlled; DB= Double Blind; II = parallel; HCTZ= hydrochlorothiazide; ITT= intention to treat; DR= Dose Response Tx=Treatment Group

Dose Response:

There is only a minimal dose-related increase in blood pressure response considering the range of 3.75 to 60 mg (Figure 1). It, therefore, does not seem reasonable to examine greater doses, unless extremely large dose escalations i.e. an order of magnitude, are planned. Study # 651 has the greatest apparent change in effect with dose but at the lowest dose in that study moexipril seems inferior to placebo. As noted above, study #651 is smallest and least reliable of the studies.

Figure 1



Perhaps the converse question is worth considering. Did the sponsor choose sufficiently low doses to study? From a pragmatic point of view, since adverse events did not increase with dose, aside from the aesthetic considerations, no strong objections can be raised that there is a pressing need for the exploration of lower doses.

Dosing Interval:

The sponsor proposes that moexipril be administered once daily and perhaps twice daily, if necessary. With respect to administering moexipril once daily, there is no compelling evidence that during chronic treatment a substantial amount of the blood pressure effect at trough, relative to peak, remains at the end of the once-daily dosing interval. Table 4 contains all the pertinent peak and trough information for moexipril. In all studies shown in Table 4, moexipril was administered once daily. There are three sets of data. Study #638 accumulated peak and trough data for subjects randomized to moexipril at several doses with and without HCTZ. Only the data in the absence of hydrochlorothiazide are shown. Study # 640 examined the effects in elderly, and study #651 was a small ambulatory blood pressure study.

Except for the study in the elderly there did not appear to be overwhelming consistency that blood pressure control was constant throughout the dosing interval. Higher doses even in the non-elderly population, however, appear to retain a greater proportion of their blood pressure effects at trough.

Nevertheless, aside from substantial peak blood-pressure responses, which did not appear to translate into increases in adverse events, the submission does not seem to contain data which suggests that overall safety is compromised either by increasing concentrations of moexipril/ moexiprilat or by increasing doses (Table 5; adapted from P. 00235 of the DRAFT SBA) . It would therefore, be reasonable, assuming that blood pressure is measured at the interdosing interval, to recommend a once-daily dosing interval for moexipril.

With respect to what action to take if the patients blood pressure is inadequately controlled on the maximum once daily dose of moexipril, the most reasonable course is to add diuretic to the therapy. There is insufficient information contained within this NDA to recommend BID therapy.

Only a single BID study was submitted (study # 622). Unfortunately, the study did not demonstrate a statistical significant treatment effect (p value for treatment effect by corrected ANOVA=0.065). In addition, the magnitude of the trough effect in the dosing range of up to 30 mg/day seems less than the effect seen with once a day therapy (see Table 2-the data are listed as total daily doses). Furthermore, the formulation used in this study is not adequately described within the submission and its relationship to the to-be marketed formulation would be totally speculative.

Although it is both intuitive and logical to expect better control of trough blood pressures when administering moexipril as a BID dose, there is a lack of empirical support for this recommendation. In fact the most logical use of the empirical data would be to suggest that once daily is superior to twice daily dosing.

Table 4

Peak and Trough, Diastolic and Systolic Blood Pressures and The Trough/Peak Ratios,-Placebo Subtracted Data (Values in Bold are Statistically Different From Placebo NA= not assessable;

Trial No. pts/group	Dose (mg)	(P) = Peak (T)=Trough	Systolic	Diastolic	Trough/ Peak
# 638 without Hydrochlorothiazide (40-48)	3 75	(T)	-0.2		
		(P)	-1.0		0.2
		(T)		+0.4	
		(P)		-0.8	NA
	7.5	(T)	-3.0		
		(P)	**-5.8**		0.52
		(T)		-0.7	
		(P)		**-4.5**	0.16
	15	(T)	**-6.3**		
		(P)	**-10.5**		0.60
		(T)		-2.2	
		(P)		**-5.7**	0.39
	30	(T)	**-7.7**		
		(P)	**-10.5**		0.73
		(T)		**-4.3**	
		(P)		**-6.8**	0.63
# 640 elderly (45-50)	7.5	(T)	-0.5		
		(P)	**-10.1**		0.05
		(T)		**-3.7**	
		(P)		**-6.7**	0.55
	15	(T)	**-8.8**		
		(P)	**-16.4**		0.54
		(T)		**-6.3**	
		(P)		**-7.7**	0.82
# 651 ambulatory (13-15)	7.5	(T)	+5.1		
		(P)	+3.3		NA
		(T)		+2.7	
		(P)		+2.5	NA
	15	(T)	-6.9		
		(P)	**-16.0**		0.43
		(T)		-2.7	
		(P)		**-11.0**	0.25

Table 5

Dose Related Adverse Events By Dose in Mono-therapy Arms of Placebo Controlled Once Daily Clinical Trials (Double-Blind Segments of Studies #623, #638, #640, #642 and #651)

Adverse Experience	Number (%) of Patients					
	Placebo (N=226)	3.75 mg (N=49)	7.5 mg (N=224)	15 mg (N=230)	30 mg (N=110)	60 mg (N=61)
Headache	27 (12)	5 (10)	18 (8)	23 (10)	13 (12)	5 (8)
Cough Increased	5 (2)	3 (6)	12 (5)	13 (6)	8 (7)	5 (8)
U. R. I.	15 (7)	2 (4)	8 (4)	15 (7)	4 (4)	3 (5)
Dizziness	5 (2)	2 (4)	11 (5)	9 (4)	3 (3)	4 (7)
Diarrhea	5 (2)	1 (2)	11 (5)	7 (3)	1 (1)	1 (2)
Flu-syndrome	0 (0)	0 (0)	9 (4)	7 (3)	3 (3)	2 (3)
Pain	10 (4)	3 (6)	6 (3)	4 (2)	5 (5)	3 (5)
Rhinitis	9 (4)	3 (6)	6 (3)	6 (3)	3 (3)	3 (5)
Fatigue	4 (2)	1 (2)	7 (3)	3 (1)	3 (3)	2 (3)
Dyspepsia	5 (2)	0 (0)	3 (1)	5 (2)	2 (2)	3 (5)
Nausea	4 (2)	0 (0)	7 (3)	4 (2)	1 (1)	0 (0)
Peripheral Edema	5 (2)	1 (2)	3 (1)	6 (3)	1 (1)	1 (2)
Pharyngitis	2 (1)	0 (0)	5 (2)	4 (2)	2 (2)	1 (2)
Flushing	0 (0)	0 (0)	4 (2)	3 (1)	2 (2)	2 (3)
Rash	2 (1)	0 (0)	5 (2)	4 (2)	1 (1)	1 (2)
Sinusitis	7 (3)	0 (0)	6 (3)	1 (<1)	3 (3)	0 (0)
Myalgia	0 (0)	1 (2)	1 (<1)	4 (2)	1 (1)	2 (3)
Chest Pain	3 (1)	0 (0)	6 (3)	0 (0)	1 (1)	1 (2)
mean exposure (SD) in days	56 (19)	57 (6)	57 (18)	56 (19)	47 (11)	39 (9)

Safety:

There is adequate data contained within this submission to define moexipril's safety profile. A total of 2,441 individuals received moexipril. Of these individuals, 1,745 were exposed to moexipril as mono-therapy, 544 patients to moexipril plus hydrochlorothiazide and 152 to moexipril and nifedipine retard. Median duration of exposure to moexipril was 2-3 months. There were 417 unique individuals exposed to moexipril for greater than 6 months.

As noted above, adverse events on moexipril did not appear to be dose related. Aside from an increase in the frequency of large first dose drop in systolic blood pressures upon standing, which may well be considered an extension of the intended pharmacological action of moexipril, no other dose related effects are discernable (see Table p. 00235 of DRAFT SBA). Parenthetically, this increased orthostatic effect was not frequently associated with symptomatic orthostasis.

Table 6 is a tabulation Moexipril's most frequent adverse events culled from placebo controlled clinical trials (Appendix 5 p 00308 of the DRAFT SBA). The duration of treatment in these studies ranged from 6-12 weeks (mean days of therapy 56± 19 for placebo and 53 ± 17 for moexipril). The adverse event profile of moexipril is only slightly increased over placebo (48.4% versus 45.1%). The specific adverse events are similar to those noted with other ACE inhibitors.

Adverse events which appear to be increased in the moexipril group over placebo are cough, dizziness, flu syndrome, flushing and myalgia. Hyperkalemia, paresthesia, increases in liver function enzymes, hyperkalemia and creatinine increases may also be increased in the moexipril treated group.

Table 6

Selected Adverse Events in Placebo Controlled Portions of Clinical Trials Number of Subjects With Event (%)

Adverse Event	Moexipril N= 674	Placebo N=226
Overall	326 (48.4)	102 (45.1)
Headache	64 (9.5)	27 (11.9)
Cough Increased	41 (6.1)	5 (2.2)
Upper Respiratory Infection	32 (4.7)	15 (6.6)
Dizziness	29 (4.3)	5 (2.2)
Diarrhea	21 (3.1)	5 (2.2)
Flu syndrome	21 (3.1)	0 (0)
Pain	21 (3.1)	10 (4.4)
Rhinitis	21 (3.1)	9 (4.0)
Fatigue	16 (2.4)	4 (1.8)
Dyspepsia	13 (1.9)	5 (2.2)
Nausea	12 (1.8)	4 (1.8)
Peripheral Edema	12 (1.8)	5 (2.2)
Pharyngitis	12 (1.8)	2 (0.9)
Flushing	11 (1.6)	0 (0)
Rash	11 (1.6)	2 (0.9)
Myalgia	9 (1.3)	0 (0)
Hyperkalemia	7 (1.0)	0 (0)
Hyperesthesia	7 (1.0)	1 (0.4)
Paresthesia	7 (1.0)	0 (0)
Insomnia	7 (1.0)	1 (0.4)
SGPT Increased	6 (0.9)	0 (0)
Somnolence	6 (0.9)	1 (0.4)
Creatinine Increased	5 (0.7)	0 (0)
Hypertonia	5 (0.7)	0 (0)

Myalgia:

The only adverse events that perhaps deserves some comment is the increase in myalgia in the moexipril group. In addition to myalgia, there appears to be an increase in "flu symptoms" presumably, these flu symptoms also contain a component of myalgia. In the only study in which CPK was measured, 25% of the subjects had elevated measurements of this enzyme (3/12). Unfortunately, no subfractioning of the CPK was attempted and consequently, the origin of the CPK is suggestive but not definitively assignable to striated muscle. Nevertheless, putting this whole picture together, the increase in CPK associated with myalgia and increase in flu-syndrome suggests that moexipril has some effect on muscle.

Moexipril, nevertheless should still be approvable. Myalgias were always mild-moderate in intensity, spontaneously resolved and did not appear in any description of discontinuations of the moexipril-treated patients. Of interest is that myalgia is noted as an adverse event in all the presently approved ACE inhibitors, either alone or as part of an autoimmune syndrome consisting of positive ANA, fever, arthritis/arthralgia, serositis and elevated ESR. In this superficial respect moexipril does not seem to be different from currently approved ACE inhibitors.

Deaths, Dropouts and Discontinuations:

Deaths were tabulated for all those who died while on therapy, within two-weeks of therapy or as a result of an event which occurred during therapy even if death occurred subsequently. A total of 6 subjects died who were enrolled in the clinical development program of moexipril. Two of the deaths occurred in subjects not taking moexipril, four in subjects treated with moexipril. Capsular summaries for the deaths are appended to this review as Appendix A.

The number of discontinuations due to adverse events from the placebo-controlled portions of the double-blind mono-therapy trials was only slightly greater for moexipril-treated patients than placebo 23 (3.4%) versus 4 (1.8%). Much of the difference could be attributable to those receiving moexipril who discontinued due to cough and rhinitis (6 (0.9%) versus 0). There were a total of 124 subjects who discontinued therapy at some point either from moexipril mono-therapy or from the combination of moexipril with either hydrochlorothiazide or nifedipine. The tabulated listings can be found on page 00244 of the DRAFT SBA; capsular synopsis are found on page on pp. 334-396 of the DRAFT SBA).

Of these who discontinued, one subject discontinued due to creatinine increases with concurrent decreases in creatinine clearance (baseline creatinine 137 umol/L baseline CCr 46.8 ml/min; on day 15 of therapy creatinine was 160 umol/l, CCr 39.5 ml/min). A follow-up exam one week post discontinuation showed no change in these parameters (creatinine 159 umol/l and CCr 39.5 ml/min). One subject developed modest thrombocytopenia (115,000 x 10^3/uL; pretherapy with moexipril which remained constant during the observation period 109- 120 x10^3/uL).

Other Issues:

Although the EER has been requested the inspection has yet to be performed. There are still some outstanding issues in chemistry, all of them minor such that the approvability recommendation

would not be affected. The last safety update was submitted on April 30, 1993 and was incorporated into Dr. Chun's review.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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

MAR 10 1994

NDA #: 20-312

Name of Drug: Moexipril hydrochloride tablets

Sponsor: G.H. Besselaar Associates

Type of Submission: Safety Update

Date of Submission: February 2, 1994

Date of Review: February 18, 1994

Reviewer: Sughok K. Chun, M.D., HFD-110

A. Resumé:

This is a Safety Update for the above-referenced NDA. The last Safety Update for Moexipril (MX) was submitted on April 30, 1993. This update provides cumulative safety data for all completed clinical trials conducted with MX. Approx 60 additional pts have been exposed to MX since the last update and are included in the new update, as well as additional long-term experience with pts previously exposed to MX. In addition, data for deaths, serious adverse experiences (AEs) and AEs resulting in discontinuation are provided for ongoing clinical trials.

This safety update provides pooled, cumulative information on the safety of MX from all completed clinical studies conducted in the United States and Europe. Since the last safety update of April 30, 1993, a one-year, open-label extension for the study GHBA-642 has been completed, as well as the second-year extension to study GHBA-640. These data are included in the pooled safety information.

The safety of MX was evaluated in 12 controlled and 6 uncontrolled studies in hypertensive pts who were treated from 1 day to 1-2 yrs. Table 1 shows the distribution of the studies and the number of pts exposed to MX. Some pts received MX both alone and in combination with HCTZ and are included in the total counts for both treatments, as are the pts who were entered in more than one study.

Table 1

DISTRIBUTION OF CONTROLLED AND UNCONTROLLED STUDIES AND NUMBER OF PATIENTS EXPOSED TO MOEXIPRIL IN THOSE STUDIES

Study Category	Protocol Numbers	Number of Studies	Number of Patients		
			Moexipril Alone	Moexipril + HCTZ	Moexipril + Nifedipine Retard
Controlled Studies					
Once-Daily Dosing (Placebo-Controlled)	622, 638, 640, 642, 644, 649, 651	7	674	288	152
Withdrawal	643	1	223	—	—
Twice-Daily Dosing	622	1	164	—	—
Active-Controlled	645, 647, 648	3	193	56	—
Subtotals	—	12	1251[a](1254)	344	152
Uncontrolled Studies					
Short-term	618, 641	2	91	23	—
Long-term	624, 638OL, 640OL, 642OL	4	753	283	—
Subtotals	—	6	844	306	—
GRAND TOTALS		18	2095[a](2098)	650	152
UNIQUE PATIENTS[b]		—	1804	612	152

a Three patients who received moexipril in both studies 638 and 643 are not included in the total.

b Newly exposed patients. (Patients who participated in more than one study are counted only once.)

Table 2 presents the total duration of exposure for pts who were exposed to MX as monotherapy in all studies combined (controlled and uncontrolled). Over 1800 hypertensive pts were exposed to MX monotherapy), with 401 hypertensive pts being treated for greater than 6 mos.

Table 2

DURATION OF EXPOSURE TO STUDY DRUG BY TOTAL DAILY DOSE
IN THE EVALUATION OF DRUG SAFETY

MOEXIPRIL ALONE

Duration of Exposure	Number (and Percent) of Patients Treated						
	3.75 mg	7.5 mg	15 mg	30 mg	60 mg	120 mg	Any dose
1 Day	0(0%)	9(1%)	8(1%)	5(1%)	1(1%)	0(0%)	13(1%)
2 - 7 Days	11(4%)	98(8%)	71(7%)	62(15%)	11(6%)	3(7%)	18(1%)
8 - 29 Days	72(24%)	381(31%)	287(29%)	140(34%)	46(24%)	8(18%)	124(7%)
1 - 2 Months (30-59 Days)	126(42%)	264(21%)	229(23%)	126(30%)	88(46%)	4(9%)	540(30%)
2 - 3 Months (60-89 Days)	56(18%)	181(15%)	135(14%)	34(8%)	19(10%)	3(7%)	343(19%)
3 - 6 Months (90-179 Days)	21(7%)	146(12%)	137(14%)	15(4%)	15(8%)	14(32%)	365(20%)
6 - 12 Months (180-359 Days)	15(5%)	51(4%)	40(4%)	12(3%)	11(6%)	12(27%)	155(9%)
> 12 Months (>359 Days)	2(1%)	111(9%)	75(8%)	21(5%)	0(0%)	0(0%)	246(14%)
Total	303	1241	982	415	191	44	1804

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB+OL) 640(DB+OL) 641(OL) 642(DB+OL) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

END

Over 2200 hypertensive pts were exposed to MX alone or in combination, with 583 of these pts being treated for greater than 6 mos. For the categories that present MX in combination with another drug, 12.5 mg, 25 mg, and 50 mg HCTZ doses and 40 mg nifedipine dose.

Demographics of pts are shown in Table 3. Most of the pts comprising the total study population were men (66%) and most of the pts were white (81%). Pt ages ranged from 20-87 yrs (mean, 56.4 yrs).

Table 3: SUMMARY OF PATIENT DATA IN THE EVALUATION OF DRUG SAFETY

Patient Data	Moexipril Alone	Moexipril + HCTZ	HCTZ Alone	Placebo Alone	Moexipril + Nifedipine
Sex					
Male	1185(65.7)	399(65.3)	117(59.4)	251(69.5)	108(71.1)
Female	619(34.3)	212(34.7)	80(40.6)	110(30.5)	44(28.9)
Race					
Caucasian	1436(79.6)	517(84.6)	172(87.3)	280(77.6)	149(98.0)
Black	244(13.5)	51(8.3)	16(8.1)	50(13.9)	0
Hispanic	81(4.5)	39(6.4)	9(4.6)	19(5.3)	0
Asian	7(0.4)	0	0	3(0.8)	0
Other	29(1.6)	4(0.7)	0	7(1.9)	3(2.0)
Unknown	7(0.4)	0	0	2(0.6)	0
Age (years)					
< 65	1243	421	108	242	125
>= 65	561	190	89	119	27
Total Patients	1804	611	197	361	152
Mean	56.8	57.2	59.7	56.9	55.4
Minimum					
Maximum					
Unknown	0	0	0	0	0
Weight (lb)					
N	1804	588	197	361	151
Mean	153.8	154.5	156.0	152.4	158.2
Minimum					
Maximum					
Unspecified	0	23	0	0	1
Duration of Hypertension (yrs)					
N	1748	589	192	350	142
Mean	11.1	10.2	11.0	10.8	7.9
Minimum					
Maximum					
Unspecified	56	22	5	11	10

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB+OL) 640(DB+OL) 641(OL) 642(DB+OL) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

Safety Data of GHBA-642 OL (one-yr extension and GHBA-640 OL (second yr extension) are reviewed. The study protocols of GHBA-642 OL and, - 640 OL are the same. They were a continuation of a double-blind, placebo-controlled, parallel group study in pts with mild to moderate essential HTN (SiDBP 95-114 mm Hg, inclusive). In the double-blind study, pts had been randomized to receive placebo, MX 7.5 mg, MX 15 mg. or HCTZ 25 mg once daily for 8 wks. All pts entered the open-label extension period receiving MX 7.5 mg +HCTZ 25 mg, and MX 15 mg +HCTZ 25 mg, in that order, were allowed if the SiDBP was ≥ 90 mm Hg.

The pts accounting of these studies were:

	640 OL	642 OL
Entered OL	172	130
Completed 1 yr	135	96
Completed 2 yrs	119	-
D/C for AE during 1st yr	18	16
D/C for AE during 2nd yr	10	-

Pt narratives of each case is shown in Table 4. Only 11 out of 28 pts in Study 640 OL, and 8 of 16 pts in Study 642 OL were d/ced the study due to probably/possibly MX related AEs during 1-2 yr extension period: cough increased 11, dizziness/headache 3, angioedema 1, abnormal kidney function test 1, erythema nodosum 1, and pain 1.

The **mean (range) of onset for cough** is shown in Table 5.

Table 5: MEAN DAY (RANGE) OF ONSET FOR COUGH

	N=361 Placel	N=1804 Moexipril	Moexipril + HCTZ
GHBA-640 OL	—	204 (61-641)	252 (108-534)
GHBA-642 OL	—	173 (78-416)	177 (142-255)
ALL STUDIES COMBINED	55 (1-104)	94 (1-706)	172 (1-673)
Duration of Treatment	1 day - 12 wks	1 day - 2 yrs	1 day - 2 yrs

Table 4

ADVERSE EXPERIENCES CAUSING DISCONTINUATION FROM STUDY: UNCONTROLLED STUDIES

Study No./ Patient No.	Age/Sex	Adverse Experience	Day of Onset*/ Day of Discon.	Study Drug	Serious	Relationship to Study Drug
640/7066	77/female	Asthenia	490/489	MX 7.5 + HCTZ 25	Yes	Unlikely
640/7087	67/male	Abdominal Pain	699/698	MX 7.5 + HCTZ 25	Yes	Unlikely
		Cholelithiasis	699/698	MX 7.5 + HCTZ 25	Yes	Unlikely
		Bilirubinemia	712/698	MX 7.5 + HCTZ 25	Yes	Unlikely
		SGOT/SGPT Increased	712/698	MX 7.5 + HCTZ 25	Yes	Unlikely
640/7096	76/female	Cholelithiasis	144/148	MX 15 + HCTZ 25	Yes	Unlikely
640/7284	75/female	Myocardial Infarct	569/569	MX 15	Yes	None
640/7302	72/female	Carcinoma	142/142	MX 7.5 + HCTZ 25	Yes	Unlikely
640/7305	65/male	Angina Pectoris	260/330	MX 15	No	None
640/7309	72/female	Carcinoma	488/497	MX 7.5	Yes	Unlikely
[illegible]	71/male	Cough Increased	59/281	MX 7.5	No	Probably
642/7225	70/male	Cough Increased	149/202	MX 7.5 + HCTZ 25	No	Possibly
		Rash	194/202	MX 7.5 + HCTZ 25	No	Unlikely
		Purpuric Rash	195/202	MX 7.5 + HCTZ 25	No	Unlikely
642/7112	56/female	Headache	162/246	MX 7.5 + HCTZ 25	No	Possibly
642/7138	64/female	Breast Carcinoma	159/180	MX 7.5 + HCTZ 25	Yes	None
642/7139	45/male	Chest Pain	229/229	MX 15 + HCTZ 25	No	Possibly
		Headache	229/229	MX 15 + HCTZ 25	No	Possibly
		Nervousness	229/229	MX 15 + HCTZ 25	No	Possibly
642/7143	47/female	Erythema Nodosum	135/151	MX 15 + HCTZ 25	No	Highly Probably
642/7050	63/male	Blindness	285/296	MX 7.5	Yes	Unlikely
		Chest Pain	285/296	MX 7.5	Yes	None
642/7120	70/male	Gastrointestinal Hemorrhage	210/222	MX 15 + HCTZ 25	Yes	Unlikely
642/7122	60/male	Facial Paralysis	170/172	MX 7.5 + HCTZ 25	Yes	Unlikely
642/7223	55/male	Impotence	258/379	MX 15 + HCTZ 25	No	Possibly
642/7020	68/male	BUN Increased	86/99	MX 7.5	No	Possibly
		Creatinine Increased	86/99	MX 7.5	No	Possibly
		Hyperuricemia	86/99	MX 7.5	No	Possibly
642/7021	77/female	Carcinoma	345/345	MX 7.5	Yes	None
642/7168	65/male	Atrial Fibrillation	421/424	MX 15	No	None
642/7085	53/female	Cough Increased	78/134	MX 7.5	No	Highly Probably
642/7090	61/male	Prostatic Carcinoma	428/442	MX 7.5	Yes	None
642/7093	56/female	Cough Increased	59/164	HCTZ 25	No	Possibly

* Relative to start of active treatment.

** Pre-treatment prior to randomization.

MX = moexipril; HCTZ = hydrochlorothiazide; PBO = placebo; V = verapamil; C = captopril; NR = nifedipine retard. Numerals following drug name abbreviations refer to the drug dose in milligrams.

Table 4 (cont.)

ADVERSE EXPERIENCES CAUSING DISCONTINUATION FROM STUDY: UNCONTROLLED STUDIES

Study No./ Patient No.	Age/Sex	Adverse Experience	Day of Onset*/ Day of Discon.	Study Drug	Serious	Relationship to Study Drug
640/7215	71/female	Diarrhea Flatulence	58/87 80/87	MX 7.5 MX 15	No No	Probably Probably
640/7001	75/male	Abnormal Vision Dizziness Nocturia	—/70 —/70 —/70	PBO** PBO** PBO**	No No No	Unlikely Unlikely Unlikely
640/7008	67/male	Dizziness Nausea	113/155 113/155	MX 15 + HCTZ 25 MX 15 + HCTZ 25	No No	Possibly Possibly
640/7053	63/female	Cough Increased	451/485	MX 7.5	No	Probably
640/7229	73/male	Carcinoma	185/185	MX 15 + HCTZ 25	Yes	None
[illegible]	55/female	Cough Increased	12/170	MX 7.5	No	H. Prob.
640/7425	74/male	Nausea Vomiting	92/142 92/142	MX 7.5 + HCTZ 25 MX 7.5 + HCTZ 25	No No	Unlikely Unlikely
640/7233	72/male	Angioedema	664/671	MX 15 + HCTZ 25	No	Probably
640/7235	72/female	Abnormal Dreams Cough Increased	123/161 123/161	MX 7.5 MX 7.5	No No	Possibly Probably
640/7236	69/female	Abnormal Dreams Anxiety Constipation Palpitation	82/184 82/184 82/184 82/184	MX 7.5 MX 7.5 MX 7.5 MX 7.5	No No No No	Unlikely Unlikely Unlikely Unlikely
640/7237	72/male	Cough Increased	97/194	MX 15	No	H. Prob.
640/7239	70/female	Angina Pectoris	113/155	MX 7.5	No	Unlikely
640/7240	76/female	Cough Increased	64/107	MX 7.5	No	Probably
640/7249	69/male	Neoplasm Gynecomastia	533/550 544/550	MX 7.5 MX 7.5	Yes No	Unlikely Unlikely
640/7256	65/female	Cough Increased	161/197	MX 7.5 + HCTZ 25	No	H. Prob.
640/7260	65/male	Depression	633/642	MX 15 + HCTZ 25	No	Unlikely
640/7262	68/male	Arrhythmia Atrial Fibrillation	323/324 323/324	MX 15 + HCTZ 25 MX 15 + HCTZ 25	No Yes	Unlikely Unlikely
640/7267	67/female	Cough Increased	92/99	MX 7.5	No	H. Prob.
640/7271	73/male	Gastrointestinal Carcinoma	453/477	MX 7.5 + HCTZ 25	Yes	None
640/7082	65/male	Pain	317/351	MX 15 + HCTZ 25	No	Possibly
640/7084	70/female	Nodal Arrhythmia	547/547	MX 7.5	Yes	Unlikely

* Relative to start of active treatment.

** Pre-treatment prior to randomization.

MX = moexipril; HCTZ = hydrochlorothiazide; PBO = placebo; V = verapamil; C = captopril; NR = nifedipine retard. Numerals following drug name abbreviations refer to the drug dose in milligrams.

One case of angioedema (#640/7233, 72 y/w/m) had a continuous 16-hr episode of angioedema of moderate intensity on Day 664 and MX 15/HCTZ was d/ced 10 days later.

One case of erythema nodosum (#642/7143, 47 y/w/F, MX 7.5) was noted dry, reddened areas on lower limbs on Day 123. On Day 135, the reddened areas became raised. HCTZ and MX was d/ced on Day 151. She was treated with prednisone. The investigator's opinion was the likelihood of a causal relationship between this event and HCTZ. Pt #642/7020 (68 y/w/m) had increased BUN, increased creatinine, and hyperuricemia with a secondary diagnosis of gout and a history of renal insufficiency which resulted in withdrawal from the study. The investigator believed the likelihood of a causal relationship between these events and the study drug to be possible, but unlikely because the screen/baseline lab values were high.

Abnormal Lab Data

Increase creatinine (mg/dl)	baseline	wk 12	1 yr
#642/7020 - 68 y/w/m, MX 7.5	1.6	1.9	
#642/7419 - 74 y/w/m MX 7.5/HCTZ 25	1.2		1.6
Albuminuria			
#642/7069 - 63 y/w/m MX 7.5	trace	1 +	
#642/7099 - 57 y/w/m MX 7.5		0	2 +
Hyperkalemia/mEq/L			
#642/7176 - 70 y/w/m MX 7.5	4.7	5.7	

Deaths: No deaths during this report period.

CONCLUSION: The safe profile and the conclusions have not changed since the last update submitted on 4/30/93.

S K Chun 3/10/94

Sughok K. Chun, M.D.

cc: Orig. NDA
HFD-110
HFD-110/CSO
HFD-110/SChun
ef:3/10/94

Borgovanni

JAN 13 1995

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA # 20-312

Name of Drug: Moexipril Hydrochloride (UNIVASC™)

Sponsor: Schwarz pharma

Type of Submissi. abeling (PC 1879)

Date of Submission: 11/29/94

Date of Review: 1/12/95

Reviewer: Sughok K. Chun, M.D. HFD-110

The safety data in the moexipril HCl labeling dated 10/94 is reviewed. There were some differences in the incidence of adverse events, abnormal renal function test and an increase of creatinine >40% from the normal baseline measurement in this labeling compared to my safety review of the original NDA 20-312 completed 8/02/93. In previous safety review I used combined total population (controlled studies and uncontrolled studies) who were exposed to the test drug. The sponsor used the incidence of adverse events and abnormal laboratory finding on the placebo controlled study population. I called the sponsor Susan Nunchuck, Ph.D., Manager of Regulatory Affairs (414-238-5474) and Carol Venetiener, G.H. Besselaar Associates (609-452-8550) who made the original NDA submission on 1/10/95 to send me a copy of Tables of Adverse Events/Laboratory Data in placebo controlled studies. They sent a Facsimilar Transmission (attached) on 1/12/95

Tables 6A, 13 and 14 consisted with the incidence quoted in this labeling.

CONCLUSION: The safety data in the labeling dated 10/94 of moexipril HCl is satisfactory.

SK Chun 1/13/95
Sughok K. Chun, M.D.

cc.
HFD-110
HFD-110/CSO
HFD-110/RFenichel
HFD-110/SChun
kb/1/12/95

SCHWARZ
PHARMA

FACSIMILE TRANSMISSION

Fax Number: 301-594-5494

TO: Kathleen Bongiovanni, CSO, Center for Drug Evaluation and Research
Sughok Chun, MD, Medical Reviewer, Center for Drug Evaluation and Research

FROM: Steven R. Pollock
Associate Director, Regulatory Affairs

DATE: January 12, 1995

TIME: 12:30

SUBJECT: Request for information from Dr. Chun

Number of pages: ___6_
If not properly received, please call: 414-238-5474

Dear Ms. Bongiovanni and Dr. Chun:

Reference is made to a telephone call for information, per the request of Dr. Chun on January 10. We forward the information to Dr. Chun to expedite the review of the safety data in the moexipril hydrochloride labeling for NDA 20-312. The information presented in this fax was provided in the annual safet late for

Table 6A refers to the information contained in the Adverse Events Table in Placebo-Controlled Studies and supports the information found on page 13 of the labeling.

Table 13 supports the information contained on page 14 in the labeling and refers to the incidence and number of patients who had minor increases in BUN in Placebo-Controlled Studies.

Table 14 supports the information contained on page 14 in the labeling and refers to the incidence and number of patients with a greater than 40% change from baseline for Creatinine in Placebo-Controlled Studies.

If you would like to further discuss this request for information, or have additional questions, please do not hesitate to contact Susan Nunchuck, Ph.D., Manager of Regulatory Affairs, at 414-238-5474. Thank-you for the opportunity at answer this im ortant question.

Sincerely,
SCHWARZ PHARMA Kremers Urban Company

Steven R. Pollock
Associate Director, Regulatory Affairs

Placebo-Controlled

On text. table as package insert

TABLE 4A

NUMBER AND PERCENT OF PATIENTS WITH ADVERSE EXPERIENCES (AE)
ALL ADVERSE EXPERIENCES
IN ORDER OF FREQUENCY

Adverse Experience	Moexipril Alone	Moexipril + HCTZ	HCTZ Alone	Placebo Alone	All Treatments
Total Number of Patients	674	288	197	226	1385
Total # Patients with Adv. Exp.	326(48.4)	146(50.7)	101(51.3)	102(45.1)	675(48.7)
HEADACHE	64(9.5)	21(7.3)	17(8.6)	27(11.9)	129(9.3)
COUGH INCREASED	41(6.1)	12(4.2)	2(1.0)	5(2.2)	60(4.3)
UPPER RESPIRATORY INFECTION	32(4.7)	8(2.8)	7(3.6)	15(6.6)	62(4.5)
DIZZINESS	29(4.3)	13(4.5)	6(3.0)	5(2.2)	53(3.8)
DIARRHEA	21(3.1)	9(3.1)	2(1.0)	5(2.2)	37(2.7)
FLU SYNDROME	21(3.1)	12(4.2)	1(0.5)		34(2.5)
PAIN	21(3.1)	5(1.7)	6(3.0)	10(4.4)	42(3.0)
RHINITIS	21(3.1)	4(1.4)	2(1.0)	9(4.0)	36(2.6)
FATIGUE	16(2.4)	10(3.5)	2(1.0)	4(1.8)	32(2.3)
DYSPEPSIA	13(1.9)	3(1.0)		5(2.2)	21(1.5)
NAUSEA	12(1.8)	1(0.3)	1(0.5)	4(1.8)	18(1.3)
PERIPHERAL EDEMA	12(1.8)	2(0.7)		5(2.2)	19(1.4)
PHARYNGITIS	12(1.8)	2(0.7)	2(1.0)	2(0.9)	18(1.3)
FLUSHING	11(1.6)	7(2.4)			18(1.3)
BACK	11(1.6)	2(0.7)	3(1.5)	2(0.9)	18(1.3)
SINUSITIS	10(1.5)	4(1.4)	2(1.0)	7(3.1)	23(1.7)
MYALGIA	9(1.3)		2(1.0)		11(0.8)
CHEST PAIN	8(1.2)	2(0.7)	2(1.0)	3(1.3)	15(1.1)
URINARY FREQUENCY	8(1.2)	6(2.1)		5(2.2)	19(1.4)
ABDOMINAL PAIN	7(1.0)	1(0.3)		2(0.9)	10(0.7)
BACK PAIN	7(1.0)	2(0.7)	4(2.0)	5(2.2)	18(1.3)

Protocols included: 638(DB) 625(DB) 660(DB) 662(DB) 666(DB) 651(DB)
The order of adverse experiences is based on their frequency in the Moexipril Alone treatment group.

TABLE 6A

NUMBER AND PERCENT OF PATIENTS WITH ADVERSE EXPERIENCES (AE)
ALL ADVERSE EXPERIENCES
IN ORDER OF FREQUENCY

Adverse Experience	Moexipril Alone	Moexipril + HCTZ	HCTZ Alone	Placebo Alone	All Treatments
HYPERKALEMIA	7(1.0)	1(0.3)			8(0.6)
HYPESTHESIA	7(1.0)		1(0.5)	1(0.4)	9(0.6)
PARESTHESIA	7(1.0)	2(0.7)	1(0.5)		10(0.7)
INSOMNIA	6(0.9)	4(1.4)	1(0.5)	1(0.4)	12(0.9)
SGPT INCREASED	6(0.9)	1(0.3)	7(3.6)		14(1.0)
SOMNOLENCE	6(0.9)	4(1.4)		1(0.4)	11(0.8)
VOMITING	6(0.9)	1(0.3)	1(0.5)	2(0.9)	10(0.7)
CONSTIPATION	5(0.7)	1(0.3)	1(0.5)	1(0.4)	8(0.6)
CREATININE INCREASED	5(0.7)	3(1.0)	3(1.5)		11(0.8)
ELECTROCARDIOGRAM ABNORMAL	5(0.7)	1(0.3)	1(0.5)	1(0.4)	8(0.6)
HYPERTONIA	5(0.7)	2(0.7)	1(0.5)		8(0.6)
HYPERURICEMIA	5(0.7)	12(4.2)	11(5.6)	2(0.9)	30(2.2)
URINARY TRACT INFECTION	5(0.7)		1(0.5)	1(0.4)	7(0.5)
ARTHRITIS	4(0.6)	1(0.3)		1(0.4)	6(0.4)
ASTHENIA	4(0.6)	3(1.0)	1(0.5)		8(0.6)
BRONCHITIS	4(0.6)	2(0.7)	2(1.0)	1(0.4)	9(0.6)
DRY SKIN	4(0.6)	1(0.3)			5(0.4)
FEVER	4(0.6)	5(1.7)			9(0.6)
GENERALIZED EDEMA	4(0.6)				4(0.3)
INJURY	4(0.6)	1(0.3)	1(0.5)	2(0.9)	8(0.6)
PRURITUS	4(0.6)	1(0.3)	3(1.5)	1(0.4)	9(0.6)
PYURIA	4(0.6)	5(1.7)	2(1.0)	3(1.3)	14(1.0)
SGOT INCREASED	4(0.6)	1(0.3)	2(1.0)		7(0.5)
TINNITUS	4(0.6)	1(0.3)			5(0.4)
ARTHRALGIA	3(0.4)	3(1.0)			6(0.4)
CONJUNCTIVITIS	3(0.4)	2(0.7)	1(0.5)	1(0.4)	7(0.5)
DYSPNEA	3(0.4)	1(0.3)	2(1.0)	3(1.3)	9(0.6)
ECCHYMOSIS	3(0.4)			2(0.9)	5(0.4)

Protocols included: 438(DB) 625(DB) 640(DB) 642(DB) 644(DB) 651(DB)
The order of adverse experiences is based on their frequency in the Moexipril Alone treatment group.

Placebo-Controlled

TABLE 13

INCIDENCE OF TRANSITIONS FROM INVESTIGATORS' NORMAL RANGES
IN CLINICAL LABORATORY TEST RESULTS
NUMBER AND PERCENT OF PATIENTS

LABORATORY TEST: BUN

	During Treatment with Moexipril					During Treatment with Placebo				
Baseline	N	Low	Normal	High	Both N&H	N	Low	Normal	High	Both N&H
Low	1	1(100%)	0(0%)	0(0%)	0(0%)	0	0(%)	0(%)	0(%)	0(%)
Normal	478	4(1%)	469(98%)	3(1%)	0(0%)	154	2(1%)	151(98%)	1(1%)	0(0%)
High	4	0(0%)	3(75%)	1(25%)	0(0%)	0	0(%)	0(%)	0(%)	0(%)

	During Treatment with Moexipril + HCTZ					During Treatment with HCTZ				
Baseline	N	Low	Normal	High	Both N&H	N	Low	Normal	High	Both N&H
Low	1	1(100%)	0(0%)	0(0%)	0(0%)	0	0(%)	0(%)	0(%)	0(%)
Normal	136	2(1%)	127(93%)	7(5%)	0(0%)	89	0(0%)	88(99%)	1(1%)	0(0%)
High	0	0(%)	0(%)	0(%)	0(%)	1	0(0%)	0(0%)	1(100%)	0(0%)

Protocols Included: 625(DB) 630(DB) 660(DB) 662(DB) 664(DB) 651(DB)

Incidence of minor increases in BUN

Placebo - Controlled

TABLE 13

INCIDENCE OF TRANSITIONS FROM INVESTIGATORS' NORMAL RANGES
IN CLINICAL LABORATORY TEST RESULTS
NUMBER AND PERCENT OF PATIENTS

LABORATORY TEST: Creatinine

	During Treatment with Monopril					During Treatment with Placebo				
Baseline	N	Low	Normal	High	Both H&L	N	Low	Normal	High	Both H&L
Low	12	9(75%)	3(25%)	0(0%)	0(0%)	1	1(100%)	0(0%)	0(0%)	0(0%)
Normal	551	12(2%)	526(95%)	13(2%)	0(0%)	196	4(2%)	188(96%)	8(4%)	0(0%)
High	18	0(0%)	5(28%)	13(72%)	0(0%)	6	0(0%)	3(50%)	3(50%)	0(0%)

	During Treatment with Monopril + HCTZ					During Treatment with HCTZ				
Baseline	N	Low	Normal	High	Both H&L	N	Low	Normal	High	Both H&L
Low	8	3(38%)	5(63%)	0(0%)	0(0%)	1	1 (80%)	0(0%)	0(0%)	0(0%)
Normal	263	6(2%)	244(93%)	13(5%)	0(0%)	164	3(2%)	148(90%)	13(8%)	0(0%)
High	12	0(0%)	1(8%)	11(92%)	0(0%)	13	0(0%)	4(31%)	9(69%)	0(0%)

only 3 pts also had BUN ↑

Increases in Creatinine

(See previous page.)

Protocols Included: 623(86) 638(86) 640(88) 642(88) 644(88) 651(88)

Placebo-Controlled

TABLE 14

INCIDENCE OF TRANSITIONS FROM PREDEFINED LIMITS (PDL)* IN CLINICAL LABORATORY TEST RESULTS
NUMBER AND PERCENT OF PATIENTS

LABORATORY TEST: Creatinine

Baseline	During Treatment with Moexipril								During Treatment with Placebo							
	N	Low		Normal		High		Both PDL	N	Low		Normal		High		Both PDL
Below PDL	0	0	(%)	0	(%)	0	(%)	0	(%)	0	0	(%)	0	(%)	0	(%)	0	(%)
Within PDL	577	3	(1%)	566	(98%)	8	(1%)	0	(0%)	200	0	(0%)	198	(99%)	2	(1%)	0	(0%)
Above PDL	4	0	(0%)	0	(0%)	4	(100%)	0	(0%)	1	0	(0%)	0	(0%)	1	(100%)	0	(0%)

Baseline	During Treatment with Moexipril + HCTZ								During Treatment with HCTZ							
	N	Low		Normal		High		Both PDL	N	Low		Normal		High		Both PDL
Below PDL	1	1	(100%)	0	(0%)	0	(0%)	0	(0%)	0	0	(%)	0	(%)	0	(%)	0	(%)
Within PDL	279	1	(0%)	271	(97%)	7	(3%)	0	(0%)	176	0	(0%)	171	(97%)	5	(3%)	0	(0%)
Above PDL	3	0	(0%)	0	(0%)	3	(100%)	0	(0%)	2	0	(0%)	1	(50%)	1	(50%)	0	(0%)

only 6 pts (2%) had increases > 40%
Other 1 pt had ± 20% outside normal but not increase > 40%

* PDL = ±20% outside normal range and/or > 40% increase from baseline
Protocols included: 438(88) 425(88) 440(88) 443(84) 444(84) 451(88)

Incidence of patients with > 40% change from baseline

KBC

MAY 16 1994

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #20,312

Name of Drug: Moexipril HCL Tablets

Sponsor: Besselaar

Type of Submission: Amendment to the Safety Data of Original NDA

Date of Submission: 5/9/94

Date of Review: 5/12/94

Reviewer: Sughok K. Chun, M.D. HFD-110 S.K. Chun 5/13/94

A. Resume:

A question was raised of serum potassium level in the original NDA 20,319 data. The mean potassium values was reported as (safety review pg 13, Table 7):

Controlled Studies

	Baseline	Endpoint*
HCTZ	3.77	3.45
Moexipril	3.92	4.03
Moexipril + HCTZ	3.81	3.56

Uncontrolled Studies

	Baseline	Endpoint*
Moexipril	3.94	3.91
Moexipril+HCTZ	3.45	3.88

Combined Studies

	Baseline	Endpoint*
HCTZ	3.85	3.96
Moexipril	3.67	3.72
Moexipril + HCTZ	4.11	4.11

* Endpoint is last postbaseline value

I called the sponsor on 4/22/94 and requested clarification of the mean potassium values submitted to the NDA on 12 July 1993. The sponsor submitted a revised table of the mean potassium values for the controlled studies, uncontrolled studies, and combined studies. The studies contained in each mean value are specified in the table.

MEAN POTASSIUM VALUES (mmol/L)

Controlled Studies

	Baseline	Endpoint*
HCTZ	3.77	3.54
Moexipril	3.92	4.01
Moexipril + HCTZ	3.81	3.56

GHBA-638 D.B., GHBA-640 D.B., GHBA-642 D.B., GHBA-643, GHBA-644, GHBA-645, GHBA-647, GHBA-648, GHBA-649, GHBA-651.

Uncontrolled Studies

	Baseline	Endpoint*
Moexipril	3.94	3.94
Moexipril + HCTZ	3.45	3.93

GHBA-624, GHBA-638 O.L., GHBA-640 O.L, GHBA-641, GHBA-618.

Combined Studies

	Baseline	Endpoint*
HCTZ	3.85	3.10
Moexipril	3.67	4.04
Moexipril + HCTZ	4.12	4.00

GHBA-638 (D.B + O.L.), GHBA-640 (D.B. + O.L.).

* Last postbaseline value

Orig
HFD-100/R.Temple
HFD-110/CSO
HFD-110/R.Lipicky
HFD-110/A.Karkowsky
HFD-110/S.Chun
WL/5-13-94

Bongiovanni

APR 22 1994

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA# 20-312

Name of Drug: Moexpril

Sponsor: G. H. Resselaar Assoc.

Type of Submission: Original NDA

Date of Review: 4/21/94

Reviewer: Sughok K. Chun, M.D. HFD-110 SK. Chun 4/22/94

A. Resume:

This is an addendum to the original safety review done 8/02/93 for the subgroup analysis of safety data. The incidence of adverse experiences (AEs) in subgroups of pts defined by age, sex, and race in the placebo controlled studies (GHBA-638, -642, -643, -644, -651 and -623) are evaluated on Moex and placebo treatments for comparison. Moex +HCTZ or HCTZ alone groups are not included in this comparison. The distribution and pts evaluated for the drug safety is shown Table A.

Table A. AGE AND SEX DISTRIBUTION OF PATIENTS IN THE EVALUATION OF DRUG SAFETY (POOLED DATA BASE[a])

	Moexipril (N=897)			Moexipril + HCTZ (N=258)			HCTZ Alone (N=197)			Placebo Alone (N=322)		
Age Interval - (years)	M	F	T	M	F	T	M	F	T	M	F	T
Less Than 65	421	204	625	148	34	182	66	42	108	152	63	215
65 and Over	157	115	272	27	29	56	51	38	89	68	39	107
Total Patients	578	319	897	175	113	288	117	80	197	220	102	322
Mean Age (years)	55.0	53.7	56.3	53.4	58.5	55.4	58.3	61.7	59.7	55.5	59.3	56.7
Minimum Age (years)	23	28	23	25	34	25	27	37	27	27	30	27
Maximum Age	78	84	84	82	78	82	83	87	87	79	83	83

Source Data: Appendix B, Table 3A.
[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623.
M = Male; F = Female; T = Total

AEs by Age

Of the 897 Moex treated pts in the pooled data base, 625 (70%) were < 65 yrs and 272 (30%) were ≥ 65 yrs. Among the 322 placebo-treated pts, 215 (67%) < 65 yrs old, and 107 (33%) were ≥ 65 years. Table B shows the incidence by age subgroup of the most frequently occurring (1% or more) AEs by decreasing order of frequency in the total Moex population.

Table B shows that moexipril treatment did not adversely affect the subgroup of patients who were 65 years of age or older.

AEs by Sex

Of the 897 pts in the pooled data base treated with Moex, 578 (64%) were men, and 319 (36%) were women. For the 322 patients treated with placebo, 220 (68%) were men, and 102 (32%) were women. Table C shows the incidence of the most frequently occurring (1% or more) AEs by decreasing order of frequency.

Table C shows that Moex treatment, when compared with placebo, did not adversely affect the subgroup of pts who were women.

AES by Race

Of the 897 pts in the pooled data base treated with Moex, 741 (83%) were non-black (including Hispanic and Oriental), and 156 (17%) were black. For the 322 pts treated with placebo, 278 (86%) were non-black, and 44 (14%) were black. Table D shows the incidence by racial subgroup of the most frequently occurring (1% or more) AEs. Thus, Moex treatment, when compared with placebo, did not adversely affect the black subgroup of pts.

AEs by Dose

AEs by Moex monotherapy dose (3.75 mg, 7.5 mg, 15 mg, 30 mg, and 60 mg) were examined for Moex treated pts in the pooled safety data base. Table E shows the distribution of dose regimens for the seven placebo-controlled studies in the pooled safety data base.

Table E does not show an appreciable dose effect with Moex.

SUMMARY

Moexipril treatment does not adversely affect demographic subgroups of pts defined by age, sex, or race and does not appear to have a clinically important dose effect.

cc.
Orig
HFD-110
HFD-110/CSO
HFD-100/R Temple
HFD-110/R Lipicky
HFD-110/R Fenichel
HFD-110/S Chun
wl/4-22-94

TABLE B
NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY AGE (POOLED DATA BASE[a])

	Number (%) of Patients				
		< 65 Years		≥ 65 Years	
Adverse Experience	Total Moexipril (N=897)	Moexipril (N=625)	Placebo (N=215)	Moexipril (N=272)	Placebo (N=107)
Total Number With Adverse Experiences	479 (53)	344 (55)	100 (47)	135 (50)	49 (46)
Headache	89 (10)	69 (11)	19 (9)	20 (7)	12 (11)
Upper Respiratory Infection	73 (8)	55 (9)	16 (7)	18 (7)	7 (7)
Cough Increased	63 (7)	43 (7)	4 (2)	20 (7)	6 (6)
Flu Syndrome	44 (5)	30 (5)	1 (<1)	14 (5)	1 (1)
Dizziness	43 (5)	31 (5)	5 (2)	12 (4)	3 (3)
Rhinitis	34 (4)	30 (5)	7 (3)	4 (1)	3 (3)
Diarrhea	33 (4)	25 (4)	2 (1)	8 (3)	3 (3)
Pain	33 (4)	23 (4)	11 (5)	10 (4)	2 (2)
Fatigue	24 (3)	20 (3)	4 (2)	4 (1)	0 (0)
Sinusitis	20 (2)	16 (3)	7 (3)	4 (1)	1 (1)
Back Pain	19 (2)	16 (3)	5 (2)	3 (1)	5 (5)
Pharyngitis	19 (2)	14 (2)	1 (<1)	5 (2)	2 (2)
Injury	16 (2)	12 (2)	4 (2)	4 (1)	0 (0)
Rash	16 (2)	8 (1)	2 (1)	8 (3)	1 (1)
Dyspepsia	15 (2)	6 (1)	4 (2)	9 (3)	1 (1)
Nausea	15 (2)	11 (2)	2 (1)	4 (1)	2 (2)
Myalgia	14 (2)	10 (2)	0 (0)	4 (1)	0 (0)
Peripheral Edema	14 (2)	11 (2)	5 (2)	3 (1)	1 (1)
Bronchitis	13 (1)	10 (2)	3 (1)	3 (1)	1 (1)
Chest Pain	12 (1)	9 (1)	4 (2)	3 (1)	1 (1)
Flushing	11 (1)	10 (2)	1 (<1)	1 (<1)	0 (0)
Hypertonia	10 (1)	8 (1)	0 (0)	2 (1)	0 (0)
Abdominal Pain	9 (1)	5 (1)	1 (<1)	4 (1)	1 (1)
Hyperkalemia	9 (1)	7 (1)	0 (0)	2 (1)	0 (0)
Nervousness	9 (1)	5 (1)	2 (1)	4 (1)	0 (0)
Paresthesia	9 (1)	9 (1)	1 (<1)	0 (0)	0 (0)
Somnolence	9 (1)	6 (1)	0 (0)	3 (1)	1 (1)
Urinary Frequency	9 (1)	8 (1)	4 (2)	1 (<1)	1 (1)
Electrocardiogram Abnormal	8 (1)	8 (1)	1 (<1)	0 (0)	0 (0)
Vomiting	8 (1)	6 (1)	0 (0)	2 (1)	2 (2)
Arthritis	7 (1)	4 (1)	0 (0)	3 (1)	1 (1)
Asthenia	7 (1)	4 (1)	0 (0)	3 (1)	0 (0)
Hypesthesia	7 (1)	7 (1)	1 (<1)	0 (0)	1 (1)
Insomnia	7 (1)	5 (1)	0 (0)	2 (1)	1 (1)
Tenosynovitis	7 (1)	7 (1)	1 (<1)	0 (0)	0 (0)
Tinnitus	7 (1)	6 (1)	0 (0)	1 (<1)	0 (0)
Urinary Tract Infection	7 (1)	4 (1)	1 (<1)	3 (1)	0 (0)
Ecchymosis	6 (1)	3 (<1)	2 (1)	3 (1)	0 (0)
Fever	6 (1)	5 (1)	0 (0)	1 (<1)	0 (0)
Infection	6 (1)	6 (1)	0 (0)	0 (0)	2 (2)
SGPT Increased	6 (1)	4 (1)	3 (1)	2 (1)	0 (0)
Cardiovascular Disorder	5 (1)	5 (1)	1 (<1)	0 (0)	0 (0)
Constipation	5 (1)	4 (1)	1 (<1)	1 (<1)	0 (0)

Source: Data: Appendix B, Tables 6A, 9A, and 9B.

[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623. Data for GHBA-644 are not presented in this table.

TABLE C
NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY SEX (POOLED DATA BASE[a])

	Number (%) of Patients				
		Male		Female	
Adverse Experience	Total Moexipril (N=897)	Moexipril (N=578)	Placebo N=220)	Moexipril (N=319)	Placebo (N=102)
Total Number With Adverse Experiences	479 (53)	294 (51)	95 (43)	185 (58)	54 (53)
Headache	89 (10)	44 (8)	17 (8)	45 (14)	14 (14)
Upper Respiratory Infection	73 (8)	47 (8)	15 (7)	26 (8)	5 (8)
Cough Increased	63 (7)	34 (6)	4 (2)	29 (9)	6 (6)
Flu Syndrome	44 (5)	28 (5)	0 (0)	16 (5)	2 (2)
Dizziness	43 (5)	31 (5)	4 (2)	12 (4)	4 (4)
Rhinitis	34 (4)	25 (4)	6 (3)	9 (3)	4 (4)
Diarrhea	33 (4)	21 (4)	3 (1)	12 (4)	2 (2)
Pain	33 (4)	22 (4)	8 (4)	10 (3)	5 (5)
Fatigue	24 (3)	14 (2)	1 (<1)	10 (3)	3 (3)
Sinusitis	20 (2)	9 (2)	5 (2)	11 (3)	3 (3)
Back Pain	19 (2)	11 (2)	3 (1)	8 (3)	7 (7)
Pharyngitis	19 (2)	13 (2)	2 (1)	6 (2)	1 (1)
Injury	16 (2)	9 (2)	3 (1)	7 (2)	1 (1)
Rash	16 (2)	10 (2)	1 (<1)	6 (2)	2 (2)
Dyspepsia	15 (2)	10 (2)	3 (1)	5 (2)	2 (2)
Nausea	15 (2)	7 (1)	2 (1)	8 (3)	2 (2)
Myalgia	14 (2)	9 (2)	0 (0)	5 (2)	0 (0)
Peripheral Edema	14 (2)	6 (1)	3 (1)	8 (3)	3 (3)
Bronchitis	13 (1)	7 (1)	0 (0)	6 (2)	4 (4)
Chest Pain	12 (1)	4 (1)	5 (2)	8 (3)	0 (0)
Flushing	11 (1)	6 (1)	1 (<1)	5 (2)	0 (0)
Hypertonia	10 (1)	9 (2)	0 (0)	1 (<1)	0 (0)
Abdominal Pain	9 (1)	5 (1)	1 (<1)	4 (1)	1 (1)
Hyperkalemia	9 (1)	6 (1)	0 (0)	3 (1)	0 (0)
Nervousness	9 (1)	3 (1)	2 (1)	6 (2)	0 (0)
Paresthesia	9 (1)	6 (1)	1 (<1)	3 (1)	0 (0)
Somnolence	9 (1)	3 (1)	0 (0)	6 (2)	1 (1)
Urinary Frequency	9 (1)	8 (1)	2 (1)	1 (<1)	3 (3)
Electrocardiogram Abnormal	8 (1)	6 (1)	1 (<1)	2 (1)	0 (0)
Vomiting	8 (1)	7 (1)	0 (0)	1 (<1)	2 (2)
Arthritis	7 (1)	4 (1)	1 (<1)	3 (1)	0 (0)
Asthenia	7 (1)	2 (<1)	0 (0)	5 (2)	0 (0)
Hypesthesia	7 (1)	4 (1)	1 (<1)	3 (1)	1 (1)
Insomnia	7 (1)	4 (1)	1 (<1)	3 (1)	0 (0)
Tenosynovitis	7 (1)	3 (1)	1 (<1)	4 (1)	0 (0)
Tinnitus	7 (1)	4 (1)	0 (0)	3 (1)	0 (0)
Urinary Tract Infection	7 (1)	2 (<1)	0 (0)	5 (2)	1 (1)
Ecchymosis	6 (1)	1 (<1)	0 (0)	5 (2)	2 (2)
Fever	6 (1)	6 (1)	0 (0)	0 (0)	0 (0)
Infection	6 (1)	3 (1)	0 (0)	3 (1)	2 (2)
SGPT Increased	6 (1)	3 (1)	2 (1)	3 (1)	1 (1)
Cardiovascular Disorder	5 (1)	3 (1)	0 (0)	2 (1)	1 (1)
Constipation	5 (1)	3 (1)	1 (<1)	2 (1)	0 (0)

Source Data: Appendix B, Tables 6A, 9C, and 9D.
[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623.

TABLE D
NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY RACE (POOLED DATA BASE[a])

	Number (%) of Patients				
		Non-Black		Black	
Adverse Experience	Total Moexipril (N=897)	Moexipril (N=741)	Placebo (N=278)	Moexipril (N=156)	Placebo (N=44)
Total Number With Adverse Experiences	479 (53)	409 (55)	131 (47)	70 (45)	18 (41)
Headache	89 (10)	77 (10)	24 (9)	12 (8)	7 (16)
Upper Respiratory Infection	73 (8)	65 (9)	21 (8)	8 (5)	2 (5)
Cough Increased	63 (7)	57 (8)	8 (3)	6 (4)	2 (5)
Flu Syndrome	44 (5)	38 (5)	1 (<1)	6 (4)	1 (2)
Dizziness	43 (5)	34 (5)	7 (3)	9 (6)	1 (2)
Rhinitis	34 (4)	30 (4)	7 (3)	4 (3)	3 (7)
Diarrhea	33 (4)	29 (4)	5 (2)	4 (3)	0 (0)
Pain	33 (4)	27 (4)	11 (4)	6 (4)	2 (5)
Fatigue	24 (3)	22 (3)	4 (1)	2 (1)	0 (0)
Sinusitis	20 (2)	15 (2)	3 (1)	5 (3)	0 (0)
Back Pain	19 (2)	16 (2)	9 (3)	3 (2)	1 (2)
Pharyngitis	19 (2)	13 (2)	2 (1)	1 (1)	1 (2)
Injury	16 (2)	13 (2)	2 (1)	3 (2)	2 (5)
Rash	16 (2)	14 (2)	3 (1)	2 (1)	0 (0)
Dyspepsia	15 (2)	14 (2)	5 (2)	1 (1)	0 (0)
Nausea	15 (2)	14 (2)	4 (1)	1 (1)	0 (0)
Myalgia	14 (2)	14 (2)	0 (0)	0 (0)	0 (0)
Peripheral Edema	14 (2)	10 (1)	5 (2)	4 (3)	1 (2)
Bronchitis	13 (1)	12 (2)	4 (1)	1 (1)	0 (0)
Chest Pain	12 (1)	10 (1)	4 (1)	2 (1)	1 (2)
Flushing	11 (1)	11 (1)	1 (<1)	0 (0)	0 (0)
Hypertonia	10 (1)	9 (1)	0 (0)	1 (1)	0 (0)
Abdominal Pain	9 (1)	7 (1)	2 (1)	2 (1)	0 (0)
Hyperkalemia	9 (1)	9 (1)	0 (0)	0 (0)	0 (0)
Nervousness	9 (1)	8 (1)	1 (<1)	1 (1)	1 (2)
Paresthesia	9 (1)	9 (1)	1 (<1)	0 (0)	0 (0)
Somnolence	9 (1)	7 (1)	1 (<1)	2 (1)	0 (0)
Urinary Frequency	9 (1)	9 (1)	4 (1)	0 (0)	1 (2)
Electrocardiogram Abnormal	8 (1)	7 (1)	1 (<1)	1 (1)	0 (0)
Vomiting	8 (1)	7 (1)	2 (1)	1 (1)	0 (0)
Arthritis	7 (1)	6 (1)	1 (<1)	1 (1)	0 (0)
Asthenia	7 (1)	7 (1)	0 (0)	0 (0)	0 (0)
Hypesthesia	7 (1)	7 (1)	1 (<1)	0 (0)	1 (2)
Insomnia	7 (1)	5 (1)	1 (<1)	2 (1)	0 (0)
Tenosynovitis	7 (1)	6 (1)	1 (<1)	1 (1)	0 (0)
Tinnitus	7 (1)	7 (1)	0 (0)	0 (0)	0 (0)
Urinary Tract Infection	7 (1)	6 (1)	0 (0)	1 (1)	1 (2)
Eczema	6 (1)	6 (1)	2 (1)	0 (0)	0 (0)
Fever	6 (1)	5 (1)	0 (0)	1 (1)	0 (0)
Infection	6 (1)	6 (1)	2 (1)	0 (0)	0 (0)

Source Data: Appendix B, Tables 6A, 9E, and 9F.
[a] Studies pooled: GHEA-638, 640, 642, 643, 644, 651, and 623.

TABLE E
NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION BY DOSE (POOLED DATA BASE[a])

	Number (%) of Patients					
Adverse Experience (AE)	Total N=897	3.75 mg N=49	7.5 mg N=336	15 mg N=341	30 mg N=110	60 mg N=61
Headache	89 (10)	5 (10)	31 (9)	35 (10)	13 (12)	5 (8)
Upper Resp Infection	73 (8)	2 (4)	25 (7)	39 (11)	4 (4)	3 (5)
Cough Increased	63 (7)	3 (6)	24 (7)	23 (7)	8 (7)	5 (8)
Flu Syndrome	44 (5)	0 (0)	22 (7)	17 (5)	3 (3)	2 (3)
Dizziness	43 (5)	2 (4)	19 (6)	15 (4)	3 (3)	4 (7)
Rhinitis	34 (4)	3 (6)	16 (5)	9 (3)	3 (3)	3 (5)
Diarrhea	33 (4)	1 (2)	17 (5)	13 (4)	1 (1)	1 (2)
Pain	33 (4)	3 (6)	11 (4)	11 (3)	5 (5)	3 (5)
Fatigue	24 (3)	1 (2)	11 (3)	7 (2)	3 (3)	2 (3)
Sinusitis	20 (2)	0 (0)	10 (3)	7 (2)	3 (3)	0 (0)
Back Pain	19 (2)	1 (2)	9 (3)	6 (2)	0 (0)	3 (5)
Pharyngitis	19 (2)	0 (0)	10 (3)	6 (2)	2 (2)	1 (2)
Injury	16 (2)	1 (2)	7 (2)	8 (2)	0 (0)	0 (0)
Rash	16 (2)	0 (0)	9 (3)	5 (1)	1 (1)	1 (2)
Dyspepsia	15 (2)	0 (0)	5 (1)	5 (1)	2 (2)	3 (5)
Nausea	15 (2)	0 (0)	8 (2)	6 (2)	1 (1)	0 (0)
Myalgia	14 (2)	1 (2)	4 (1)	6 (2)	1 (1)	2 (3)
Peripheral Edema	14 (2)	1 (2)	5 (1)	6 (2)	1 (1)	1 (2)
Bronchitis	13 (1)	0 (0)	4 (1)	7 (2)	2 (2)	0 (0)
Chest Pain	12 (1)	0 ( )	7 (2)	3 (1)	1 (1)	1 (2)
Flushing	11 (1)	0 (0)	4 (1)	3 (1)	2 (2)	2 (3)
Hypertonia	10 (1)	0 (0)	6 (2)	4 (1)	0 (0)	0 (0)

Source Data: Appendix B, Table 10A.

[a] Studies pooled: GHBA-638, 640, 642, 643, 644, 651, and 623. Data for GHBA-644 are not presented in this table.

This document represents the medical officer summary of the phase I and phase II studies of moexipril. It is one of three sections which when combined, constitute the medical officer's review. Dr. Rodin's review details the efficacy studies of moexipril and Dr. Chun's review summarizes the safety portion of the moexipril submission. Although the documents were written in a modular fashion, there was free interchange of observations between the three reviewers.

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Study No. 1- GHBA-628 Volumes 1.52

Name of Study: A Pnase 1, Open-Label, Drug Disposition Study to Determine the Absorption, Metabolism and Excretion of (^{14}C)-Labelled Moexipril Following Oral and Intravenous Administration to Healthy Male Volunteers

Principal Investigator:

Site of Investigation (Dates): GHBA/Hazleton Clinic;

Formulations: Intravenous formulation: Batch No. WE91013160
Oral Formulation: 15 mg Capsule Lot No. 912118
Radioactivity. ^{14}-C carbon label located on the 1-position of the tetrahydroisoquinoline ring.

Protocol: A total of eight normal volunteers were to be studied. Baseline assessments included medical history, physical examination, vital statistics and vital signs , a 12-lead ECG, hematology, serology, fasting biochemistry and urine analysis with the appropriate informed consent.

Patients were to randomized to one of two sequences. One sequence designated **Panel A** was to receive two single-doses of ^{14}C-labeled moexipril as a tracer, formulated with non-radioactive moexipril . The first dose of moexipril was administered orally, followed three weeks later by an intravenously administered dose of ^{14}C-labeled moexipril . A second group of four individuals designated **Panel B,** received moexipril for six consecutive days. Dosing of moexipril on day one and day six included ^{14}C-labeled compound admixed with moexipril to serve as a tracer. For both Panels A and B oral doses of moexipril were 15 mg, the intravenous dose was 5-mg administered over a 15-minute period.

Measurements included pharmacokinetics with samples collected as follows:
Intravenous: pre-dose; end of 15-minute infusion (designated as time =0), 5, 10, 15, 30, and 45 minutes, 1, 1.5, 2, 2.5, 3.5, 4, 5, 6, 9, 12 and 24 hours post dose.
Oral: 0 hour(pre-dose) 15, 30, 45 min , 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12 and 24 hours post dose. For those allocated to Panel B measurements were taken at the end of day one and six.

Assays were performed both for whole blood as well as serum.

Urine was collected at the following times or intervals: pre-dose (for approximately 12 hours prior to dosing) , 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hours.
Stool was collected at the following intervals: (for approximately 12 hours prior to dosing) , 0-12, 12-24, 24-48, 48-72 and 72-96 hours.
Total radioactivity was counted either directly (urine, blood) or after centrifugation (plasma). In addition, aliquots of blood and plasma were separated and assayed by GC/MS for determination of individual chemical entities. Stool samples were combusted and the ^{14}C-liberated CO_2 was trapped and measured. Pooled urine and stool samples were assayed for metabolites.

Other measurements performed during the study included plasma for ACE inhibition, ECGs, vital signs and safety assessments.

Results: A total of 9 volunteers were recruited, one volunteer was discontinued due to ineligibility at baseline (history of ethanol abuse, drug use). Among those who were enrolled, ages (36-53; mean 43.4 years) weights (61.2-88.7 ; mean 73.5 Kg) and height (167-190; mean 177.5 cm) were similar in both panels. The pertinent kinetic parameters are listed below (Table 1.1)

Based on the dose of 15 mg orally (a mid-range therapeutic dose) the bioavailabilty of the oral formulation is 22% of the iv formulation based on AUCs of plasma moexipril and 19% based on plasma moexiprilat. Drug does not seem to readily accumulate in red cells since the concentrations of plasma radioactivity are

approximately 40% greater than those in whole blood (assuming adequate corrections are made for quenching).

There does not appear any accumulation with concentrations of either moexipril or moexiprilat with multiple dosing since concentrations are nearly equivalent at one and six days dosing. It should, however, be appreciated that this is a small study and consequently it has little power to differentiate whether even *substantial* accumulation occurs. The serum profile of parent drug and active metabolites as well as the profile in stools and faeces are shown below:

Table 1.1

Pharmacokinetic Parameters After administration of labeled moexipril

	Panel A		Panel B	
Parameter Mean (SD)	Intravenous Dose	Oral Dose	Day 1 Oral Dose	Day 6 Oral Dose
Plasma Radioactivity				
C_{max}	567 (104)	271 (126)	280 (101)	253 (89)
T_{max}	----	1.1 (0.3)	1.2 (0.4)	0.9 (0.1)
AUC_{0-t}	462 (116)	835 (387)	717 (353)	645 (269)
$AUC_{0-\infty}$	475 (120)	870 (390)	759 (357)	676 (294)
t1/2	1.0[a]	2.5[a]	1.7[a]	1.9[a]
Blood Radioactivity				
C_{max}	301 (51)	153 (81)	152 (47)	149 (45)
T_{max}	----	1.1 (0.3)	1.2 (0.4)	0.9 (0.1)
AUC_{0-t}	297 (109)	517 (289)	505 (278)	550 (225)
$AUC_{0-\infty}$	319 (121)	566 (303)	593 (309)	827 (443)
t1/2	1.4[a]	3.7[a]	2.6[a]	5.4[a]
Plasma Moexipril				
C_{max}	580 (107)	74 (60)	92 (52)	66 (34)
T_{max}	----	1.0 (0.4)	0.9 (0.4)	0.7 (0.1)
AUC_{0-t}	205 (48)	137 (387)	139 (57)	99 (52)
$AUC_{0-\infty}$	207 (48)	139 (68)	141 (56)	101 (51)
$t_{1/2}$	1.34[a]	0.8[a]	1.3[a]	1.1[a]
Bioavailability		22(8.0)		
Plasma Moexiprilat				
C_{max}	98 (31)	26 (18)	24 (15)	28 (11)
T_{max}	0.8 (0.1)	2.1 (0.9)	1.8 (0.3)	1.4 (0.2)
AUC_{0-t}	172 (49)	91 (47)	100 (25)	112 (32)
$AUC_{0-\infty}$	178 (47)	99 (43)	129 (33)	123 (36)
$t_{1/2}$	3.4[a]	4.4[a]	11.3[a]	5.0[a]
Bioavailability		18 (3)		
Moexipril Excretion (total as % dose)	91 (1.7)	89 (2.8)	91 (4.1)	87 (1.7)
Urine	65 (5.1)	15 (3.7)	14 (4.0)	13 (5.0)
faeces	26 (4.9)	74 (1.6)	77 (7.2)	74 (5.5)

[a] concentrations are in units of ng equivalent/ml; Time is in hours, AUC is in ng mequivalent*hr/ml

Table 1.2
Radioactivity Profile in Plasma (as %of radioactivity)

	PANEL A				PANEL B			
	5 MG I.V.		15 MG ORAL		15 MG ORAL DAY 1		15 MG ORAL DAY 6	
compound:	10 min	1 hr	1 hr	2 hr	1 hr	2 hr	1 hr	2 hr
P1	–	–	5.3	ND	3.6	4.3	—	—
moexiprillat	30.8	72	7.1	17	2.6	9.3	6.1	2.2
P2	ND	6.8	ND	6.8	—	—	—	—
P3	–	—	ND	7.3	—	—	ND	3.3
DKmoexiprillat	6.2	7.0	25	38	14	30	19	37
Moexipril/P4	58	7.5	55	19	66	38	58	43
DKMoexipril	–	—	4.8	4.8	6.6	10	15	ND
P5	—	—	—	—	—	—	ND	4.4
P6	—	—	—	—	—	—	ND	8.8
P7	—	—	—	—	ND	4.3	—	—
Remainder	5.4	4.4	2.9	7.9	6.6	3.7	1.4	1.1

DK-stands for diketopiperazine metabolite; ND-not detected

Table 1.3
Radioactivity Profile in Urine (as %of dose administered)

	PANEL A		PANEL B	
	5 MG I.V.	15 MG ORAL	15 MG ORAL DAY 1	15 MG ORAL DAY 6
compound				
U1	1.5	0.4	0.1	0.3
U2	0.4	0.6	0.1	0.4
Moexiprillat	39	5.9	7.1	6.6
U3	1.2	0.5	0.4	0.5
U4	0.5	0.9	0.6	0.8
DKMoexiprilat	3.1	4.1	3.8	2.1
Moexipril	18	1.7	1.7	1.0
U5	—	0.2	—	—
DKMoexipril	0.7	0.7	0.3	0.3
Remainder	1.0	0.3	0.3	0.1

DK-stands for diketopiperazine metabolite

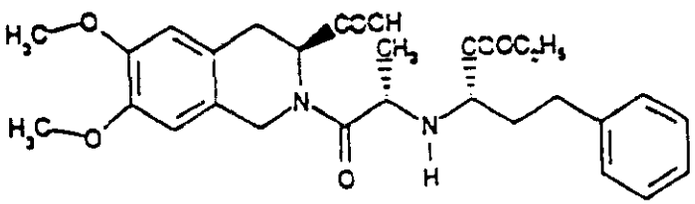
The stucture of moexipril m moexiprilat and the corresponding diketopiperazine derivatives are shown in Figure 1.1

Table 1.4
Radioactivity Profile in Faeces (as %of dose administered)

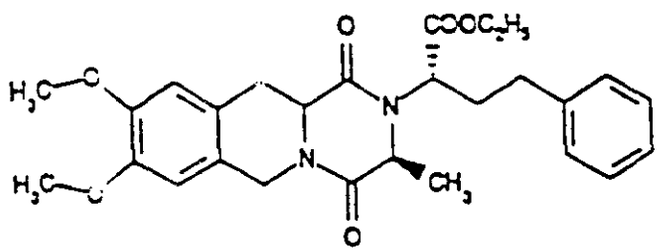
	PANEL A		PANEL B	
	5 MG I.V.	15 MG ORAL	15 MG ORAL DAY 1	15 MG ORAL DAY 6
compound				
F1	—	0.8	0.4	0.8
F2	0.2	0.5	—	0.3
F3	1.2	5.0	3.7	4.2
Moexiprilat	15	52	55	54
F4	0.8	1.4	1.4	1.5
F5	0.6	1.3	1.0	1.0
F6	—	0.6	—	—
DKMoexiprilat	2.2	5.9	4.7	4.8
Moexipril	0.1	1.5	—	—
Dkmoexipril	0.1	—	0.01	—
Remainder	0.6	1.4	1.8	1.8

DK-stands for diketopiperazine metabolite

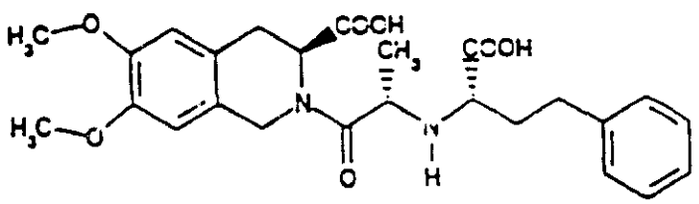
Figure 1.1
Moexipril and Some Metabolites.



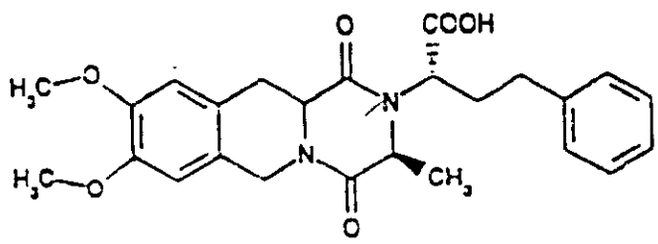
MOEXIPRIL



DIKETOPIPERAZINE MOEXIPRIL



MOEXIPRILAT



DIKETOPIPERAZINE MOEXIPRILAT

There appears to be a large amount radioactivity which is of not accounted for by either moexipril or moexiprillat. The maximal plasma concentrations of the combined moexipril and moexiprillat only add up to 92-116 nequivalents/ml (Table 1.1). The maximal radioactivity , however, corresponds to concentrations of 253-280 neq/ml. Thus, only about 40% of the radioactivity after oral administration appears to be moexipril and/or moexiprillat. Much of the plasma concentration of radioactivity after oral administration appears in the form of the diketopiperazine derivative of moexiprillat as well as a the P4 metabolite which co-migrates with moexipril.

When moexipril is administered intravenously , there is rapid production of moexiprillat so that by 1 hour 72% of the radioactivity is in the form of moexiprillat. The fate of the moexiprillat is dependent upon the route of administration. When moexiprillat is administered IV approximately 55% of the dose could be recovered as moexiprillat with nearly 3/4 of the moexiprillat recovered in urine. When, however, moexipril is administered orally approximately 60% of the dose could be recovered as moexiprillat with nearly 90% of the moexiprillat recovered in the stool.

(Comment: One potential explanation is that moexipril, when administered orally, is rapidly metabolized pre-systemically to moexiprillat and efficiently excreted. When moexipril is administered intravenously, however, moexipril is peripheral converted to moexiprillat and is preferentially excreted in the urine. Coupled with the low bioavailability of moexipril it seems that large amounts of moexipril are pre-systemically cleared with poor access of the resulting mioexiprilat to the circulation. It is unclear if the site of conversion of moexipril to moexiprillat is hepatic or peripheral in nature, the large difference in route of excretion of moexiprillat when administered orally or intravenously would more suggest that hepatically generated moexiprillat would not easily gain access to the circulatioln-assuming that presystemic circulation implies hepatic metabolism. Consequently, it is possible that peripehral esterases may be important in the generation of moexiprilat.)

Although some metabolites are noted on day 6 i.e. P5 and P6, they were not reproducibly seen during the long term therapy (i.e. they were seen at six hour but not at one hours). The overall urine and faecal pattern of metabolites does not suggest that there was any indication of accumulation of metabolites on day 6 (compare the data from day 6 with either the single oral dose for the first of the 6 days of treatment.

ACE inhibition: ACE-inhibition was substantial and persistent whether moexipril was administered as an oral or intravenous formulation. Nearly complete ACE-inhibition was noted at 2 and 4 hours post IV administration of moexipril. There was still nearly 50% of the ACE-inhibition noted at 24 hours and 4 days. Slightly less ACE-inhibition was noted after oral administration of moexipril (approximately 85%). Persistence of approximately 50% of ACE inhibition was noted 24-96 hours post dose.

Safety:

None of the adverse events that were reported were severe. Adverse events included flushing, redness and headache.

Study No. 2- PHAKI 750/1990 Volumes 1.55
Name of Study: Pilot Study-Evaluation of the Pharmacokinetics of Moexipril- A new Ace Inhibitor-Following Single Oral Dosing in Healthy Male Volunteers.
Principal Investigator:
Site of Investigation (Dates):
Formulations: Oral Formulation: 15 mg Capsule Lot No. 900572
Protocol: Normal volunteers with no confounding medical problems or medication were to receive one dose of 2 x 15 mg moexipril. Blood for parent compound and metabolites was to be sampled at the following times: 0 hour (pre-dose), 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after dose.

Urine samples were to be collected at the following intervals : pre dose , 0-12 hours and 12-24 hours post dose.

Results: A total of five male volunteers enrolled. All completed the study. The kinetic constants that were derived are tabulated below;

Parameter Mean (+ SD)	Moexipril	Moexiprilat
C_{max} ng/ml)	49 (22)	37 (21)
T_{max} (hr)	1.5 (1.4)	2.1 (1.1)
AUC_{0-24} (hr*ng/ml)	75 (31)	163 (69)
AUC_{0-t} (hr*ng/ml)	73 (30)	158 (74)

Maximal plasma ACE inhibition (97%) occurred at 4 hours post dose. Onset of ACE inhibition was rapid with 28% decrease in ACE activity by 0.5 hours. ACE inhibition persisted for at least 24 hours , at the last measurement 72% of the ACE activity (relative to baseline) was inhibited.

The median amount of moexipril and moexiprillat excreted in the urine were 365 ug and 992 ug respectively.

Safety : There were no reported adverse events

Study No 3- PHAKI794 Volumes 1.56
Name of Study: An Open -Label, Phase I, Two-Way, Crossover Study to Investigate the Bioequivalence of Two Different Formulations of Moexipril in Healthy Volunteers.
Principal Investigator:
Site of Investigation (Dates):
Formulations: Oral Formulation: - (Preparation 1) 15 mg Moexipril Hydrochloride (Formulation 4A) Coated Tablet Batch/Lot No./950512
Oral Formulation : (Preparation 2)15 mg Moexipril Hydrochloride (Formulation of Syntex) Capsule; Batch /Lot no. 913168.

Protocol: A total of 30 healthy subjects were to receive preparation 1 and 2 in an open, randomized cross-over design. Each volunteer was to receive a single 30 mg dose (2 x 15 mg capsule or tablet) with a 1-week washout period followed by the alternate formulation. Dosing was done under fasting conditions. Pharmacokinetic samples were taken at 0, 1/12, 1/6, 1/3, 1/2, 3/4, 1,1 1/2, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose for the measurement of both moexipril and moexiprilat. Blood pressure in the sitting position was measured at 1, 2 and 4 hours post drug administration.

Results: Although 30 volunteers were to be enrolled, 37 such volunteers were eventually treated under this protocol. One patient was excluded from analysis because of concurrent therapy during the washout phase. The average age (27.3 SD 4.4 yrs), weight (75.6 SD 6.2 Kg) and height (179.3 SD 6.0 cm) of the enroled subjects was unremarkable. The sponsor's calculated pharmacokinetic results for both formulations for moexipril and moexiprillat as well as the calculated confidence intervals are shown below.

		Moexipril			Moexiprilat	
Parameter	Formulation	Formulation	C.I.	Formulation	Formulation	C.I.
Mean + SD	4A	Syntex		4A	Syntex	
AUC-1[a]	307.8 (157)	313.5 (195)	86-112	149.2 (51)	148.9 (46)	88-111
AUC-3[b]	346.0 (146)	326 (195)	86-112	174.9 (50)	171.1 (43.1)	89-110
C_{max}[c]	182.9 (73)	181.6 (82)	88-113	47.1 (17)	49.8 (24.4)	84-112
T_{max}[d]	0.98 (0.33)	0.98 (0.33)	88-125	1.60 (0.35)	1.65 (0.26)	83-117
k	0.456 (0.13)	0.504 (0.14)		0.084 (0.022)	0.087 (0.018)	
t1/2	1.64 (0.48)	1.49 (0.48)	105-127	8.88 (2.46)	8.29 (1.68)	96-115

a-calculated by the trapezoidal rule, from 0 hour to the last quantified sample (h*ng/ml)
b- calculated by the trapezoidal rule with the terminal portion calculated by extending the curve based on the terminal t1/2 (h*ng/ml)
c- Peak concentration (ng/ml)
d- sampling time at peak concentration 9 hours) -non[parametric method was used to calculated confidence intervals.

The results would suggest that the two studied formulations are equivalent. Both the parent compound as well as the major metabolite are within the usually accepted confidence intervals.

Of interest was that the at least one additional terminal half-life of moexiprilat must be present since a large number of volunteers had moexiprillat at measurable levels at the 0 time point of the cross-over treatment.

Safety: The only serious adverse episode was a vaso-vagal response which occurred prior to the second dosing of the formulation. Other adverse events were headache, headache with dizziness or pressure in the head.

Study No 4- PHAKI 792 Volumes 1.59
Name of Study: An Open -Label, Phase I, Two-Way, Crossover Study to Investigate the Bioequivalence of Two Different Formulations of Moexipril in Healthy Volunteers.
Principal Investigator:
Site of Investigation (Dates):
Formulations: Oral Formulation: - (Preparation 1) 15 mg Moexipril Hydrochloride (Formulation 4) Coated Tablet Batch/Lot No. 915513
Oral Formulation : (Preparation 2)15 mg Moexipril Hydrochloride (Formulation of Syntex) Capsule; Batch /Lot no. 913168.

Protocol: A total of 30 healthy patients were to receive preparation 1 and 2 in an open, randomized cross-over design. Each volunteer was to receive a single 30 mg dose (2 x 15 mg capsule or tablet) with at least a 1-week washout period between doses. Drug was administered under fasting conditions. Pharmacokinetic samples for both moexipril and moexiprilat were collected at the following times: 0, 1/12, 1/6, 1/3, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose. Blood pressure in the sitting position was measured at baseline and 1, 2 and 4 hours post dose.

Results: Thirty volunteers were enrolled into the study. The average age (27.0 years SD 5.7), weight (71.4 Kg SD 6.8) and height (177.8 cm SD 8.1) were unremarkable. The sponsor's calculated pharmacokinetic results for both formulations for moexipril and moexiprillat as well as the calculated confidence intervals are shown below. The concentration related parameters which were arithmetically determined were log transformed prior to the statistical analysis for confidence intervals.

		Moexipril		Moexiprilat		
Parameter	Formulation	Formulation	90% C.I.	Formulation	Formulation	90% C.I.
Mean + SD	4	Syntex	ratio	4	Syntex	ratio
AUC-1[a]	300.3 (175)	326.5 (173)	77-101	144.5 (56)	137. (53)	94-118
AUC-3[b]	328.1 (175)	343.9 (169)	80-107	165.0 (56)	153.5 (54.3)	97-119
C_{max}[c]	180.0 (90)	197.9 (80)	77-99	48.0 (22)	48.1 (23.3)	85-123
T_{max}[d]	0.97 (0.27)	1.04 (0.38)	100-150	1.45 (0.33)	1.59 (0.32)	83-108
k	0.473 (0.15)	0.474 (0.15)		0.095 (0.029)	0.096 (0.018)	
t1/2	1.67 (0.76)	1.63 (0.66)	88-116	7.96 (2.35)	7.48 (1.39)	95-111

a-calculated by the trapezoidal rule, from 0 hour to the last quantified sample (h*ng/ml)
b- calculated by the trapezoidal rule with the terminal portion calculated by extending the curve based on the terminal t1/2 (h*ng/ml)
c- Peak concentration (ng/ml)
d- sampling time at peak concentration 9 hours) -non-parametric method was used to calculated confidence intervals.

The results would suggest that the two studied formulations are nearly equivalent. Both the parent compound as well as the major metabolite are within or close to the usually accepted confidence intervals.

Blood pressure decreases were noted at 1 hr (systolic/diastolic change from baseline in mm Hg; -5.8/-6.5) was maximal at 2 hours (-8.3/-7.5) and persisted at the end of the four hour observation period (-6.3/ -6.3). Pulse rate dropped 4.5 bpm.

Of interest was that the at least one additional terminal half-life of moexiprilat must be present since a large number of volunteers had moexiprillat at measurable levels at the start of the cross-over treatment.

Safety: No serious adverse events were noted. The most frequent adverse event was headache which

was reported in 8 volunteers treated with preparation A and 9 volunteers who received preparation B. Dryness of mouth in 1 participant swelling of the back o the hand in 1 participant and diarrhea in 1 participant were other tabulated adverse events.

With respect to laboratory abnormalities, those which I considered significant are noted below.

Subject # 4 had a K^+ at baseline of 4.83 mmol/l at baseline and 5.3 at discharge.

subject #6 had a Ca^{++} at baseline of 2.37 mmol/l and at discharge 2.25 (normal 2.27-2.64 mmol/l)

subject #7 had an elevated total bilirubin at discharge 22.5 baseline was 10.2 (normal range 3-22).

subject #10 had a low calcium at discharge 2.26 mmol/l baseline value was 2.41.
this subject also had a low glucose at discharge 4.1 mmol/l (normal 4.2 -6.5)

subject #19 had a low calcium at discharge 2.26 mmol/l -baseline was 2.35 mmol/l

subject #21 excreted 30 kg/dl of albumin in the urine at discharge.

subject #23 had a low calcium at discharge 2.23 mmol/l -baseline was 2.52 mmol/l.

subject #27 had a high K^+ at baseline 5.15 mmol/l but normal discharge K^+ 4.80 mmol/l

subject #29 had a high urea at discharge 7.7 mmol/l baseline was 5.9 mmol/l (normal 3.2-7.5)

Conclusion: Formulation 4 is seen to be nearly bioequivalent to the syntex formulaiton.

Study No 5- PHAKI 758 Volumes 1.61

Name of Study: An Open -Label, Phase I, Three-Way, Crossover Study to Investigate the Bioavailability and Pharmacokinetics of Three Different Dosage Formulations of Moexipril in Healthy Volunteers.

Principal Investigator:

Site of Investigation (Dates):

Formulations: - All formulations were manufactured by Schwarz Pharm AG

Oral Formulation: (Preparation 1) 15 mg Moexipril Hydrochloride Capsule

Oral Formulation: (Preparation 2) Moexipril Hydrochloride, 30 mg Powder

Oral Formulation: (Preparation 3) 15 mg Moexipril Hydrochloride Encapsulated Tablet

Protocol: A total of 12 healthy subjects were to receive the three preparations in an open-label, randomized cross-over design. Each volunteer was to receive a single 30 mg dose (2 x 15 mg capsule or tablet or 30 mg oral solution-preparation 2) with at least a 1-week washout period between doses. Dosing was done under fasting conditions. Pharmacokinetic samples were collected at 0, 1/12, 1/6, 1/3, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose for both moexipril and moexiprilat. Blood pressure in the sitting position was measured at baseline and 1, 2 and 4 hours post dose. Subsequent amendment of the protocol discontinued the measurement for moexiprilat since the formulations were not bioequivalent.

Results: The average age (28.5 years SD 5.1), weight (74.7 kg SD 9.7) and height (180.3 cm SD 7.6) were unremarkable. The maximal group-averaged systolic/diastolic blood pressure changes relative to baseline were 2.8/5.5, 11/10.4; 11.3/ 9.3 for formulations 1,2 and 3 respectively. There was insufficient information to decide if trough was reached or blood pressure declined further . Heart rate changes were modest. The maximal heart rate change (group means) of 4.6 BPM with the oral solution (preparation B) and the least of 1.9 occurring with preparation 3.Pharmacokinetic data for moexipril are as shown below:

Parameter Mean +, SD	Preparation A Capsule	Preparation B Solution	Preparation C Encapsulated Tablet
AUC-1a	86.8 (47)	88.7 (40)	110.4 (48.7)
AUC-3b	89.6 (50)	103.6 (46)	117.2 (55)
Cmax	63.3 (36)	65.2 (34)	77.7 (37)
Tmax	0.71 (0.3)	0.58 (0.12)	0.73 (0.2)
k	0.963 (0.37)	1.10 (0.31)	1.08 (0.43)
t1/2	0.82 (0.31)	0.69 (0.25)	0.74 (0.29)

a-calculated by the trapezoidal rule, from 0 hour to the last quantified sample (h*ng/ml)

b- calculated by the trapezoidal rule with the terminal portion calculated by extending the curve based on the terminal t1/2 (h*ng/ml)

c- Peak concentration (ng/ml)

d- sampling time at peak concentration 9 hours) -non-parametric method was used to calculated confidence intervals.

None of the three formulations could be considered bioequivalent. Surprisingly , the encapsulated preparation has a higher bioavailability than the oral solution.

Safety: All adverse events were mild. There were 11 episodes of headache, distributed nearly equally among the three preparations . Two additional volunteers complained of tiredness (1 during preparation A and one with preparation B) .

Study No 6- PHAKI 756 Volumes 1.63

Name of Study: An Open -Label, Phase I, Two-Way, Crossover Study to Investigate the Bioequivalence of Two Different Dosage Forms of Moexipril (Tablet and Capsule) in Healthy Volunteers.

Principal Investigator:

Site of Investigation (Dates):

Formulations: all formulations were Manufactured by Schwarz Pharm AG;

Oral Formulation: (Preparation 1) 15 mg Moexipril Hydrochloride - Coated Tablet Batch no. 903529

Oral Formulation: (Preparation 2) 15 mg Moexipril Hydrochloride, Capsule. Batch no 902512

Protocol: A total of 12 normal heathy volunteers were to be treated under fasting conditions with the test articles in an open, randomized cross-over design. Each volunteer was to receive a single 30 mg dose (2 x 15 mg capsule or tablet) with at least a 1-week washout period between doses. Dosing was done under fasting conditions.Pharmacokinetic samples were collected at times 0, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose for assay of both moexipril and moexiprilat. Blood pressure in the sitting position was measured at baseline and 1, 2 nd 4 hours post drug administration.

Results: A total of 13 subjects were treated with the test articles. One patients withdrew after the first treatments due to "personal" reasons. The age (29.9 yrs SD 4.6) weight (71 kg SD 9.6) an height (176.1 cm SD 7.8) were unremarkable.

Systolic/diastolic changes over the 4 hour observation period showed a maximal group average change of -12.1/-11.6; and -8.1/-11.6 for preparations 1 and 2 respectively. Pulse rates were essential unaffected (maximal average change less than 1 BPM).

The pharmacokinetic parameters are displayed below. It is obvious that Formulation 1 is less bioavailable than formulation 2.

	Moexipril		Moexiprilat	
Parameter Mean + SD	Formulation 1	Formulation 2	Formulation 1	Formulation 2
AUC-1[a]	56.3 (28)	86.3 (28.1)	78.3 (36)	128.2. (57.6)
AUC-3[b]	67.9 (30)	85.6 (30)	104.2 (3956)	148.2 (56)
C_{max}[c]	45.2 (20)	58.5 (23)	29.9 (16)	44.2 (19)
T_{max}[d]	0.69 (0.30)	0.83 (0.27)	1.3 (0.3)	1.5 (0.3)
k^e	0.8685 (0.25)	0.773 (0.30)	0.355 (0.138)	0.335 (0.159)
t1/2	0.877 (0.32)	1.07 (0.52)	39 (0.324)	2.84 (2.06)

[a]-calculated by the trapezoidal rule, from 0 hour to the last quantified sample (h*ng/ml)

[b]- calculated by the trapezoidal rule with the terminal portion calculated by extending the curve based on the terminal t1/2 (h*ng/ml)

[c]- Peak concentration (ng/ml)

[d]- sampling time at peak concentration 9 hours) -non-parametric method was used to calculated confidence intervals.

Safety: One patient reported a headache categorized as mild. Sponsor states no relevant changes in clinical chemistry. Data not supplied.

Conclusion : The formulations were not bioequivalent.

Study No 7- PHAKI 759 Volumes 1.65
Name of Study: An Open -Label, Phase I, Three-Way, Crossover Study to Investigate the Bioequivalence of Three Different Formulations of Moexipril in Healthy Volunteers.
Principal Investigator:
Site of Investigation (Dates):
Formulations: All formulations manufactured by Schwarz Pharm AG (even the Formulation of
Oral Formulation: (Preparation 1) 15 mg Moexipril Hydrochloride Tablet Batch no. not stated
Oral Formulation : (Preparation 2)15 mg Moexipril Hydrochloride, Tablet. Batch no not stated
Oral Formulation : (Preparation 3)15 mg Moexipril Hydrochloride, (Formulation of Capsule. No Batch no given.

Protocol: A total of 12 normal heathy volunteers were to be treated under fasting conditions with the test articles in a three-way open, randomized cross-over design. Each volunteer was to receive a single 30 mg dose (2 x 15 mg capsule or tablet from each formulation) with at least a 1-week washout period between doses. Dosing was done under fasting conditions. In addition to pharmacokinetic samples which were collected at times : 0, 1/12, 1/6, 1/3, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose for the analysis of both moexipril and moexiprilat, blood pressure in the sitting position was measured at the at baseline and 1, 2 and 4 hours post drug administration.

Results: A total of 14 patients were treated with the test articles. Two patients withdrew after the first treatment. Neither of the discontinuations appeared to be due to adverse reactions. Although the pharmacokinetic parameters of the three formulations with respect to moexipril did not substantially differ, the sponsor did not feel that the formulations were suitable for further development. No data on moexprilat were tabulated.

Safety: Headache was the most common adverse event, which was noted in 9, 8 and 8 subjects, who were administered treatments 1, 2 and 3 respectively.

In addition, one subject each had modest increases in bilirubin (maximum value measured = 20; normal range 0.0-17.0 umol/l); GGTP (maximum value 38.1; normal range 0.0-28U/l) and glucose (maximum value 7.80; normal range 4.2-5.6 mmol/l) .

Study No 8- PHAKI 791 Volumes 1.67
Name of Study: An Open Label, Phase I, Three-Way, Crossover Study to Investigate the Bioequivalence of Three Different Formulations of Moexipril in Healthy Volunteers.
Principal Investigator:
Site of Investigation (Dates):
Formulations: All formulations manufactured by Schwarz Pharm AG (even formulation of Syntex)
Oral Formulation: - (Preparation 1) 15 mg Moexipril Hydrochloride (Formulation 3) Tablet Batch no. 913169
Oral Formulation : (Preparation 2)15 mg Moexipril Hydrochloride (Formulation 4), Tablet. Batch no 913170
Oral Formulation : (Preparation 3)15 mg Moexipril Hydrochloride, (Formulation of Syntex) capsule. Batch no 912118.

Protocol: A total of 12 normal heathy volunteers were to be treated, under fasting conditions, with the test articles in a three-way, open, randomized cross-over design. Each volunteer was to receive a single 30 mg dose (2 x 15 mg capsule or of either tablet formulation) with at least a 1-week washout period between doses. Dosing was done under fasting conditions. Pharmacokinetic samples for both moexipril and moexiprillat were collected at times: 0, 1/12, 1/6, 1/3, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose). Blood pressure in the sitting position was measured at baseline and 1, 2 nd 4 hours post drug administration.

Results: A total of 13 subjects were treated with the test articles. One subject did not return after the second treatment. The discontinuation did not appear to be due to adverse reactions. The age (29.3 years SD 5.5), weight (75.0 Kg SD 7.8) and height (180.9 cm SD 5.7) of the volunteers was unremarkable. Mean maximal blood pressure effects were -5.7/-10.9; -9.1/-10.5, and -6.8/-10.2 for preparations 1, 2 and 3 respectively. The maximal effect on blood pressure may in reality be somewhat greater since the last (four hour) time point demonstrated the maximum blood pressure response. Pulse rates were only modestly elevated above baseline (2-3 BPM), however, the 4 hour time point during preparation B treatment demonstrated an 8.6 BPM increase.

With respect to the constants of moexipril these are listed below. Moexiprillat was not further determined.

		Moexipril	
	Preparation -	Preparation 1	Preparation 2
Parameter	Syntex	(Formulation 3)	(Formulation 4)
AUC-1[a]	86.6 (42)	83.4 (58)	84.2 (58)
AUC-3[b]	90.2 (42)	89.2 (60)	88.1 (58)
C_{max}[c]	71.3 (28)-	65.7 (31)	68.4 (40)
T_{max}[d]	0.81 (0.26)	0.79 (0.21)	0.67 (0.12)
k^e	1.259 (0.34)	1.250 (0.40)	1.357 (0.35)
t1/2	0.584 (0.14)	0.606 (0.19)	0.559 (0.22)

a-calculated by the trapezoidal rule, from 0 hour to the last quantified sample (h*ng/ml)
b- calculated by the trapezoidal rule with the terminal portion calculated by extending the curve based on the terminal t1/2 (h*ng/ml)
c- Peak concentration (ng/ml)
d- sampling time at peak concentration 9 hours) -non-parametric method was used to calculated confidence intervals.

Safety: Headache and tiredness were the most common adverse events. One volunteer sustained a "mild" brief blackout when getting up. This event occurred 1 1/2 hours after dose. In addition, one subject each had modest increases in SGPT (maximum value 76, normal range 0.0-56 U/L) and ESR (maximum value 27 mm/1 h; normal range 0-08 mm/1 h) .

Study No 9- PHAKI 751 Volumes 1.69
Name of Study: Bioequivalence Study With Hydrochlorothiazide in Healthy Male Volunteers.
Principal Investigator:
Site of Investigation (Dates):
Formulations: Oral Formulation: - (Preparation 1) Hydrochlorothiazide 12.5 mg capsule, Schwarz Pharma Batch no 900629.
Oral Formulation : 25 mg hydrochlorothiazide (Merck Sharp & Dohme, U.S.A. batch no WE 10116

This study was to test the bioequivalence of two formulation of hydrochlorothiazide. No moexipril was given.

Only urinary concentrations of hydrochlorothiazide were assayed.

Study No 10- PHAKI 795 Volumes 1.71
Name of Study: Examinations on Dose Linearity of Moexipril in Healthy Volunteers.
Principal Investigator:
Site of Investigation (Dates):
Formulations: Oral Formulation: - Moexipril Hydrochloride (Formulation 4)
Manufactured by Schwarz Pharm AG; powder

Protocol: Twenty-Four normal individuals with no concurrent medical problems were to be treated in a randomized, four-way crossover, open label design study. Each individual was to receive the four doses of moexipril (3.75, 7.5, 15 and 30 mg) with at least a 1-week washout period between doses. The formulation was administered as reconstituted powdered moexipril in 200 cc of water. Dosing was done under fasting conditions. Pharmacokinetic samples to assay moexipril and moexiprillat were collected at 0, 1/12, 1/6, 1/3, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose. Blood pressure in the sitting position was measured at baseline,1, 2 and 4 hours post drug administration.

Results: A total of 24 volunteers were enrolled. All completed the study. The age (29 years SD 5.2), weight (71.7 kg SD 9.4) and height (175 cm SD 6.3) were unremarkable. Group mean maximum effects on baseline subtracted systolic and diastolic blood pressures were -6.2/-7.6; -7.8, -7.1; -12.3/ -12.1; -11.4, -8.5) for the 3.75, 7.5, 15 and 30 mg doses, respectively. Mean pulse rates dropped substantially with maximal drops from baseline of 5.7, 12.8, 7.0 and 7.4 BPM for the 3.75 through 30 mg doses, respectively. The maximum hemodynamic effects were noted at the 2-4 hour time points.

With respect to the kinetic constants derived form the study, these are displayed below:

Table 10.1
Moexipril Parameters After Treatment With Moexipril at the Stated Doses (Mean ± SD)

Parameter	3.75 mg moexipril	7.5 mg moexipril	15 mg moexipril	30 mg moexipril
AUC-1[a]	54.3 (49)	106 (87)	166.7 (80)	322.5 (191)
AUC-3[b]	125 (61)[n=3]	106 (52)[n=6]	216 (79)[n=7]	320.6 (180)[n=8]
C_{max}[c]	29.9 (17)	61.9 (36)	99.5 (45)	183 (79)
T_{max}[d]	0.89 (0.44)	0.80 (0.14)	0.92 (0.34)	0.77 (0.38)
k^e	0.41 (0.22)[n=3]	0.39 (0.17)[n=6]	0.34 (0.20)[n=7]	0.23 (0.14)[n=8]
t1/2	2.37 (1.8)[n=3]	2.14 (1.14)[n=6]	3.0 (2.3)[n=7]	3.98 (2.1)[n=8]

Moexiprilat Parameters After Treatment with Moexipril at the Stated Doses (Mean ± SD)

Parameter	3.75 mg moexipril	7.5 mg moexipril	15 mg moexipril	30 mg moexipril
AUC-1[a]	37.3 (38)[n=15]	52.8 (52)	82.3 (50.)	144.7 (90)
C_{max}[c]	5.8 (6.1)[n=15]	7.7 (6.7)	18.9 (1 .1)	40.6 (24)
T_{max}[d]	1.97 (0.99)[n=15]	1.64 (0.56)	1.72 (0.73)	1.3 (0.44)
k^e	0.028(0.016)[n=10)	0.056 (0.039) [n=15]	0.066 (0.02)[n=13]	0.098(0.08)[n=13]
t1/2	31.0(15.6)[n=10]	21.0 (16.6)[n=15]	12.4 (6.7)[n=13]	9.37 (4.9)[n=13

a-calculated by the trapezoidal rule, from 0 hour to the last quantified sample (h*ng/ml)
b- calculated by the trapezoidal rule with the terminal portion calculated by extending the curve based on the terminal t1/2 (h*ng/ml)
c- Peak concentration (ng/ml)
d- sampling time at peak concentration [hours) -non parametric method was used to calculated confidence intervals.

With respect to dose proportionality, the 90% confidence intervals, dose corrected, which are rather broad are shown below.

Table 10.2
Confidence intervals Compared to the 15 mg Dose

	Moexipril		Moexiprilat	
Confidence Intervals:	AUC-1	C_{max}	AUC-1	C_{max}
3.75 mg/15 mg				
lower limits	89.1	94.9	129.0	76.0
upper limits	143.08	137.1	205.3	143.0
7.5 mg/15 mg				
lower limits	90.3	94.2	91.3	50.4
upper limits	144.9	136.1	145.3	94.8
30 mg/15 mg				
lower limits	73.1	73.7	70.4	80.4
upper limits	117.3	106.4	112.2	151.2

It should be appreciated that the study does not show dose proportionality for moexipril or moexiprillat. Since the formulations were administered as solutions the non-linearity could best be attributable to the chemical entity and not to any formulation specific problems. The lack of dose proportionality does not suggest that safety will be compromised since the lower doses appeared to have the higher C_{max} and AUC values.

Safety: The number of subjects experiencing adverse events were four, four, six and three in the 3.75 through 30 mg dose groups, respectively. There was one severe reaction- cold sweat at 50 minutes post 30 mg dose, lasting 15 minutes. The other adverse events were common for those seen with vasodilators and included headache (n=6), tiredness/feeling of weariness (n=11), dizziness (n=3).

Study No 11- Protocols 925-3, -4, -6 Volume 1.72
Name of Study: Plasma Concentration of CI-925 and Its Active Metabolite (CI-929) Following Single Rising Dose Administration of CI-925 in Mild to Moderate Hypertensive Subjects, Protocols 925-3, -4, -6
Principal Investigator:

Date of Study: Not stated, although the analytical report is dated March, 1986.
Formulations: Capsules- 1 mg (Lot no CL 225113), 2 mg (Lot no CL 226113), 4 mg (lot no. CL 227113), 7.5 mg (lot no. CL 228113), 15 mg (lot no CL 229113), 30 mg (lot no. CL 164094), 60 mg (Lot no CL 165094);

Protocol. This was an open label dose escalating study. Enrolment required that the subjects be hypertensive with supine diastolic blood pressure between 95-115 m Hg. Exclusion criteria included concurrent medical problems and/or concurrent medications. Subjects were to receive two doses of CI-925 (moexipril?). The first dose of CI-925 was dependent on the last dose of the previous subject. If that subject sustained a clinically significant ADR, the dose would be decreased to 1 level below that of the previous subject, otherwise the dose will be equal to the higher dose of the preceding subject. The second dose received by each subject will depend on the response to the first dose. Should adverse events occur, the subject would not receive the second dose, If the dose has no effect or suboptimal effect (definition not stated as to what constitutes optimal effect) the dose would be increased. The sequence of doses is shown below. All doses were administered after an overnight fast. Doses were separated by 2 days.

Subject no.	Dose 1	Dose 2
1	1 mg	2 mg
2	2 mg	4 mg
3	4 mg	7.5 mg
4	7.5 mg	15 mg
5	15 mg	30 mg
6	30 mg	60 mg
7	60 mg	120 mg
8	60 mg	120 mg

Measurements included plasma concentrations, plasma renin activity , ACE activity and aldosterone at times= 2, 6, 12, 24 and 48 hours post-dose. To assess safety ECG and blood pressures were to be followed.

Results: The study summary was poorly done with no line entries or tabular lists to assess safety or hemodynamic effects of CI-925. Only a study summary was available to read. A total of 25 patients were enrolled. No patient withdrew due to adverse episodes although two patients did not receive the second scheduled dose. Blood pressure drops were noted 4-8 hours post dose. All doses of > 4 mg with the excetpion of the 15 g dose resulted in substantial blood pressure drops (> 10 mm Hg). Surprisingly, heart rate drops of 8-9 beats per minute were noted in the 15 and 30 mg dose.

Assay was performed by gas-liquid chromatographic method. The assay was unable to reproducibly assess concentrations in those dosed with less than 15 mg.

Study No 12- Protocol CM 1394 Volume 1.72
Name of Study : A Single Rising Dose Efficacy and Pharmacokinetics of RS-10085 in Patients with Mild to Moderate Hypertension.
Principal Investigator and site:

Date of Study : October 20, 1986-February 6, 1987
Formulations: Capsules- 3.75,7.5 and 30 mg were all derived from the same drug substance Lot no. (.5604-73-IS). The other doses used in the study were administered as multiple of the three listed doses.

Protocol: This was a placebo-controlled, single dose study. Subjects were to be sequentially enrolled into progressively higher dose groups. Within each dose group there were six patients. Four of these patients were to receive active treatment and two placebo. Progression to the next dose level group was dependent on the absence of any demonstrated safety concerns after the previous dose. Subjects were of either gender, between the ages of 21-70 with stable uncomplicated baseline hypertension (sitting diastolic blood pressures c. between 95-114 mm Hg). Subjects were excluded if they had confounding medical problems. Primary variables measured for efficacy included supine and standing blood pressure and heart rate. Pharmacokinetics of RS-10085 and the de-esterified active product RS-10029 were measured at baseline and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 and 48 hours post dose. Assay of samples for the two chemical entities differed based on the dose. For dose groups of less than or equal to 7.5 mg, a radioimmunoassay was employed. For dose levels of 15 and greater, gas chromatography was used. Safety assessments included ECG, laboratory assessments and the tabulation of adverse episodes.

Results: A total of 30 subjects (gender distribution =20 male, 10 female ; race distribution= 21 caucasian, 5 blacks , 1 Asian and 3 other) were enrolled. Blood pressure effects as a function of dose, given the modest size of the individual treatment groups were difficult to quantify. There was a substantial drop in placebo (pooled from each of the treatment groups so that there were a total of 10 placebo patients) diastolic blood pressure during hours 3-12 of the study. During that time, placebo blood pressure decreases ranged from 7.6 -16 mm Hg. There was a trend towards greater diastolic blood effects with increasing dose, although the trend was not overwhelming. The range of blood pressures (not placebo corrected) noted during 2-12 hours were in the respective dose groups 4-8.5 mm Hg (3.75 mg); 5.0-16.5 mm Hg (7.5 mg); 12.5-20 mm Hg (15 mg); 7.5-25.3 mm Hg (30 mg) and 8.0-22 mm Hg (60 mg).

The pharmacokinetic constants as well as the method of analysis are shown below. For the 15 mg dose both GC and RIA were performed and although there were some differences in measurements the numbers were fairly close (differed by less than approximately 25%):

Table 18.1
Pharmacokinetics of RS-10085 and RS-10029 After Single Dose Treatment With RS-10085 Mean (+ SE)
N=4/Group

	RS-10085				RS-10029			
Dose (mg)	method	$AUC_{0-\infty}$ ng/ml•hr	C max ng/ml	T1/2 hr	method	AUC0-∞ ng/ml•hr	C max ng/ml	T1/2 hr
3.75	NS	NS	NS	NS	RIA	36.9 (5.1)	3.2 (1.0)	12..4 (3.9)
7.5	NS	NS	NS	NS	RIA	88.0 (15)	5.5 (2.0)	23.4 (3.9)
15	GC	92.4 (24)	54.7 (14)	1.0 (0.4)	GC	138 (5.4)	19.1 (3.9)	14.9 (4.6)
30	GC	152.8 (27)	87.3 (13)	0.9 (0.3)	GC	160 (17)	44.9 (8.3)	1.7 (0.2)
60	GC	665 (344)	384 (216)	1.4 (0.3)	GC	386 (55)	131(30)	2.2 (0.5)

NS-not stated; GC-determined by gas chromatography; RIA-determined by radio-immuno assay

The T max values for RS-10085 ranged from 0.9-1.0 hr. The T max for RS-10029 ranged from 2.5 $\pm$ 0.5 for the 3.75 mg dose to 1.4$\pm$0.2 for the 60 mg dose. T_{max} decreased in a dose related manner.

RS-10029 is a potent inhibitor of serum ACE activity. The EC50 for ACE inhibition calculated from the 3.75 mg dose was 0.41 ng/ml (?). Plasma renin activities did not seem reproducibly or consistently elevated.

With respect to moexxipril pharmacokinetic values, both the high Cmax and $AUC_{0-\infty}$ values were due to one subject (subject # 43) whose measured C max (1012 ng/ml) and AUC (1648 hr.ng/ml) were substantially greater than the other individuals randomized toi the 60 mg dose group. This subjects Cmax was measured at the earliest time point and actually may have substantially exceded this value had earlier time points been measured. The moexiprillat kinetics also seem to be somewhat greater than predicted based on dose proportionality. The large SE due to the small sample size make any conclusions hazardous.

Safety: Eight of the 20 patients assigned to the various doses of RS-10085 and 4 of 10 subjects randomized to placebo reported adverse episodes. Headache was the most common adverse event. It occurred in 7 treated patients with an intensity reported as moderate in 2 patients severe in 1 patient and mild in the rest.

There was no evidence of severe blood pressure drops (diastolic blood pressures less than 60 mm Hg).

Study No 13- Protocol CM 1394 Volume 1.73
Name of study: A Phase I, Open Label Study to Determine the Pharmacokinetics of Orally Administered Single and Multiple Doses of Moexipril in Healthy Elderly and Younger Male Subjects.
Principal Investigator:

Date of Study : October 2, 1991-October 10, 1991
Formulations: Capsules- 15 mg Batch no 912118

Protocol: This was a single-center, open-label, pharmacokinetic study comparing healthy elderly (65-80 years old) to healthy younger (18-45 years old) males after administration of both single and multiple doses of moexipril. Inclusion criteria required that individuals be healthy and in the appropriate age range. Exclusion criteria included: hypersensitivity or intolerance to ACE-inhibitors; 2) significant cardiovascular,hepatic, renal, hematologic, endocrine, neuropsychiatric, GI or metabolic disorders; 3) elevated creatinine clearance based on the Cockcroft-Gault equation of less than 50 for those 65-70 years old and less than 40 for those 71-80 years old. For younger patients exclusion required creatinine clearance of < 90 ml/min.; 4) presence of sodium depletion; 5) ethanol or drug abuse

Individuals received doses of 15 mg of Moexipril on days 1 through 5 after an overnight fast. On day 1 and 5 full kinetic screens for moexipril and moexiprilat were performed. Kinetic screen consisted of sampling blood and assaying samples at predose and 0.5, 0.75, 1, 1.5 2, 3, 4, 6, 8, and 12 hours post dose), collecting and assaying urine samples of moexipril and moexiprilat (-1 to 0 hours (predose) and 0-2, 2-4, 4-6, 6-8, 8-12 and 12-24 hours post dose). Vital signs both sitting and standing were measured at pre-dose and 0.5, 1, 1.5, 2, 3,4, 6, 8 and 12 hours post-dose). On days 2, 3 and 4 hemodynamic and kinetic measurements were taken at trough. Two additional kinetic measurements (at 24 and 48 hours after the last dose on day 5) were collected. One serum sample pre-dose to measure protein binding was collected prior to dosing.

Results: A total of 24 male subjects equally divided between the elderly (65-80 years old) and the young (18-45 years old) were enrolled into the study. All subjects completed the study. Clearly, the mean (SE) ages differed (69.9 $\pm$1.23) versus (30.9 $\pm$ 2.39) for the elderly and young, respectively. Weight and height differed only by approximately 3-5%, with the elderly slightly leaner (74.6 vs 78.4 kg) and slightly shorter 172 verus 177 cm . Systolic blood pressures, both sitting and standing for the elderly were greater than those of the young (e.g. sitting systolic blood pressure elderly was 120.8 $\pm$ 3.11 versus 106.9 $\pm$ 2.29). Calculated creatnine clearance for the elderly were (mean $\pm$ SE) 71 $\pm$ 4.6 ml/min and for the younger subjects 115 $\pm$ 4.2 ml/min..

The time course for the sitting systolic and diastolic blood pressure changes for the elderly and younger patients are shown in Figures and 13.1 and 13.2. (pg 74-88 and 74-89; not reproduced here). Maximum sitting and standing, diastolic and systolic blood pressure drops for the elderly occurred at 6 hours post dose on both days 1 and 5 . The maximal effects on systolic and diastolic blood pressures (group means) ranged from 12-16 mm Hg systolic to approximately 14 mm Hg diastolic from the single baseline measurement. For the younger patient group. the effects on blood pressure were less impressive.. The maximal change from baseline for the young was approximately 5 mm systolic and 5-12 mm diastolic. There were slight increases in pulse rate

With respect to the kinetic constants there are shown below:

Table 13.1

Parameter	Moexipril		Moexiprillat	
	Elderly	Young	Elderly	Young
Day 1				
C_{max} [ng/ml]	140 ± 48	119 ± 64	24 ± 8	17 ± 16
T_{max} [h]	1.1 ± 0.3	0.9 ± 0.3	1.9 ± 0.2	1.6 ± 0.4
$AUC_{(0-t)}$ [ng/ml*h]	294 ± 151	238 ± 157	102 ± 28	75 ± 44
A_{max} [ug]	143 ± 48	159 ± 75	339 ± 172	326 ± 268
Day 5				
C_{max} [ng/ml]	124 ± 66	94 ± 42	31 ± 12	24 ± 11
T_{max} [h]	1.3 ± 0.5	0.9 ± 0.3	1.9 ± 0.4	1.5 ± 0.3
$AUC_{(0-t)}$ [ng/ml*h]	261± 173	192± 119	135± 23	101± 30
A_{max} [ug]	119 ± 57	166 ± 71	473 ± 144	614 ± 346

Values are mean ± SD.
Abbreviations: C_{max}= maximal plasma concentration; T_{max} =Time to maximal concentration
$AUC_{(0-t)}$= Area under concentration-time curve model independent A_{max}= cumulative urinary excretion

The C_{max} and AUC_{0-t} were consistently higher in the elderly group when compared to the younger subjects. Statistical significance, however was achieved only on day 5 for AUC. Only 3-5% of the dose could be accounted for by urinary excretion of moexipril + moexiprillat. Although the kinetics of moexipril did not seem to change between day 1 and day 5 the kinetics of moexiprillat for both the young and the elderly suggest some accumulation as judged by C_{max}, AUC_{0-t} and A_{max}.

Safety: Two of the 12 elderly reported adverse experience. One subject (no 11) reported dizziness on day 3. The other subject (no 14) reported dyspepsia, no subjects discontinued.

With respect to laboratory values:
subject # 24 had an elevation of SGPT from 48 to 82 (normal for age <75 U/l).

Conclusion: Kinetics in the elderly healthy males are somewhat different than those of younger healthy males. It is not clear to what extent the kinetic differences are due to differences in renal function. Creatinine clearances as calculated from the COckcroft-Gault equation would not suggest sufficient renal dysfucntion to account for the chantes in kinetics based on study GHBA 629. Although there does not seem to be accumulation of moexipril over time, moexiprillat seems to substantially accumulate as judged by AUC_{0-t}, C_{max} and A_{max}.

Study No 14- Protocol GHBA 629 Volume 1.76
Name of Study: A Phase I, Open Label Study to Investigate the Safety, Tolerance and Pharmacokinetics of a Single Dose of Moexipril in Subjects with Different Levels of Renal Function
Principal Investigators:

Date of Study : October 26, 1990-February 24 1992
Formulations: Capsules- 15 mg (site 1) batch no. 902512; (site 2) batch no. 910534

Protocol: This was a two-centered, open-labeled study describing the effect of varying degrees of renal function on the kinetics of single doses of 15 mg moexipril. A total of 16 patients (later amended to 21 patients) were to be enrolled into a single study center (later amended to two study centers). Subjects were to be categorized based on renal function as **normals** (creatinine clearance > 90 cc/min), **Mild insufficiency** (creatinine clearance of 66-90 ml/min); **moderate insufficiency** (creatinine clearance of 41-65 ml/min); and **severe insufficiency** (creatinine clearance of 10-40 ml/min). Four subjects per group were to be enrolled (later amended to 4 subjects/group except the severe insufficiency where 8 subjects were to be enrolled). The creatinine clearance was calculated from the Cockcroft-Gault equation. Renal function was not independently determined by either iothalimate or inulin clearance.

Subjects, in order to be eligible for enrollment, had to have creatinine clearances, as calculated above, within the prescribed range. Patients had to have stability in Ccr based of not more than a 30% change within 3 months of the first visit. (Does this mean that they could have had a Ccr the day before visit 1 and have say a 25% difference and still be considered eligible for enrollment?). Patients must be able to withdraw from hypertensive therapy for at least 2 weeks and diuretic therapy for at least 48 hours. Patients need be male or female (with appropriate constraints on fertility) and between the ages of 19-69, with normal weight and no ECG changes (except 1st degree AV block or LVH by voltage criteria or non-specific ST-T wave changes) or had changes that have been stable for one year.

Exclusion criteria included: 1) severe hypertensive disease (Keith-Wagner scale grade 3 or 4, sitting DBP > 105 mm Hg, CVA or hypertensive encephalopathy; 2) unilateral or bilateral renal stenosis; 3) history or evidence of cardiac disease; 4) other significant disorder such as hepatic, pulmonary, endocrine, metabolic, gastro-intestinal or hematologic disease; 5) ethanol or drug abuse.

All medications were to be stopped 7 days prior to the first dose of moexipril or tapered and withdrawn over the seven day period. Eligible patients were seen 1 day later where vital signs, ECG and laboratory tests were performed and Ccr was measured. Six days later subjects received the 15 mg dose of moexipril. Vital signs were measured at 0(pre-dose), 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 , 12 and 16 hours; urine was collected at the following intervals: -2-0(pre-dose), 0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours post dose. Blood samples for assay of moexipril and moexiprilat were collected at 0(pre-dose), 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 , 12 and 16 hours; as well as daily samples.

Results: A total of 21 patients were enrolled into the study, with normal (n=4), mild (n=4); moderate (n=5) and severe (n=8) subjects per group. Eleven of the subjects came from Dr. Williams study center including all the normals, Twelve subjects including six of the eight severe renal failure patients were enrolled from Dr. Oldenbroeck's study center. All patients except one normal renal function patient were male. The mean ages of the different groups varied. The normal group had the lowest age 34± 2.6; the groups with some renal dysfunction were somewhat older (averages 49.5 ±52,8), Weights varied between the groups. The severely impaired group being the lightest (70.9 ± 4.64) and the moderate insufficiency the heaviest (85.2 ± 8.8). None of the normals had a history of hypertension. Two of the moderate and six of the severerenal dysfunction patients had a history of hypertension.

With respect to the systolic and diastolic blood pressure responses, peak responses occurred at 3-6 hours post dose. The largest fall in blood pressures was in the severe renal impairment group-mean sitting systolic/diastolic decrease (30/19) compared to the normal group (16/14). The mild and moderate renal groups had supine systolic/diastolic blood decreases of 23/20 and 31/15 mm Hg respectively.

The pharmacokinetic parameters for moexipril and moexiprillat derived from this study are tabulated below:

Table 14.1

	Moexipril GROUP				Moexiprillat GROUP			
Parameter mean (SD)	I	II	III	IV	I	II	iii	IV
C_{max} [ng/ml]	46.0 ±15.9	41.7 ±11.4	37.9 ±20.7	39.9 ±13.3	17.1 ± 9.6	23.7 ± 9.7	18.4 ± 12	25.9 ± 18
T_{max} [h]	0.8 ± 0.2	1.0 ± 0.4	1.1 ± 0.3	1.1 ± 0.6	1.6 ± 0.3	1.8 ± 0.3	1.9 ± 0.2	2.8 ± 1.6
AUC_{0-t} [ng/ml.h]	55.9 ±26.4	55.9 ±13.1	64.6 ±25.9	72. ±27.9	150 ±57	148 ±31	166 ±38	268 ±152

Group: I- no renal disease (n-4);- II- mild renal disease (n=4) ; III-moderate renal disease (n=5); IV-severe renal disease (n=8).

There seems to be little differences in the pharmacokinetic parameters of moexipril in progressing across the grades of renal dysfunction, although the trend is towards greater AUC with increases in renal dysfunction.

With respect to moexiprilat, however, substantially higher maximal concentrations of moexiprilat are observed.as well as increases in AUC as a function of deteriorating renal function. There is, furthermore, much greater variability in the predicted AUC and T max (and to some extent C_{max}). There was fairly large variability within the severe renal dysfunction group. Some patients with

marked dysfunction had AUC similar AUC to those individuals with normal renal function. Others with similar degree of renal dysfunction had markedly increased moexiprillat AUCs. Thus, patient #6 (the first bar under severe) had normalized creatinine clearance of 22.7 ml/min/1.73 M^2 and had an AUC of 106 ng.hr/ml. Patient# 9 (second bar under severe) had a creatinine clearance of 30.3 ml/min/1.73 M^2 and had a AUC of 516 ng.hr/ml.

With respect to urinary excretion of moexipril and moexiprilat , the parameters are shown below:

Table 14.2
Urinary Excretion of Moexipril and Moexiprilat Related to Degree of Renal Function

	Moexipril GROUP				Moexiprilat GROUP			
Parameter mean(SD)	I	II	III	IV	I	II	iii	IV
Amount [ug]	203 ±105	152 ±37	116 ±71	98 ±61	531 ± 338	628 ± 122	479 ± 226	621 ± 37
Excretion time [h]	13 ± 7.6	33 ± 18	22 ± 16	34 ± 13	102 ± 23	120 ± 0	106 ± 22	106 ± 19
$t_{1/2}$ elim [h]	1.05 ±0.16	1.2 ±0.1	1.9 ±0.9	2.2 ±0.7	1.46 ±0.6	2.9 ±1.2	5.0 ±4.1	5.3 ±3.6

Group: I- no renal disease (n-4);- II- mild renal disease (n=4) ; III-moderate renal disease (n=5); IV-severe renal disease (n=8).

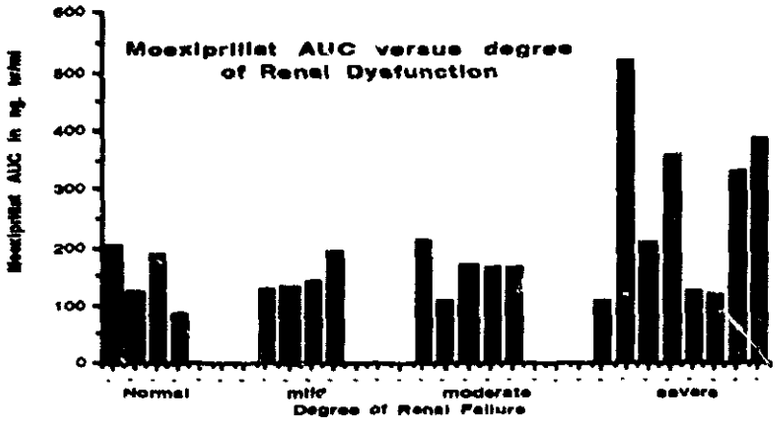
Overall total excretion of moexipril plus moexiprilat did not change in progressing through the various degrees of renal failure. The urinary excretion, however, amounted to only approximately 5% of the dose (c 750 ug out of a dose 15 mg).

Safety: Adverse events- Six clinical adverse events were reported by five individuals. Five of these events were headaches, four of which were classified as mild and one as moderate. One subject also had a UTI.

With respect to laboratory assessments, there were many lab values that were outside the normal range. Th is not unexpected in a population with substantial renal dysfunction.

The sponsor has tabulated a list of laboratory values that they considered noteworthy (see page vol 76-39) I have looked through the line listings of laboratory listings and the Table lists more events than I would consider noteworthy. Of note was that serum glucose levels rose in three of the 4 renal groups (the

Figure 14.1



exception was the moderate renal insufficiency), in considering the pre-dose value to the post dose value (day 2) Eleven patients had post dose glucose levels elevated (53%)whereas only 3 patients had pre-dose glucose levels elevated (14%).

One patient of note is patient #13 (severe renal dysfunction) whose post-dose creatinine as well as BUN substantially increased. There was no noted hyperkalemia in this small group of individuals with renal disease

Conclusion: This is a small study, using only single doses in a mid-dose range of moexipril, there is consequently little information as to how larger doses or longer duration would interact with renal dysfunction. Even within this modest study, some concern can be raised that the hemodynamics effects are more excessive in patients with any degree of renal function. Again the data base is small and the magnitude the effects are not sufficiently significant to definitively draw conclusions.

Study No 15 - Protocol GHBA 636 Volume 1.80
Name of Study: An Open Label Study to Investigate the Absorption, Metabolism and Pharmacokinetics of Sing Dose of Moexipril in Subjects with Hepatic Cirrhosis
Principal Investigators:

Date of Study : August 27, 1991-January 24 1992
Formulations: Capsules- 15 mg batch no. 905041;

Protocol:This was to be an open label, kinetic study of single doses of moexipril in patients with biopsy proven hepatic cirrhosis. The protocol stipulated that 12 patients were to be enrolled. All medication excluding lactulose, neomycin and diuretics were to be stopped 1 week prior to dosing. The cirrhosis specific medications listed above, however, were to be stopped 24 hours prior to study. Inclusion criteria included males or females (with appropriate means to prevent pregnancy), between the ages of 21-69, with hepatic cirrhosis of any etiology (except biliary cirrhosis) and relatively stable hepatic function as judged by SGOT and SGPT which do not differ by more than 50% over 1 week. Exclusion criteria included hypersensitivity to ACE inhibitors, inability to stop other medications, presence of concurrent confounding medical problems including cardiovascular (history of MI, CHF; valvular disease), pulmonary, endocrine metabolic or hematologic disease, GI disease(that might interfere with absorption of drug) , malignancy, hyperkalemia, sitting systolic blood pressure of < 95 mm Hg, history of portocaval shunt. creatinine clearance of < 60 ml/min., positive hepatitis B surface antigen, Pt or PTT > 40% above normal, alcohol abuse during the past six months. .

Along with a history subjects will be examined before dosing. Vital signs will be measured with each blood sample that is collected at the following times: 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, and 12, 24 , 48, 72 and 96 hours post dose. Urine sample for moexipril will be collected at hours -2 to 0, 0-2, 2-4, 4-6, 6-8 8-12 ,12-24, 24-48, 48-72 and 72-96 hours post dose.

Laboratory assessment will be performed at pre-study screen day (-14), day 1 (pre-dose), day 2, and day 5.

Results: A total of 12 patients were enrolled into the study. All patients had hepatic cirrhosis secondary to alcohol abuse. There were 7 females and 5 males, mean age was 54.2 (SE ±2.75 years) and height 170.6 (SE ±3.18 cm) and weight 73.7 (SE ±3.16 Kg). Stigmata consistent with liver disease were noted in all patients including palmar erythema, telangiectasias, spider nevi, hepatomegaly . Even though all patients had some stigmata of liver dysfunction, evidence of severe dysfunction was infrequently reported. Thus, no patient had ascites and only one patient had subclinical hepatic encephalopathy listed as a pre-study condition. Only 3 patients were taking lactulose prior to the study and only two patients were taking diuretics to prevent "fluid retention".

[comments: this patients population has probably modest liver disease based on the clinical exam and medication history]

Mean sitting blood pressure drop was approximately -12/-12 mm Hg with an initial drop in sitting pulse of approximately 7 BPM. Peak effects were generally noted at between 4-8 hours.

The pharmacokinetic constants of those with hepatic dysfunction these are displayed below:

Table 15.1
Pharmacokinetic Parameters in Patients With Cirrhosis

Mean Parameter value (SD)	Moexipril	Moexiprilat
C_{max}	154 (60)	16.2 (8.7)
T_{max}	0.85 (0.27)	2.5 (1.9)
AUC_{0-t}	324 (180)	228 (70)
$t_{1/2}$ elim	1.65 (0.69	3.51 (2.3)

C_{max}= maximal plasma concentration (ng/ml); T_{max} =Time to maximal concentration (hr)
$AUC_{(0-t)}$= Area under concentration-time curve model independent (hr.ng/ml)

The sponsor has tabulate the pharmacokinetic parameters from normals derived from other studies as comparative data. The numbers are dose normalized to a 1 mg/dose in each study.

Table 15.2
Pharmacokinetic Parameters of Moexipril Normalized to a 1 mg Dose from Various Other Studies

	Moexipril			Moexiprilat		
Study number	C max [ng/ml]*	T max [h]	AUC 0-t [ng.h/ml]*	C max [ng/ml]*	T max [h]	AUC 0-t [ng.h/ml]*
GHBA-636-cirrhosis	10.3 (4.0)	0.85 (0.27)	21.6 (12)	1.08 (0.58)	2.5 (1.9)	15.2 (4.6)
GHBA-625-normals	8.2 (2.1)	0	14.6 (5.9)	2.36 (1.05)	0	6.8 (2.5)
GHBA-627-normals	8.5 (3.8)	0	13.5 (6.0)	2.26 (0.84)	0	7.5 (2.0)
GHBA-633-normals	6.6 (2.9)	0	10.0 (4.8)	1.19 (0.74)	0	3.9 (2.1)

* Normalized to a 1 mg doses

[comment: It is unclear why the sponsor chose these particular studies as adequate comparisons. No argument is presented that the formulations which were used in these studies were equivalent. It should also be appreciated that dose proportionality is not strictly noted for moexipril consequently normalizing all parameters to 1 mg dose is only an approximate way of comparing across studies.

Based on the above data, the peak concentrations as well as the AUCs of moexipril and moexiprilat are higher for minimally cirrhotic patients than for normal individuals.The $T_{1/2}$ elimination of moexipril and moexiprilat are also shown in Table 15.1. The elimination half-lives are difficult to compare with normals since the $t_{1/2}$ seems to be dose dependent

Of note was that with the exception of 1 patient, nearly all moexiprilat excretion was completed by 24 hours. Patient No. 8 additionally excreted approximately 126 ug (~1% of the dose but 22% of the amount excreted) over the remaining collection periods. There was substantial variability in the amount of moexipril plus moexiprilat that were excreted renally, this ranged from 92 Ug to 825 ug.

Safety: One patient reported both mild dizziness and lightheadedness on the day of dosing, the events resolved spontaneously. None of the laboratory values seemed to change with respect to treatment. Change in this case defined as values that were stable at pre-study and pre-dose, that altered post dose and remained so altered or that re-approached pre-dose values by day 5.

Conclusion, Single doses of moexipril result in higher concentrations of moexipril and moexiprillat and greater AUCs for both drug and active metabolite in patients with hepatic cirrhosis. It is however, not possible from this study to predict whether, with long term therapy in these patients, excessive accumulation of either moexipril or moexiprilat will occur, since this was a single dose study and the dose which was chosen for study was in the mid-range of therapy. The relationship of the formulation used in this study relative to other studies can only be surmised. Comparisons across studies should therefore be approoached with a healthy degree of skepticism.

No comparative age matched and weight matched controls are available to separate out which changes are formulation related and which changes are disease or demographics related. The cirrhotic subjects which were enrolled here are somewhat older than are the normal volunteers usually enrolled into pharmacokinetic studies. Since there is a modest age effect this might partly contribute, but not totally explain the enhanced moexipril and moexiprilat levels in cirrhotic subjects.

The degree of hepatic dysfunction in this study appears to be modest based on the few people with either a history of ascites or hepatic encephalopathy. Albumin seemed to be only modestly decreased pre-dose mean 35 g/l (SD ± 1.2) normal range 38-50 g/l. iut would have been nice to see how the general profile of moexipril metabolites are changes with hepatic cirrhosis (i.e. the diketopiperazine moexiprillat Unfortunately complete metabolite patterns are not available.

It is unclear what impact greater degrees of hepatic dysfunction, longer durations of therapy would have on the kinetics of moexipril.

Study No 16 Protocol GHBA 625 R Volume 1.82
Name of Study: A Phase I, Randomized, Single-Dose, Open-Label, Three-Way Crossover Study to Determine the Possible Interaction of Moexipril with Hydrochlorothiazide in Normal Volunteers.
Principal Investigators:

Date of Study : November 19, 1990-December 9 1990
Formulations: Moexipril Capsules- 30 mg batch no. 903549;
Hydrochlorothiazide (HCTZ) 25 mg Merck, Sharp and Dohme (UK),Batch WE 10142-Lot no. 893881
Protocol: This was an open label, three-way cross-over study in normal males of moexipril, HCTZ or the combination of HCTZ + moexipril. A total of 12 subjects were to receive, in random order, a single dose of each regimen followed by a one week washout period. The dose of moexipril was 30 mg/day, that for HCTZ was 25 mg/day. Eligible subjects were normal males between the ages of 18-45. Specifically excluded were individuals with sensitivity to any of the medications, history of drug use or confounding medical problems. Patients received the dosage while fasting.

Patients received dosing on days 1, 8 and 15. Blood samples for moexipril and moexiprilat were collected for assay and vital signs were measured at the following times: pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 16, 24, and 48 hours post-dose. Urine specimens for moexipril and moexiprilat assays were collected at the following intervals: -1-0 (pre-dose), 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24, 24-48 hours post dose. Laboratory assessments were performed pre-study and pre-dose as well as 1 day post dose.

Results: A total of 13 subjects were enrolled into the study of which 12 were evaluable. One subject was discontinued prior to drug treatments because of a baseline laboratory abnormality. The mean age (SE) was 32.8 (1.7)years, weight 70.8 (1.9) Kg and height 173.3 (1.3) were not remarkable. Maximal effect on blood pressure occurred at approximately 3-7 hours post dose with either moexipril or moexipril + HCTZ regimens. For the HCTZ group there did not appear to be any credible peak in effect. The maximal effects for sitting systolic/ diastolic blood pressures were -12/-8, -4/-5, and -7/-9 for moexipril, HCTZ and Moexipril + HCTZ respectively. Pulse rates increases of 6-8 BPM for each group were the greatest at 4 hours post dose.

With respect to the pharmacokinetic parameters of moexipril and moexiprilat these are shown below. There was no period effect so that the parameters listed are combined values, independent of the period when the regimen was received. Urinary excretion of HCTZ alone and after the combination showed no differences in the gross kinetics (data not shown).

Table 16.1

	Moexipril		Moexiprilat	
Parameter: Mean ± SD	Moexipril Alone	Moexipril + HCTZ	Moexipril alone	Moexipril + HCTZ
C_{max} [ng/ml]	245 ± 64	241± 85	71 ± 32	69 ± 34
T_{max} [h]	1.2 ± 0.3	0.8 ± 0.2	1.6 ± 0.4	1.6 ± 0.5
AUC_{0-t} [ng.h/ml]	437 ± 177	416 ± 173	203 ± 74	215 ± 71
Total Urinary excretion [ug]	334 ± 133	452 ± 295	1205.3 ± 673	1462 ± 796

These results show that the pharmacokinetic constants of plasma concentrations moexipril as well as moexiprilat when given alone or with HCTZ do not markedly change. Urinary excretion , however, may be moderately affected by the presence of HCTZ. Thus, when moexipril is administered alone, the total urinary excretion of moexipril (334 ug) plus moexiprilat (1205 ug) is 1559 ug or 5.2 % of the administered dose. When administered with HCTZ the urinary excretion of moexipril (452 ug) and moexiprilat (1462 ug) the total excretion is 1914 ug or 6.4% of the dose. Neither the total excretion of moexipril or moexiprilat was statistically significantly different, however, there could be substantial differences that would not picked up by this rather small study.

Safety: Five of the twelve subjects reported adverse episodes during the course of the study. All were mild. The five events were either headache or URI symptoms.

Given the large number of laboratory assessments it is not surprising to find a large number of laboratory values outside the normal range. The sponsor lists these values in Tables H-M of the submission for this protocol (vol. 83, p 56-61). One patient had an elevated potassium post moexipril (5.6 meq/l)which was normal pre-moexipril (4.6 meq/l). When this individual received moexipril + HCTZ the pre-treatment K+ was 4.1 meq/L and increased to 4.6 meq/l.

Conclusion: This is a modest data base using a reasonably high dose of moexipril (30 mg). There did not appear to be differences in the kinetic parameters of either moexipril or moexiprilat after this single dose. Urinary excretion of moexipril and moexiprilat were, however, slightly (although not statistically) higher after HCTZ.

Study No 17 Protocol GHBA 626 Volume 1.86
Name of Study : A Phase I, Open-Label Study to Determine the Possible Interaction of Moexipril with Digoxin in Normal Volunteers.
Principal Investigators:

Date of Study : October 15, 1990-November 9, 1990
Formulations: Moexipril Capsules- 30 mg batch no. 902513
Digoxin 0.25 mg Wellcome (UK), Batch WE 10115

Protocol: This was a pharmacokinetic study defining the interaction between Digoxin and Moexipril. Each subject received one dose of moexipril with steady state digoxin (7 days) therapy as well as one dose of moexipril while off digoxin. Each subject also received a single dose of digoxin under steady state conditions of digoxin. There were two possible regimens by which subjects could receive both drugs.

The schematic of the regimens are shown below:

FIGURE 17.1

TREATMENT SEQUENCE A

DAY 1 Moexipril 30 mg Single Dose Only	Washout period (Days 2-7)	DAY 8 Digoxin Loading Dose 0.25 mg Q 6 h x 4
DAY 9-15 Digoxin 0.25 mg/day	Day 16 Moexipril 30 mg plus Digoxin 0.25 mg (single dose)	Day 17 Digoxin 0.25 mg Single dose

TREATMENT SEQUENCE B

DAY 1 Digoxin Loading Dose 0.25 mg Q 6 h x 4	DAY 2-8 Digoxin 0.25 mg/day	DAY 9 Moexipril 30 mg plus Digoxin 0.25 mg (single dose)
DAY 10 Digoxin 0.25 mg Single dose	Washout Period DAY 11-22	Day 23 Moexipril 30 mg Single Dose Only

Under the first regimen (Regimen A) subjects received a single dose of moexipril followed by a washout period of 1 week. Subjects then received digoxin as a loading dose with one week of therapy to attain steady state (8 days). Each individual then received a single does or moexipril while on steady state digoxin. Lastly, subjects received a final dose of digoxin. The total duration of study in this regime was 17 days

Subjects allocated to Regimen B first had the loading dose followed by steady state treatment with digoxin. This was followed by a single dose of moexipril superimposed on steady state digoxin therapy. Kinetics of single dose digoxin at steady state digoxin was next measured. After a 12 day washout period subjects received a single dose of moexipril. The total duration of this regimen was 23 days.

A total of 12 subjects were to be involved, randomized equally between the two dosing sequence. Subjects were to be normal males between 18-45 years old with normal weight (± 15%). Exclusion criteria included history of sensitivity to either class of drugs, confounding medical or psychiatric problems, drug or alcohol dependence, or baseline abnormality in laboratory assessment. Subjects were to take the medications fasting.

Vital signs were monitored and blood was collected for moexipril and moexiprilat determination at the following times: 0 hours (pre-dose),0.5, 0.76, 1, 1.5, 2, 3, 4, 6, 8, 12,16, 24, and 48 hours. Urine were similarly collected after the moexipril doses at the following times -1- 0 (pre-dose), 0-1, 1-2, 2-4, 4-6, 6-8,8-12, 12-24, and 24-48 hours post dose. Vital signs were also monitored and digoxin radioimmunoassay samples were collected once at the penultimate day of digoxin st(ady state treatment

(time not stated), and on the last day of treatment at the following hours: 0, 1, 2, 3, 4, 8, and 12 on the both during steady state digoxin monotherapy and at the equivalent time points during digoxin moexipril concurrent therapy. Safety evaluations included frequent laboratory assessments and ECGs.

Results: A otal of 17 patients were enrolled into this study of which 12 received therapy. Four subjects were termi.ated because of baseline laboratory abnormalities at pre-study screen, the fifth subject was held as reserve and not needed. Six subjects were allocated to each treatment regimen. The demographics of the enrolled subjects are shown below:

Table 17.1
Demographics of Study GHBA 626

Values are Mean (± SE)	AGE (years)	Height (cm)	Weight (Kg)
Sequence A (n=6	33 ± 3.0	174.7 ± 1.66	71.2 ± 3.01
SEquence B (n=6)	34 ± 1.15	177.5 ± 4.15	75.3 ± 3.86

Blood pressure and pulse responses were difficult to assess given the long duration of observation, the inadequate definition of baseline blood pressures and the small number of patients per study group , [comment: On a semi-quantitative basis (so much depends on how you define baseline i.e. single zero time point measurement or mean of the pre-study measurements), there were modest drops in blood pressure both systolic and diastolic coupled with increases in pulse rates.]

With respect to digoxin levels there did not appear to be a sequence related difference based on ANOVA. Thus, the table below lists the pharmacokinetic constants for digoxin independent of treatment regimen.

Table 17.2
Pharmacokinetic Parameters of Digoxin With and Without Moexipril

Parameter (Mean + SD)	Digoxin Alone	Digoxin With Moexipril
C_{max} [ng/ml]	1.46 ± 0.59	1.57 ± 0.41
T_{max} [hr]	1.25 ± 0.35	1.33 ± 0.49
AUC_{0-t} {ng.h/ml]	13.5 ± 4.9	14.3 ± 3.5

Although the means for the pharmacokinetic measurements are close to each other the small study still gives wide latitude to the confidence intervals. Thus for the C_{max} the 95% confidence intervals between groups encompasses relative to digoxin alone (-0.323 tho + 0.540) for the AUC the 95% confidence intervals span (-2.76 to + 4.402). Thus, concentration increases or AUC increases of 30% would not be picked up by this small study.

With respect to moexipril the pharmacokinetic measurements are shown below:

Table 17.3
Pharmacokinetic Parameters of Moexipril/Moexiprilat With and Without Digoxin

	Moexipril Alone		Digoxin + Moexipril	
Parameter: Mean ± SD	Moexipril	Moexiprilat	Moexipril	Moexiprilat
Cmax [ng/ml]	130.3 ± 75	51.6 ± 31.4	151.5 ± 72	57.3 ± 33
T max {hr	0.88 ± 0.29	1.58 ± 0.29	1.04 ± 0.37	1.75 ± 0.34
AUC 0-t {ng.h/ml]	236.1 ± 176.5	169.2 ± 68.7	238.5 ± 107.7	176.9 ± 71.3
Urinary Excretion {ug}	352.2 ± 201.8	1118.9 ± 389	375 ± 155.6	1405.1 ± 605

Similarly, the 95 % confidence intervals for the difference between treatments are quite large. Even though there was no statistical significant difference between the measured parameters, there still might be substantial differences in use of digoxin with moexipril. For example, the C_{max} of moexipril could be more than 50% greater with digoxin and not be detected with this data.

Table 17.4

95% Confidence intervals for the difference for the pharmacokinetic measurements Digoxin versus Alone

Parameter	Moexipril	Moexiprilat
C_{max} in ng/ml	-41.2 to + 83.5	- 21.53 to +33.0
T_{max} in hr	-0.114 to + 0.447	-0.099 to 0.432
AUC_{0-t} in hr.ng/ml	-122. 41 to + 125.6	-51.5 to + 66.99
Urinary Excretion in ug	- 102.7 to +202.4	-144.5 to + 716.8

Safety: A total of 3 subjects reported adverse events were reported during this study, all while only taking digoxin. One subject reported two episodes of headache also abdominal cramps . One subject complained of abdominal craps and episodic diarrhea The third patient had periorbital edema and transient rash .

Given the large number of laboratory assessments it is not surprising that there were intermittent abnormalities. The sponsor tabulates these abnormalities in Table B and C (vol. 86-p 50, 52). Laboratory values that were normal prior to moexipril treatment and were abnormal post treatment and for which no normal values are subsequently available are shown below:

Subject # 3 inorganic phosphate-had a inorganic phosphorus of 1.62 mmol/l after dose of digoxin plus moexipril. Baseline value was 0.99 mmol/l. This was the last value and no normal values are available. Calcium was normal throughout the study.

Subject #1 glucose- Blood glucose was elevated at the end of the study 5.7 mmol/l (range 3.9-5.6) after treatment with moexipril alone- No normal values are available.

Subject #10 urea Subjects urea was elevated at the end of the study 7.4 mmol/l. after treatment with moexipril alone. No normal values are available. Creatinine levels , although within normal range were increased from baseline value 101 umol/l normal values 53-110.

Subject #12 Glucose was elevated at the end of the study after dose of moexipril alone (5.8 mmol/l). No repeat values are available

creatinine- Elevated at the end of the study (111 umol/l normal range 53-110) Urea was also increased but had been elevated several times during the study.

Conclusion: This was a small study that did not show either any physiologic (i.e. blood pressure) or pharmacologic interaction between moexipril and digoxin. As noted above the power to discern differences in such a small study is limited. The doses of digoxin used in this study were reasonable and the serum concentrations achieved were also reasonable. the dose of moexipril (30 mg) was also in the reasonable therapeutic range.

Study No 18 Protocol GHBA 627 Volume 1.89
Name of Study: A Phase I, Open-Label, Two -Way Crossover Study to Determine the Possible Interaction of Moexipril with Cimetidine in Normal Volunteers.
Principal Investigators:

Date of Study : November 26, 1990-December 18, 1990
Formulations: Moexipril Capsules- 30 mg batch no. 903549
Cimetidine 400 mg Smith Kline & French (Great Britain), Batch WE 10141
Protocol: This was a pharmacokinetic study defining the interaction between cimetidine and moexipril. Each subject received one dose of moexipril during steady state cimetidine (4 days) therapy as well as one dose of moexipril while off cimetidine. Each subject also received cimetidine in the absence of moexipril for a total of two days to assess cimetidine's pharmacokinetics.There were two possible regimens by which subjects could receive both drugs (figure 18 1).

FIGURE 18.1

TREATMENT SEQUENCE A

DAY 1 moexipril 30 mg single dose Only	Days (4-7) cimetidine 400 mg Q 8 hours	DAY 8 cimetidine 400 mg Q 8 hours plus moexipril 30 mg
DAY 9-10 cimetidine 400 mg Q 8 hours		

TREATMENT SEQUENCE B

DAY 1-4 cimetidine 400 mg Q 8 hours	DAY 5 cimetidine 400 mg Q 8 hours plus moexipril 30 mg	DAY 6-7 cimetidine 400 mg Q 8 hours
DAY 8-11 Washout period	Day 12 moexipril 30 mg.	

Under the first regimen (Regimen A) subjects received moexipril as a single dose followed by cimetidine 400 mg Q 8 hours for 4 days, presumably to approach cimetidine steady state. A single dose of moexipril is superimposed on the cimetidine steady state. Cimetidine in the absence of moexipril is continued for an additional 2 days. The total duration of study in this regimen was 10 days.

Regimen B establishes cimetidine steady state followed by the single dose of moexipril superimposed on

cimetidine. Cimetidine treatment is then continued for an additional 2 days. Following a three day washout period a single dose of moexipril is administered. The total duration of study in this regime was 12 days.

A total of 12 subjects were to be studied, randomized equally between the two dosing sequence. Subjects were to be normal males between 18-45 years old with normal weight (± 15%). Exclusion criteria included history of sensitivity to either class of drugs, confounding medical or psychiatric problems, drug or alcohol dependence, or baseline abnormality in laboratory assessment. Subjects were to take the medications fasting.

Vital signs were monitored and blood for moexipril determination was collected at the following times post dose: 0 hours (pre-dose), 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12,16, 24, and 48 hours. Urine were similarly collected after the moexipril doses at the following intervals: -1- 0 (pre-dose), 0-1, 1-2, 2-4, 4-6, 6-8,8-12, 12-24, and 24-48 hours post dose. Vital signs were also monitored and cimetidine samples collected prior to cimetidine treatment and 48 and 24 hours before and on the day when moexipril and cimetidine were administered concurrently (effectively these represent AM trough levels). Safety evaluations included frequent laboratory assessments and ECGs.

Results: A total of 17 patients were enrolled into this study, of which 15 received at least one dose of medication and 12 who completed the randomized regimen. One subject was terminated because of a positive alcohol reading. One patients was withdrawn due to late arrival at study site. One patient was prematurely withdrawn on day 5 of sequence B due to mid-axillary pain (ECG and X-ray were negative). Six subjects were allocated to each treatment regimen. Their demographics are shown below:

Table 18.1

Values are Mean (± SE)	AGE (years)	Height (cm)	Weight (Kg)
Sequence A (n=6)	32 ± 2.32	173.3 ±2.21	70.0 ± 3.54
Sequence B (n=6)	33 ± 1.95	178.9 ± 3.28	77.5 ± 2.52

Blood pressure and pulse responses were difficult to assess, given the long duration of observation, the inadequate definition of baseline blood pressures and the small number of patients per study group.

On a semiquantitative basis subjects allocated to sequence A had a substantial sitting systolic and diastolic response when cimetidine was administered with moexipril (systolic /diastolic change of -14/-15 mm Hg) which persisted for approximately 5 hours. The corresponding response on moexipril alone was more subdued -7/-12 mm Hg was not as precipitous in onset and did not appear to last as long. The corresponding response for those randomized to Sequence B, were also quite modest, -9/ -6 on moexipril plus cimetidine and -9/5 for moexipril alone. Given, however, the small sample size and multiple measurements it is difficult to ascertain whether either the treatment or the sequence makes any differences in blood pressure response.

With respect to cimetidine the A. M. trough levels are shown below.

Table 18.2

Plasma Cimetidine concentrations (ug/ml) (mean ± SD)

Sequence A			Sequence B		
Day 6	Day 7	Day 8	Day 3	Day 4	Day 5
0.32 +0.12	0.31 +0.09	0.46 ±0.15	0.26 ±0.14	0.23 ±0.06	0.37±0.11

From the above data it is not clear if steady state cimetidine concentrations have been achieved since the measured concentrations on the day of concurrent therapy appear to be substantially greater than the other two values.

With respect to moexipril, the pharmacokinetic measurements are shown below. Since there was no effect of order of treatment on kinetics, the parameters listed below lump the data for those randomized to sequence A with those randomized to sequence B :

Table 18.3
Pharmacokinetic Parameters of Moexipril and Moexiprillat withand Without Cimetidine

	Moexipril alone		Cimetidine + Moexipril	
Parameter: Mean ± SD	Moexipril	Moexiprilat	Moexipril	Moexiprilat
C_{max} [ng/ml]	254 ± 115	68 ± 25	206 ± 85	82 ± 45
T_{max} (h)	0.9 ± 0.3	1.5 ± 0.4	1.0 ± 0.3	1.6 ± 0.4
AUC_{0-t} (ng.h/ml)	406 ± 179	226 ± 59	378 ± 123	255 ± 85
Urinary Excretion (ug)	480 ± 379	1429 ± 609	378 ± 199	1339 ± 570

There was no statistical significance to the difference in parameters for moexipril and moexiprilat when drug was administered with or without cimetidine. The confidence intervals, although not stated within this submission, would be wide.

There is one unusual subject with respect to the excretion pattern of both moexipril and moexiprillat. This subject had equivalent results during both legs of the study with and without cimetidine. This subject (patient # 16) continued to excrete moexipril in the urine during the 24-48 hour interval (this was the last interval collected). No other subject longer than the 8-12 hour interval. Cumulative urinary excretion of moexipril for this individual were higher than any of the other subjects studied. Conversely, this subject had the lowest excretion of moexiprilat during either leg of therapy. Moreover, the total urinary excretion of moexiprilat ended with the 6-8 hour urine collection. Most other subjects

still had urinary moexiprilat excretion at 24-48 hour urine samples. The total urinary excretion of moexiprillat for this subject was the loweest during both legs of the study. Plasma concentrations of both moexipril and moexiprilat were not remarkable.

Safety: A total of 6 subjects reported adverse events were reported during this study.

Table 18.4
Adverse Events and Outcomes

Subject#/ Sequence	Adverse Event	Most Recent Treatment	Severity	Outcome
Subject #4/A	1. palpitations	cimetidine days 9,10	mild	1. continued
Subject # 7 /A	1. headache	moexipril	mild	1. continued
Subject # 10/A	1. URI	Moexipril	mild	1. continued
Subject # 12/A	1. Chest pain 2. Dizziness 3.left sided axillary pain	1. moexipril 2. moexipril 3. moexipril	1. mild 2. moderate 3. severe	1-3. all occurred on day 1 of moexipril therapy..subject discontinued
Subject # 1/B	1. headache	1. Cimetidine + Moexipril	1. Mild	1. Continued
Subject # 3/B	1. diarrhea 2. dizziness with standing	1. Cimetidine 2. Cimetidine + Moexipril	1. mild 2. mild	1. continued 2. continued

Given the large number of laboratory assessments it is not surprising that there were intermittent abnormalities noted. The sponsor tabulates these abnormalities in Table B and C (vol 89-p 52, 55). Laboratory values that were normal prior to moexipril treatment and were abnormal post moexipril treatment and for which no normal values are available are shown below:

Pt # 5- Platelet count was 407 x 10^{9}/L post moexipril + cimetidine (reference range 150-400 x 10^{9}/L).

Conclusion: This was a small study that did not show either any physiologic or pharmacologic interaction between moexipril and cimetidine. As noted above the power to discern differences in such a small study is limited.

Study No 19 Protocol GHBA 631 Volume 1.93
Name of Study : A Phase I, Open-Label, Randomized, Two -Way Crossover Study to Evaluate the Possible Interaction of Moexipril with Warfarin Pharmacokinetics and Pharmacodynamics in Healthy Male subjects:
Principal Investigators:

Date of Study : February 15, 1991- March 25, 1991
Formulations: Moexipril Capsules- 15 mg batch no. 905041
Warfarin Tablets 5 mg WE
10195

Protocol: This was a pharmacokinetic study defining the interaction between Moexipril and Warfarin. Each subject received one dose of warfarin with moexipril and one dose of warfarin in the absence of moexipril. Subjects were randomized so that half received the co-administered medications first and half received warfarin alone first.

The schematic of the regimens are shown below:

FIGURE 19.1

TREATMENT SEQUENCE A

DAY 1 Warfarin 50 mg x 1	Day 6 Measurements of warfarin	*First Washout Period*	
DAY 15 Moexipril 15 mg plus Warfarin 50 mg x 1	Days 16-20 Moexipril 15 mg daily	*Second Washout period*	Day 29 Final Visit

TREATMENT SEQUENCE B

DAY 1 Moexipril 15 mg plus Warfarin 50 mg x 1	DA Y 2-6 Moexipril 15 mg daily	*First Washout Period*	
DAY 15 Warfarin 50 mg x 1	Day 20	*Second Washout period*	Day 29 Final Visit

Under the first regimen (Regimen A), subjects received warfarin as a single dose followed by a washout period and finally the concomitant administration of moexipril and single dose of warfarin. Moexipril treatment was continued during the assessment of the kinetics of warfarin. Under the second regimen Sequence B subjects receive concomitant moexipril with warfarin followed by an additional 4 days of moexipril. After an additional washout period warfarin was continued alone.

A total of 10 subjects were to be studied, randomized equally between the two dosing sequences. Subjects were to be normal males between 18-45 years old with normal weight (± 15%). Exclusion criteria included history of sensitivity to either class of drugs, confounding medical or psychiatric problems, drug or alcohol dependence, or baseline abnormality in laboratory assessment. Subjects were to take the medications fasting.

Vital signs were monitored both sitting and standing at 1, 2, 3, 4, 24, 48, 72, 96 and 120 hours post dose of moexipril. Blood for warfarin isomers was to be collected at the following times post dose: 0 hours (pre-dose),1, 2, 4, 8, 12, 24, 36, 48, 72 , 96 and 120 hours post dose Clotting (PT and PTT) studies were to be performed pre-administration of warfarin. PT was also measured daily for six days and then every two days till 12 days post warfarin and dose. PTT was, in addition to baseline, measured on days 1, 3, 5, 8 and 12 days post warfarin dose. Safety evaluations included frequent laboratory assessments and ECGs.

Results: A total of 10 patients were enrolled into this study. All completed therapy. Five subjects were allocated to each treatment regimen. Their demographics are shown below (Table 19.1):

Table 19.1
Demographics of Sttudy

Values are Mean (±SE)	AGE (years)	Height (cm)	Weight (Kg)
Sequence A (n=6	22.2 ± 0.86	177.2 ±1.66	74.5 ± 3.76
Sequence B (n=6)	21.2 ± 0.86	177.7 ± 2.88	74.9 ± 2.52

With respect to vital signs, maximal blood pressure changes (relative to pre-study baseline) occurred after the co-administration of moexipril with warfarin. For those randomized to sequence A the group mean sitting blood pressures changes were -19/-10 systolic/diastolic respectively at 2 hours post dose, Pulses dropped approximately 14 BPM at 1 hour post dose. For those randomized to sequence B the maximal effects were -10/-8 mm Hg at 2-3 hours post dose. Pulse also decreased 11 BPM at 3 hours post dose. The kinetic parameters of Warfarin isomers after warfarin administration with and without moexipril are shown below (Table 19.2):

Table 19.2
Pharmacokinetic Parameters of Warfarin When Single Doses are Administered WIth and WIthout Moexipril

Parameter mean + SD	S(-)-Warfarin		R (+)-Warfarin	
	Warfarin Alone	Warfarin + Moexipril	Warfarin Alone	Warfarin + Moexipril
C_{max} [ug/ml]	2.85 ± 0.35	2.79 ± 0.37	2.80 ± 0.42	2.81 ± 0.34
t_{max}[hr]	1.8 ± 0.92	2.5± 3.4	2.1± 1.1	2.5± 3.4
AUC_{0t}[ug/ml.h]]	94.8 ± 15.7	95.3 ± 18.4	124.2 ± 21	124.8 ± 26

Concomitant treatment of moexipril did not seem to change the pharmacokinetic parameters of warfarin , although the variability of the T_{max} with concurrent moexipril treatment seems so much greater than the variability of T_{max} when warfarin is given alone. The increased T max variability does suggest some interaction with moexipril and warfarin.

With respect to clotting function These are tabulated below :

Table 19.3

	PT			PTT		
Sequence/ Treatment	Baseline	Maximum Effect	Difference	Baseline	Maximum Effect	Difference
Sequence A/ warfarin alone	10.08 ± 0.22	21.5 ± 0.98	11.4 ± 2.55	32.66 ± 0.48	43.12 ± 1.24	10.46 ± 2.59
warfarin + moexipril	10.18 ± 0.22	18.86 ± 0.77	8.7 ± 1.81	32.62 ± 0.73	41.82 ± 1.46	11.70 ± 3.29
Sequence B/ warfarin + moexipril	10.18 ± 0.20	21.10 ± 1.33	11.0 ± 3.3	29.74 ± 1.19	40.52 ± 1.79	10.78 ± 1.59
warfarin alone	10.18 ± 0.20	19.06 ± 0.63	8.9 ± 1.2	30.08 ± 0.96	38.8 ± 1.36	8.74 ± 0.82

There was no overall difference in PT or PTT with warfarin alone or with concurrent moexipril treatment. Interestingly and unexplained was that there was a substantial period effect for PT values ($p<0.01$).

Safety: All subjects except one had adverse events noted during the study.The adverse events were all classified as mild except for one case of abdominal cramps and nausea (subject 1009) and one headache (subject #1002) which were classified as moderate.

With respect to laboratory abnormalities, since there were frequent laboratory assessments it is inevitable that abnormalities will present. None of these abnormalities, these are listed in sponsor's table B and (vol. 93 p. 46-47). None of these seemed to be relate to either drug

Conclusion: This is a sub-optimum study. It is unclear why the study was not performed on top of moexipril at steady state. The fact that moexipril single doses seems to change the variability of t_{max} may suggest that some interaction is present.

Study No 20 Protocol GHBA 633 Volume 1.95
Name of Study: A Phase I, Randomized, Single-Dose, Open Label, Three -Way Crossover Study to Determine the Possible Interaction of Moexipril with Nifedipine Retard in Normal Volunteers.
Principal Investigators:

Date of Study : April 29, 1991-May 29, 1991
Formulations: Moexipril Capsules- 15 mg batch no. 905041
Nifedipine Retard 20 mg Tablet Bayer(Germany), Batch WE 10219

Protocol: This was a pharmacokinetic study defining the interaction between nifedipine and moexipril. Each subject received, in random order, one dose of moexipril, one dose of nifedipine or one dose of the combination. There was a one week washout period between treatments.

A total of 12 subjects were to be studied. Subjects were to be normal males between 18-45 years old with normal weight (± 15%). Exclusion criteria included history of sensitivity to either class of drugs, confounding medical or psychiatric problems, drug or alcohol dependence, or baseline abnormality in laboratory assessment. Subjects were to take the medications fasting.

Vital signs were monitored and blood for moexipril-moexiprilat and/or nifedipine determination were collected at the following times post dose: 0 hours (pre-dose),0.5, 0.75, 1,1.5, 2, 3, 4, 6, 8, 12, and 16 hours post dose. Vital signs were also measured at 24, and 48 hours post dose. Urine were similarly collected after both the nifedipine and moexipril doses at the following intervals: -1-0 (pre-dose), 0-1, 1-2, 2-4, 4-6, 6-8,8-12, 12-24, and 24-48 hours. Urine collected in conjunction with the nifedipine dose were not further analyzed. Safety evaluations included frequent laboratory assessments and ECGs.

A total of 13 patients were enrolled into this study of which all received at least one dose of medication and 11 who completed the study. One subject withdrew from the study for, as the sponsor states, "social reasons". The second individual terminated from the study for "operational reasons". These terminations are not further defined in the submission. The demographics of the subjects who received medication was similar to those enrolled in other pharmacokinetic studies (age 33.4 SD 1.66 years, height 173.9 SD 1.39 cm; Weight 69.2 SD 1.13 Kg).

The effect of treatments were rather modest with respect to blood pressure. Maximal systolic/diastolic drops were approximately (-6 to -8)/ (-6-10) mm Hg. Maximal pulse increase was approximately 8-10 BPM.

Summary kinetic parameters are shown below (table 20.1):

Table 20.1
Pharmacokinetic Constants of Moexipril, Moexiprilat and Nifedipine After Single Doses of Elther Moexipril, Nifedipine or the Combination

	Moexipril-Moexiprilat				Nifedipine	
	Moexipril Alone		Moexipril + Nifedipine		Nifedipine Alone	Nifedipine ± Moexipril
Parameter	Moexipril	Moexiprilat	Moexipril	Moexiprilat	Nifedipine	Nifedipine
C_{max} [ng/ml]	99.7 ±44	17.9 ± 11	122 ±51	24.7 ± 15	50 ± 18	62 ± 26
t_{max} [h]	1.0 +± 0.2	1.7 ± 0.3	1.0 ±0.4	1.5 ± 0.3	2.4 ±2.1	1.3 ± 0.7
AUC_{0-t} [ng/ml.h]	149.5 ±71	59 ±31	193 ± 75	71 ± 29	271 ± 92	316 ± 106
Urinary Excretion [ug]	173 ±107	402 ±243	221 ±98	496 ±240	not done	not done

In comparing single treatment to combined treatment, all three of the measured drugs or active metabolite were increased during simultaneous treatment of nifedipine with moexipril when compared to treatment with either drug alone. None of the differences, however, attained statistical significance.

Safety: Four patients reported a total of 23 adverse experiences/intercurrent illnesses. All were mild. These experiences/illnesses included headache (3 subjects), dizziness (1 subject) and sore upper lip (1 subject).

The laboratory abnormalities noted in subjects during this study are listed in sponsor's table B-G; vol. 95 p 48-53).

Pt #1 had an elevated potassium value 5.4 mmol/l after moexipril treatment but subsequently had a normal potassiu n value with concurrent moexipril/nifedipine (4.0 mmol/l). This subject had increased urinary WBC after moexipril (26-50 WBC/cmm)

Pt #8 had elevated potassium levels 5.4-5.6 mmol/l before moexipril treatment and after each dosing i.e after moexipril, nifedipine or the combination.

pt # 6 had a high eosinophil count (8%) post moexipril WBC count was normal.

Conclusion: This is a single dose inter-actional study between low doses of nifedipine and low doses of moexipril. Normal nifedipine dosages are 10-40 mg TID or up to 120 mg/day, consequently, the 20 mg nifedipine retard is clearly at the low end of the dosing regime (particularly if there is any

diminished bioavailability in the retard form relative to the immediate release formulation.) Moexipril will probably be dosed at 7.5 to 30 mg and this makes the used dosage in this study rather modest. Any interpretation is further confounded in that neither drug is any where near steady state.

The results of this study do not show statistically significant changes in the kinetic parameters of either moexipril, moexiprilat or nifedipine although there was a tendency to increased concentration with concomitant therapies.

Study No 21 Protocol PHAKI 796 Volume 1.99
Name of Study: Evaluation of the Bioavailability of Moexipril Under Fasting and Nonfasting Conditions in Healthy Volunteers.
Princip. investigators:
Site of Investigation (Dates):
Formulations: Oral Formulation: - Moexipril Hydrochloride 15 mg coated tablet Manufactured by Schwarz Pharm AG; powder. Batch no 920512

Protocol This was a randomized, cross-over, pharmacokinetic study of one 15 mg moexipril tablet administered either under fasting conditions or 1/2 hour after a standardized meal. The meal was a relatively high fat (39 gram) high calorie (1042 kcal) breakfast. Normal male, non-smoking volunteers with no confounding medical problems were eligible for enrollment. Patients received one of the two regimens followed by a one week washout period. Plasma concentrations of both moexipril and moexiprilat were measured for 24 hours post dose.

Results: A total of 24 males were enrolled into this study, all completed both arms of the study. The mean age was 28.7 (SD 5.9) years, and weight was 72.9 (sd 6.2) Kg. The results of the study are summarized below. The sponsor uses geometric means to define the data. The large food effect seen in this study makes it an academic question as to whether arithmetic or geometric means should be analyzed. The kinetic constants are shown below:

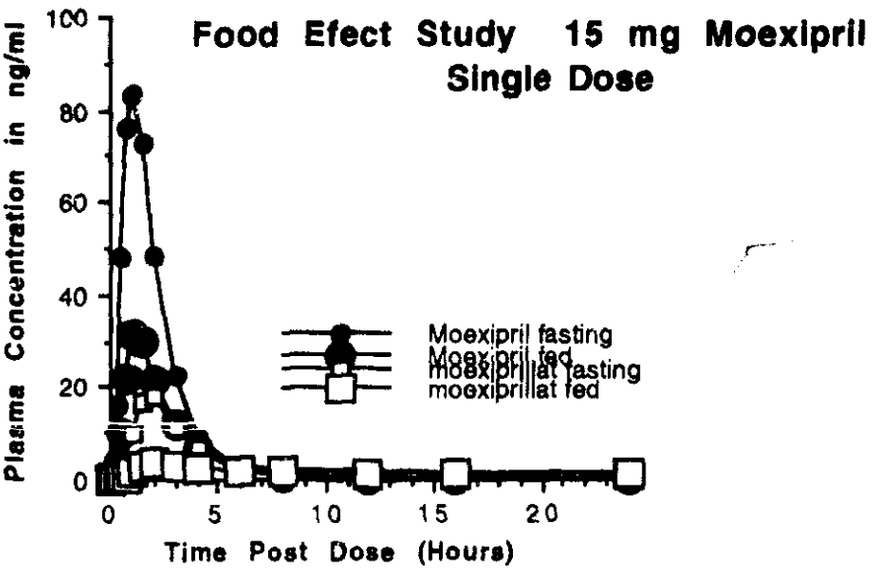
Table 21.1

	Fasting		Fed	
Parameter	Moexipril	Moexiprilat	Moexipril	Moexiprilat
AUC_{0-24}	179.6 +79	80.8 + 24	75.48 + 42	37.7 + 12
C_{max}	101.2 + 45	19.9 + 9.0	42.1 + 23	4.03 + 2.24
T_{max}	1.09 +0.4	1.73 + 0.4	1.38 +0.7	2.25 + 0.9

All values with the exception of Tmax for moexipril were statistically different in considering fasted versus fed. A graphical description of the data for moexipril and moexiprilat are shown below (Figure 21.1): Both moexipril and moexiprilat are substantially reduced under fed conditions.

Safety: Only two adverse events were reported. One patient reported headache and a second subject reported dizziness. One additional subject at follow up exam reported bronchitis.

Figure 21.1


Food Efect Study 15 mg Moexipril
Single Dose
Plasma Concentration in ng/ml
100
80
60
40
20
0
0
5
10
15
20
Time Post Dose (Hours)
Moexipril fasting
Moexipril fed
moexiprilat fasting
moexiprilat fed

Study No 22 Protocol GHBA 617 Volume 1.102
Name of Study: Bioavailability of Moexipril (RS-10085) When Administered with Food
Principal Investigators:
Site of Investigation (Dates):

June 17, 1987-August 20, 1987

Formulations Oral Formulation: - Moexipril Hydrochloride 30 mg capsules Batch no 197-122; Formulation number was F10085-23

Protocol This was a randomized, open-label, cross-over pharmacokinetic study of one 15 mg moexipril administered under fasting conditions or after a standardized meal. The meal consisted of:

3 1/2 ounces of orange juice 2 fried eggs 3 strips bacon
1 slice of toast with butter and grape jelly 1 cup coffee +cream +sugar

For the fed portion of the study subjects received moexipril after eating most of the standardized meal. For the fasting doses, moexipril was administered after an overnight fast.

Normal male, non-smoking volunteers, with no confounding medical problems, were eligible for enrollment. Patients received one of the two regimens followed by a three day washout period. Vital signs were assessed and plasma concentrations of both moexipril and moexiprilat were collected for assay for 24 hours post dose.

Moexiprilat (RS-10029) was analyzed by RIA.

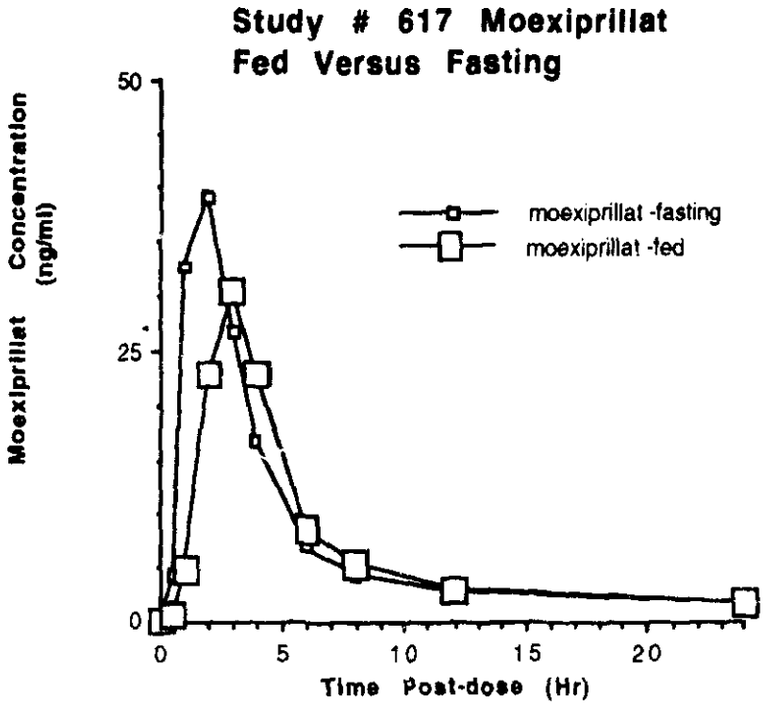
Results: A total of 12 subjects were entered into the study and completed both phases of the study. The demographics of the studied group (mean ± SE) were: age (36.5 ± 3.57 years); weight (76.2 ± 2.55 Kg) and height (177.1 ± 2.11 cm).

The kinetic constants for moexiprilat are shown below and the study results are graphically displayed as Figure 22.1 .

Table 22.1
Study #617 Moexiprilat after Moexipril 30 mg Fed or Fasting

parameter mean (SD)	Moexiprilat after moexipril Fed	Moexiprilat after moexipril Fasting
C_{max}	31.5 (± 14.3)	43.01 (± 19.5)
T_{max}	2.8 (± 0.6)	1.5 (± 0.5)
$AUC_{0\text{-}24\,h}$	158.2 (± 61)	173.8 (± 56)

Figure 22.1



Both C_{max} and T_{max} were statistically different between fed and fasting regimens. The $AUC_{0-24\ h}$ confidence intervals spanned 74.4-110% for fed versus fasting regimens.

Safety: A total of six subjects had 10 adverse events (5 episodes of lightheadedness, one each of headache, sluggish, nausea, blood in stool and blood after bowel movement).

With respect to laboratory abnormalities, those of interest are shown below: Most subjects had hemoglobin and hematocrit drops when comparing pre and post therapy values -these will not be included.

subject #1 Had a CPK of 83 MU/ml at baseline (ml: 5-200) and 482 post therapy.
subject #2: Had a WBC count of 5.0 x 10^3 pre therapy and 4.2 x 10^3 post therapy.
Subject #4 Had a serum iron of 138 ug/Dl at baseline and 185 ug/Dl (ml 30-175) post therapy
Subject #6 Had a WBC count of 5.2 x 10^3 pre therapy and 4.0 x 10^3 post therapy.
Subject #7 Had a CPK of 108 MU/ml at baseline (ml: 5-200) and 222 post therapy.

Had a serum iron of 69 ug/Dl at baseline and 219 ug/Dl (ml 30-175) post therapy

subject #8 Had an of 292/cmm at baseline and 584/cmm post therapy

subject # 12 Had a CPK of 116 MU/ml at baseline (ml: 5-200) and 236 post therapy.

comments: The results of this study which show only a modest food effect which differs markedly from the previous study (study PHAKI 796) in which a substantial food effect was noted. The reason for this discrepancy is not clear, however, there were differences in dose (30 mg in this study 15 mg in the previous study) and methodology (RIA versus GC-mass spectroscopy) and possible formulations.

Several abnormalities, not previously noted were seen in this study such as increased serum iron and increased CPKs. The CPK is particularly of interest since the rise in CPK for subject #1 is extremely high. It is difficult to determine if the CPK was related to or unrelated to therapy (i.e. perhaps due to unrecorded heavy exercise). In the absence of information to the contrary, it is probably reasonable to assume that CPK elevations were due to moexipril therapy.

Study No 23 Protocol 952-2 Volume 1.104
Name of Study: Pharmacokinetic Assessment of CI-925 and CI-929 Following Multiple Dose Administration of CI-925 to Healthy Volunteers
Principal Investigators:)
Site of Investigation:- Not stated
Formulations: Not stated
Date of Study : Not stated but report was issued on July 16, 1986

This is an incomplete report. Only the abstract of this report is presented. No safety data is supplied with the report and for that reason this report is unsatisfactory.

Briefly, a total of 16 patients (12 males, 4 females) were randomized to receive either placebo or doses of CI-925 of 30, 60 or 120 mg. Doses were administered once daily on days 1 and days 15. Doses were given twice daily (60,120 and 240 mg/day/bid)on days 2-14. Measurements of CI-925 and the active metabolite CI-929 were made. The lower assay limit of detection for both CI-925 and CI-929 was . Below are the kinetic constants as shown by the sponsor. **It should be noted that often these constants may have been derived form 2 or 3 measured serum values for a given individual and that not all individuals had sufficient measured values to even approximate AUC or Cmax. Consequently, this reviewer has little confidence in their accuracy.**

The data from this study are not very reliable. It is in fact difficult to determine either that steady state has been attained by the 15 day of treatment or if there is dose proportionality.

No safety data is shown, although all the 12 treated subjects apparently completed the course of therapy.

	30 mg dose				60 mg dose				90 mg dose			
	CI-925		CI-929		CI-925		CI-929		CI-925		CI-929	
parameter (mean ±SE)	day 1	15	day 1	15	day 1	15	day 1	15	day 1	15	day 1	15
Cmax (ng/ml)	122 ± 28	84 ± 12	80 ±21	75 ±21	92 ± 28	117 ± 26	80 ±15	124 ± 37	197 ± 64	221 ± 71	218 ±35	221 ±29
T max (hr)	1.3 ± 0.3	1.3 ±0.3	2.0	1.7 ± 0.3	1.3 ±0.3	1.5 ±0.3	1.5 ± 0.3	1.7 ±0.3	1.3 ± 0.3	1.3 ±0.3	18 ± 0.5	1.3 ±0.3
AUC hr.ng/ml	224 ± 24	157 ± 38	254 ± 76	206 ± 55	107 ± 15	246 ± 11	245 ± 48	418 ±103	458 ± 114	375 ± 96	653 ± 157	755 ± 116

Study No 24 Protocol GHBA 619 Volume 1.105
Name of Study: Evaluation of the Pharmacokinetic Profile of Three Controlled Release Formulations of RS-10085-197, An ACE-inhibitor, in Normal Volunteers.
Principal Investigators:
Site of Investigation (Dates):

Formulations:- Three -30 mg oral formulations were used in this study, designated as Fast release (formulation A), medium release (formulation B) and slow release (formulation C). The specifics of the three formulations are shown below. All formulations were all administered as capsules.

Ingredient (as % of formulation)	Formulation A (Formulation no. F10085-039)	Formulation B (Formulation no. F10085-038)	Formulation C (Formulation no. F10085-037)
Moexipril	19.0	18.2	17.4
Microcrystalline cellulose	76.0	72.8	69.6
Coating Suspension	4.0	8.0	12.0
Talc	1.0	1.0	1.0
Total	100	100	100

Date of Study : February 8, 1988-March 25, 1988
Protocol: This was a randomized open-label, three period crossover study of single doses of moexipril (30 mg) administered orally as one of the three above noted formulations. Enrollment was limited to normal males between the ages of 18-35. All three formulations were to be administered under fasting conditions with a one week period between doses. Measurements of vital signs as well as blood specimen collection for drug/active metabolite as well as ACE activities were to be taken at 0, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72 and 96 hours after each dose.Hematology, blood chemistry, urine analysis as well as ECG were performed at baseline and termination of study.

Results: A total of 12 subjects were enrolled (9 Whites, 2 Blacks and 1 other). All completed the study, one patient, however, did not complete plasma evaluations for period 2.
The pharmacokinetic variables of the three formulations are shown below (Table 23.1).

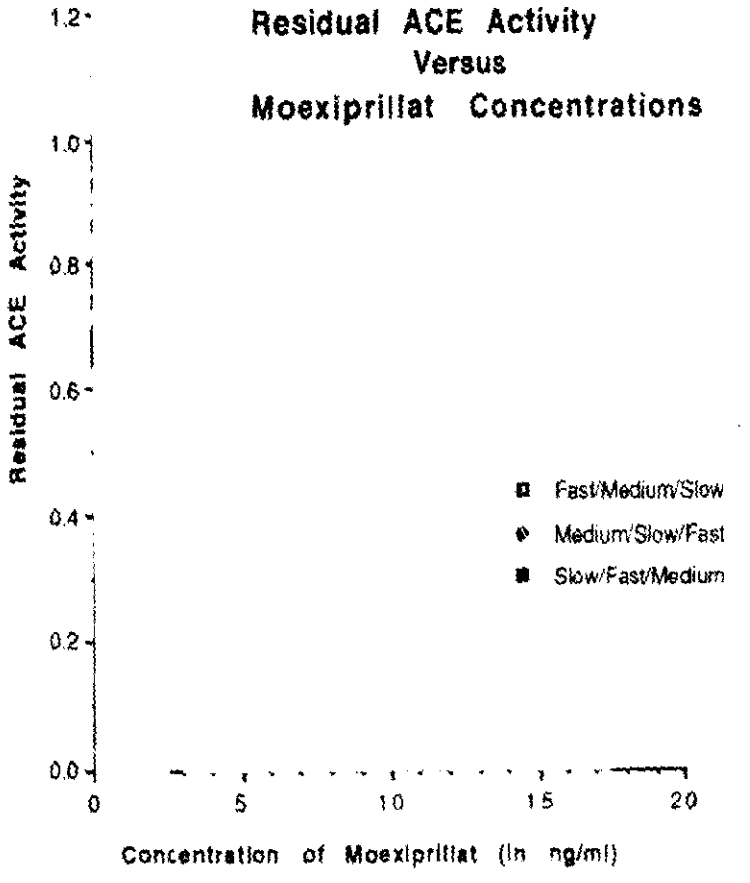
There are obvious kinetic differences among the different formulations. Relative bioavailability, as measured by either moexiprilat AUC or C_{max}, are decreased with the slower moexipril formulations.

With respect to ACE inhibition, there seems to be a correlation between the concentration of moexiprilat and residual plasma ACE activity (Figure 23.1). Based on this graph approximately 50% of plasma ACE is inhibited at approximately 0.7-3 ng/ml of moexiprilat. Concentrations above 5 ng/ml inhibit more than 90% of the ACE activity.

Table 23.1
Moexiprilat Kinetic Constants after Single doses of Three Formulations as Capsules

Variable	Formulation A	Formulation B	Formulation C
Number of patients	12	12	11
C_{max} (ng/ml)	9.7 ± 1.4	4.0 ± 1.3	2.3 ± 0.4
T_{max}	3.2 ± 0.3	9.5 ± 0.3	10.9 ± 4.2
AUC_{0-24} (hr.ng/ml)	89.1 ± 7.83	39.9 ± 7.0	30.0 ± 3.82
AUC_{0-96}	202 ± 20	120 ± 12	101 ± 14

Figure 23.1



It should be appreciated, however, that the above analysis assumes that ACE activity would be relatively constant throughout the whole day.

[comment: None of the enrolled subjects had measurable moexiprilat at the 0 time point of the first regimen (limit of detection 50 ng/ml). Most of the subjects, however, had measurable moexiprilat at the baseline time points during the crossover regimens. One subject had concentrations measured at 2.42 and 2.33 ng/ml 7 days after receiving the fast and the medium formulations. For this individual (subject # 107) the moexiprilat concentrations dropped only from 3.06 to 2.42 in going from day 5 to day 8 post dose of the "fast formulation"and from 2.91 to 2.33 in going from day 5 to day 8 post dose of the "medium formulation". These results would suggest that there is a substantially long tail to the termination half-life (> 7 days). This individual is not unique in that other individuals also had easily measurable moexiprilat concentrations 1 week post single dose.]

Safety: Three subjects had 4 adverse events(headache(n=3), somnolence (n=1).There were no discontinuations from the study.

There were several laboratory abnormalities noted in those entering and completing the study.

Subject # 107 inorganic phosphorus increased from 3.7 at baseline to 4.7 post treatment.
SGOT increased from 36 at baseline to 56 (ml < 50) post treatment and remained elevated-maximal value was 86 at 7 weeks approximately 5 weeks post treatment.
SGPT increased from 20 to 94 U/l (ml < 55). This value gradually returned to normal after approximately 3 additional weeks

Subject # 112 SGPT increased from baseline value of 21 U/l to 95 post therapy. SGOT, however remained normal.

Subject # 113 SGPT increased from 33 U/l at baseline to 158 at end of therapy. Six days later SGPT decreased to 50 U/l.
SGOT also increased from 22 U/l at baseline to 59 at end of study. Six days later the SGOT Was 18.

Subject 108 had an increase of eosinophils from none at baseline to 11% .post therapy.
Subject 109 had a normal platelet count at baseline which was decreased post-treatments
Subject 104 had trace protein in urine post therapy.

Study No 24 Protocol GHBA 625A Volume 1.107
Name of Study: A Phase I, Randomized, Single-Dose, Open Label, Three-Way Crossover Study to Determine the Possible Interaction of Moexipril with Hydrochlorothiazide in Normal Volunteers
Principal Investigators:
Site of Investigation (Dates):

(July 17, 1990-August 27, 1990)

Formulations:- Moexipril- Capsule 30 mg Batch # 901508- Schwarz Pharama
HCTZ- Tablet 25 mg WE10107 Ciba-Geigy

Protocol: This was a randomized, single dose, three way crossover study in which patients received, in random order, either moexipril (30 mg), hydrochlorothiazide (25 mg), or the combination of moexipril and hydrochlorothiazide. There was a 1 week washout period between dosing. Enrollment was limited to normal males. Subjects were to have vital signs measured as well as serum concentrations of moexipril and moexiprilat collected for assay. Urinary concentrations of moexipril, moexiprilat as well as hydrochlorothiazide were also collected for pharmacokinetic analysis.

Results: A total of 16 subjects were enrolled. Only 11 completed the study. One subject was discontinued prior to randomization. One subject discontinued prior to receiving any drug. One subject discontinued for personal reasons following H CTZ administration. Three other subjects discontinued due to problems with processing the collected pharmacokinetic samples. Maximal blood pressure effects were modest. For moexipril alone the maximum supine BP decreases were --5.9/-8.1 (systolic/ diastolic) with a maximal pulse increase of approximately 6.3 BPM. For HCTZ alone the supine BP decreases were -4.6/-4.5, with a pulse increase of 8.7 BPM. For the combination the maximal effect was -9.3/-10.6 mm Hg; maximal pulse increase was 10.9 BPM.

No pharmacokinetic data was submitted. No reason was given.

The most common adverse event was dizziness (n=5 from Moexipril + HCTZ; n=1 from moexipril). Headache (n=3 moexipril + HCTZ; n=1 moexipril; n=1 HCTZ). Given he large number of laboratory assessments, it was not surprising that there were substantial number of intermittently abnormal values recorded. None of these values seemed to be reproducible or consistent.

Study No 25 Protocol CL 4220 Volume 1.107
Name of Study: In Vitro Binding Studies of RS-10085-197 and RS-10029-007 to Plasma Proteins.
Principal Investigators:

This study explored the protein binding properties of RS-10085 and the diacid metabolite RS-10029 to plasma from humans, monkeys and dogs. The hydrolytic action of rat plasma was too rapid to accurately measure RS-10085.

Binding measurements were done at 25° C. Preliminary studies indicated no substantial temperature dependence to either drug or acid metabolite binding over the range of 4-37° C. The sponsor states that equilibrium was attained by 20-24 hours. [comment: presumably this duration to equilibrium is due to permeation of the dialysis membrane and not to binding per se]

Table 24-1 below (corresponding to Table 1 vol. 107; p. 449) summarizes the study results.

BINDING OF [^{3}H]-RS-10029 AND [^{14}C]-RS-10085 TO PLASMA FROM DOGS, MONKEYS, RATS AND HUMAN VOLUNTEERS AT 25° FOR 24 HOURS[1]

Compound	Initial[2] Conc. (ug/ml)	% Bound in Plasma From			
		Dog[3]	Monkey[3]	Rat[3]	Human[4]
-10029	0.02	39.5	55.0[5]	--[7]	73.9 ± 1.3
	0.1	34.9	50.3[6]	64.1	--
	0.5	33.3	41.8	60.4	74.2 ± 1.2
	1.0	33.1	38.5	--	71.4 ± 1.4
	2.5	32.6	39.6	60.0	68.4 ± 1.1
	4.0	34.7	38.0	--	--
	5.0	34.4	37.9	59.6	73.2 ± 1.1
	Mean ± S.E.	34.6 ± 0.9	43.0 ± 2.6	61.0 ± 0.9	72.2 ± 1.1
I-10085	0.3	88.9	88.8	--	90.7 ± 0.4
	0.5	88.0	88.3	--	90.2 ± 0.4
	1.0	87.8	88.2	--	--
	1.5	88.1	87.9	--	90.1 ± 0.2
	2.0	86.9	87.9	--	--
	5.0	87.1	86.7	--	89.8 ± 0.1
	10.0	86.5	88.2	--	90.0 ± 0.4
	Mean ± S.E.	87.6 ± 0.3	88.0 ± 0.2	--	90.2 ± 0.2

Only monkey showed concentration dependent binding , limited to the diacid metabolite. Rat, dog and human did not demonstrate any dose-related binding in the concentration range of 20-5000 ng/ml for RS-10029 and 300-10,000 ng/ml for RS-10085. Binding of RS-10085 in humans was approximately 90% and for RS-10029 it was approximately 72%. There did not seem to competition between RS-10089 and RS-10085 binding. In comparing the six plasma samples (3 males and 3 females) there was surprising little variability both in the binding of RS-10085 and RS-10029.

Section Conclusions:

ADME of Moexipril- In Humans- Moexipril is rapidly converted to, among other entities, moexiprilat which is the presumed active ACE inhibitor. When moexipril is administered as an oral formulation (in this study as a capsule, see below under "Formulation" for additional considerations) its bioavailability is only 18% or 22% as judged by parent moexipril or moexiprilat AUCs, respectively.

There are marked difference in the overall metabolic profile and excretion patterns of moexipril when moexipril is administered intravenously when compared to when moexipril is administered orally. When ^{14}C-tracer doped moexipril (with the label located on the tetrahydroisoquinolone ring) is administered intravenously, the predominant route of excretion of radioactivity is renal (65%) . The most abundant products are moexipril and moexiprillat (18 and 39% of the administered radioactivity, respectively) . When the same ^{14}C-tracer doped mixture is administered orally, however, the majority of the drug is excreted as moexiprillat (52%) in the faeces. These results suggest that there is substantial pre-systemic de-esterification of moexipril to moexiprilat. Since the ratio of intravenous to oral AUCs of both moexipril and moexiprilat are nearly equivalent, it seems that little moexiprilat that is transformed pre-systemically gains access to the circulation. If large amounts of moexiprilat gained access to the circulation, the AUC of moexipril based on the intravenous to oral ratio of moexiprilat AUCs would be substantially greater than the AUC ratio based on parent moexipril.

The site of conversion of moexipril to moexiprilat pre-systemically is unclear. If the site were hepatic in nature then this conversion would have to be immediately followed by clearance of the drug via the biliary system (the fact that the bioavailability of the moexipril when assessed either by moexipril or moexiprilat are the same suggest the systems which convert intravenous and orally administered moexipril to moexiprilat are not linked). The alternate hypothesis is that substantial transformation of moexipril to moexiprilat occurs in the gut, either in the lumen or by the bowel wall upon absorption.

There must be substantial peripheral conversion of moexipril to moexiprillat as judged by the ready conversion of intravenous moexipril to moexiprilat when moexipril is administered intravenously.

In considering plasm C_{max} concentrations of orally administered ^{14}C- doped moexipril, only approximately 40% of the measured radioactivity can be accounted for by moexipril and moexiprilat. Much of the residual radioactivity seems to be the diketopiperazine derivative of moexiprilat as well as a species designated as P4 which co-migrates with moexipril. Although there is nothing from the data that suggests these metabolites accumulate with time, the small number of subjects and the large variability would make this reviewer temper any such conclusion. There are a large number of, as yet unidentified, metabolites of moexipril in plasma, urine and faeces.

Plasma protein binding for humans was approximately 90% for the parent compound (RS-10089) and 72% for the diacid metabolite (RS-10029). There did not appear to be any temperature dependence not concentration in the range of 20-5000 ng/ml for RS-10029 and in the concentration range of 300-10,000 ng/ml for RS-10085. There did not appear to be an interaction at the level of protein binding between moexipril and moexiprilat.

Formulations: A large number of pharmacokinetic studies were included in this submission. In only one study (study PHAKI 794) was the Coated Tablet formulated by Schwarz Pharm AG (formulation 4A) bioequivalent to the formulation (also manufactured by Schwarz Pharm AG). In a second study, (capsule PHAKI 792) a formulation of coated tablet (formulation 4) was nearly bioequivalent to a capsule formulation (Formulation

A large number of other formulations were studied which were not bioequivalent to the Coated

Formulation. Thus, the results of study PHAKI 756 demonstrate that the Coated Formulation of moexipril to be only approximately 60-66% as bioavailable as moexipril when it is administered as a capsule. Since a capsular formulation was used to derive bioavailability estimates in study GHBA-628 the estimate of the bioavailability of the to-be-marketed Coated Formulation is, in reality, approximately 12-15%.

The rate of dissolution seems to markedly effect the degree (i.e. AUC) and not just the speed of moexipril absorption. In study GHBA 619 moexipril was administered as three different formulations. Each of these formulations was constructed to deliver moexipril at different rates. The formulations differed in the amount of microcrystalline cellulose that was compounded into the tablet and amount of coating suspension surrounding the moexipril capsule. Not only was the rate of absorption of moexipril delayed (i.e. Tmax progressively prolonged) but surprisingly, the AUCs and C_{max} were coincidently diminished with the slower release formulations. Although dissolution data for the three formulations which were studied in GHBA 619 are not shown in the submission, a similar observation that dissolution and bioavailability are linked was noted in a published report (Grass, G.M.; and Morehead, W. T.; Pharmaceutical Research, 1989 6: 759-765). In that report dissolution data, of what appears to be the same moexipril formulations which were administered in this study, is presented. The authors suggest that kinetics of moexipril might be limited to the proximal portions of the GI tract. Dissolution of moexipril more distally within the GI tract may not lead to its intact absorption.

Food Effects: Two studies were performed to define the effects of food on moexipril. In one study (PHAKI 796) subjects received the coated tablet formulation with and without a high calorie/high fat meal. Based on either C_{max} or AUC, the bioequivalence of moexipril either as moexipril or as moexiprilat when moexipril is administered with food was only 42% of these values when moexipril is administered fasting. In a second study (GHBA 617), moexipril was administered as the capsule formulation with and without a high fat/high calorie breakfast. In this study the relative bioequivalence, based either on moexipril or moexiprilat was approximately of 90%. The reason for the apparent differences in bioavailability, aside from differences in formulation performance, are not clear.

ACE-inhibition: There is relative consistency that across studies that moexipril administration causes rapid and prolonged inhibition of plasma ACE activity. Figure 23.1 strongly suggests that there is a inverse correlation between residual ACE activity and concentration of moexiprilat. At concentrations of approximately 0.5-2 ng/ml nearly 50% of residual plasma ACE-activity is inhibited. At approximately 4 ng/ml approximately 90% of plasma ACE activity is inhibited.

Dose Proportionality: Several studies were submitted that broach the issue of dose proportionality. PHAKI 795 studied the kinetics of moexipril (Formulation 4) over a dose range of 3.75 to 30 mg. Dose proportionality could not be established either for moexipril or moexiprilat. The study results, however, were suggestive of a diminution of AUC and C_{max} (when normalized to dose) at the higher doses.

The data derived from study CM 1394 would make one draw a different conclusion. In this study, moexipril was also administered as a single dose, but in the range of 3.75-60 mg, in a capsule formulation. In CM 1394 both the AUC and C_{max} for both moexipril and moexiprilat increased in an excessive manner as the doses increased (see Table 18.1). This excess in AUC and C_{max} is more convincing for moexipril but also seems to hold true for moexiprilat. Almost all the large apparent dose-related increases in the moexipril parameters, however, seem to be the result of a single outlier. The apparent increases in moexiprilat parameters, however, cannot be explained by a single outlier. It should be noted, however, that the variability in the measured moexiprilat parameters are so large that the confidence intervals still would include values consistent with dose proportionality.

Lastly, Protocol 952-2 with an unstated formulation has dose response data through 90 mg that are

inadequate and unreliable.

This is, at best, confusing data. The extent to which this apparent inconsistency of data is due to the relative paucity of good studies or due to the vagaries of the different formulations is unclear.

Accumulation with Multiple Doses: There is some data available that moexiprilat levels seem to accumulate with multiple doses. This is not surprising since, like other ACE-inhibitors, there is good evidence that moexiprilat has a long terminal half-life. This long terminal half-life is occasionally observed as residual moexiprilat levels at baseline during cross-over studies. For example most of the subjects in study GHBA 619 had measurable levels of moexiprilat at baseline measurement of the cross-over period. In this study subjects received three doses of moexipril (30 mg), each dose separated by one week . In other studies, only occasionally, could baseline moexiprilat levels be detected at cross-over regimens. Most of these studies, however, treated subjects with 15 mg doses of moexipril. Since the limit of quantitation of moexiprilat is 0.5 ng/ml, halving the thirty mg dose dropped the anticipated levels of moexiprilat to near the limits of quantitation. Consequently many of these individuals may have had moexipril present but at sub-detectable levels.

With respect to accumulation after multiple doses, the most convincing study is CM 1394 which compared the pharmacokinetics of elderly to young subjects. There did not appear to be any substantial accumulation with time of moexipril during the 5 day dosing period. However, there appeared to be an accumulation of moexiprilat as judged by C_{max}, AUC and urinary excretion of moexiprilat. This accumulation was noticeable for both the elderly and the young.

Special Populations:

a-Elderly- One study (CM 1394) is submitted which demonstrated modest differences between elderly and young both acutely and after five days of therapy. The dose was 15 mg a mid-range dose. In general elderly had higher C_{max} and AUC for both moexipril and moexiprilat both on day 1 and at presumed steady state, day 5. The increases were on the order of 25-35%. the studies were too small and of too short duration to discern any potential safety issues.

b-renal failure- One study (GHBA 629) dealt with the kinetics of moexipril in renal failure patients. Subjects, categorized as either normal or mild , moderate or severe renal disease, received a single mid-range dose (15 mg) of moexipril capsules. Since the size of the study was small and the duration of treatment short little comfort can be derived from this study. There is a trend to suggest that the severe renal failure group differs in kinetics from the normals and mild renal failure group (see Tables 14.1, 14.2 and figure 14.1), particularly for the increase in AUC with moexiprilat.

c-hepatic failure: One study (GHBA 636)was done in a small number of subjects (n=6) with probably mild-moderate hepatic dysfunction. Based on across-study comparisons of pharmacokinetic parameters of those with hepatic disease to those parameters derived from pharmacokinetic studies in normals, there appear to be modest differences. Once again, no labeling can be endorsed except to caution that the kinetics of the drug are indeed altered even in subjects with modest hepatic dysfunction.

Interaction Studies: A total of five studies were reported within this NDA examining the interaction potential between moexipril and each of the following :

1) hydrochlorothiazide(study GHBA 625);
2) digoxin (study GHBA 626);
3) cimetidine (GHBA 627);
4) warfarin (GHBA 631); and
5) nifedipine (GHBA 633).

In none of these studies was an interaction noted. Caution should be used in making any labeling claims

based on these studies. In some studies dose of both drugs was suboptimal (i.e. with nifedipine). In the majority of the other studies the confidence intervals for equivalence were large and even if there were interactions between moexipril and the moiety it would in all likelihood not have been considered significant.

Safety:

Creatinine Phosphokinase Elevation: The only unusual safety issue that is derived from these phase I and phase II studies was the unexplained elevation of creatinine phosphokinase in the only study (GHBA 617) that measured this enzyme. In one subject CPK rose from 83 MU/ml at baseline to 482 post therapy (normal 5-200 MU/ml). Two additional subjects had suspicious rises in CPK post therapy that were above the normal range. No individual had abnormal baseline CPK values.

Although it is possible that this elevation is spurious, arising from some artifactual muscle damage (i.e. IM shots or heavy exercise) no such data is presented.

Abraham Karkowsky, M.D., Ph.D. HFD-110

K. BOONGIOVANNI

AUG 2 1993

NDA #20-312 Moex

SAFETY REVIEW

Reviewer: Sughok Chun, M.D. Date 8/02/93

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SAFETY REVIEW OF ORIGINAL NDA SUBMISSION

NDA # 20-312

Name of Drug: MOEX (moexipril HCl) tablets

Sponsor: G.H. Besselaar Associates
Agent for Schwartz Pharma A.G.
Monheim, Germany

Type of Submission:

Date of Submission: 12/18/92 original, 4/30/93 (#005), 6/04/93 (007), 6/04/93 (#008), 6/23/93 (#010), 7/12/93 (#013), 7/20/93 (#014).

Date of Review: 7/27/93

Reviewer: Sughok K. Chun, M.D. HFD-110

Resume:

The sponsor's summary of safety data of the original submission (12/18/92), the first safety update (4/30/93 #005), and combined data (6/23/93) are reviewed. The study population are shown table 1 below.

Table 1: Patient Population

	Moexipril Alone	Moexipril + HCTZ	HCTZ Alone	Placebo Alone	Moexipril + Nifedipine
Controlled Studies (1)	1254	344	197	360	152
Uncontrolled Studies (2)	710	239			
Combined Studies (3)	1745	544	197	360	152

(1) Protocols Included: 622(DB) 623(DB) 638(DB) 640(DB) 642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 651(DB).

(2) Protocols Included: 618(OL) 624(OL) 638(OL) 641(OL) Many of pts were extension of controlled studies.

(3) Protocols Included: 618 (OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL) 642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

See Appendix I for the study designs and subjects characteristics.

All adverse experiences (AEs), including intercurrent events, are reported regardless of relationship to study drug.

A specific AE is counted only once for each patient (pt), provided the pt had not changed treatment regimen (in study No. GHBA-638 OL, pts could have received monotherapy or combination therapy). If a pt changed treatment regimens and had another episode of the same AE, that AE was counted twice, once in each treatment regimen group. If a particular AE was reported as both a clinical and a laboratory/ECG AE for the same pt, that AE was counted only once.

This review will discuss the most frequently reported clinical and laboratory AEs for all submitted data. The number (%) of pts with AE, number (%) of pts discontinued for AE, number (%) of pts with serious AE, mean time of onset of AE (minimum days, maximum days), and mean duration of AE (only frequent AE) during the clinical studies, are listed in Appendix II.

The number and percent of pts reported common AE, more likely or probably related to the drug therapies during the clinical trials are shown in Table 2.

Among the most common AEs are nervous system; headache and dizziness which occur early phase of treatment and upper respiratory system symptoms; cough, flu like syndrome, bronchitis, rhinitis, pharyngitis occur after > 2-3 mos of treatment. Kidney function deterioration (increased serum K and/or creatinine, albuminuria, urine cast etc.) and hyperglycemia occur with > 2-3 mg of Moex treatment.

Table 2
NUMBER AND PERCENT OF PATIENTS WITH ADVERSE EXPERIENCES (AE)
ALL ADVERSE EXPERIENCES (COMBINED)
BY BODY SYSTEM

Adverse Experience	Moexipril Alone	Moexipril + HCTZ	HCTZ Alone	Placebo Alone	Moexipril + Nifedipine
Total Number of Patients	1745	544	197	360	152
Total # of Patients with Adv. Exp.	995(57.0)	326(59.9)	101(51.3)	170(47.2)	56(36.8)
Headache	224(12.8)	47(8.6)	17(8.6)	40(11.1)	5(3.3)
Flu Syndrome	71(4.1)	32(5.9)	1(0.5)	4(1.1)	3(2.0)
Fatigue	70(4.0)	22(4.0)	2(1.0)	5(1.4)	1(0.7)
Fever	13(0.7)	10(18)			
Face edema	6(0.3)				
Peripheral edema	38(2.7)	9(1.7)		8(2.2)	4(2.6)
Generalized edema	5(0.3)				
Flushing	25(1.4)	8(1.5)		1(0.3)	3(2.0)
Hypotension	5.(0.3)	3(0.6)			
Postural Hypotension		6(1.1)			
Postural dizziness	7(0.4)	8(1.5)	1(0.5)	1(0.5)	
Syncope	3(0.2)	5(0.9)		1(0.3)	
Sinus bradycardia	3(0.2)	2(0.4)			
Diarrhea	70(4.0)	22(4.0)	2(1.0)	5(1.4)	
Dyspepsia	41(2.3)	11(2.0)		5(1.4)	
Nausea	39(2.2)	14(2.6)	1(0.5)	5(1.4)	
Hyperkalemia	11(0.6)	1(0.2)			1(0.7)
Hyperglycemia	8(0.5)	11(2.0)	3(1.5)	2(0.6)	
Hyperuricemia	8(0.5)	19(3.5)	11(5.6)	2(0.6)	
Gout	5(0.3)	4(0.7)	2(1.0)	3(0.8)	
SGPT increase	14(0.8)	7(1.3)	7(3.6)	3(0.8)	4(2.6)
Creatinine increase	6(0.3)	3(0.6)	3(1.5)		
Myalgia	25(1.4)	4(0.7)	2(1.0)		1(0.7)
Dizziness	98(5.6)	32(5.9)	6(3.0)	9(2.5)	5(3.3)
Hypertonia	24(1.4)	8(1.5)	1(0.5)		1(0.7)
Upper repesp infection	175(10.0)	39(7.2)	7(3.6)	26(7.2)	4(2.6)
Cough increase	146(8.4)	43(7.9)	2(1.0)	11(3.1)	4(2.6)
Pharyngitis	60(3.4)	18(3.3)	2(1.0)	3(0.8)	3(2.6)
Rash	39(2.2)	6(1.1)	3(1.5)	4(1.1)	1(0.7)
Hematuria	16(0.9)	5(0.9)	1(0.5)	1(0.3)	1(0.7)
Albuminuria	7(0.4)	4(0.7)	2(1.0)		
CLcreat. decrease	2(0.1)		1(0.5)		

Review of short term phase I pharmacokinetic studies on normal subjects where subjects were closely monitored showed mild to moderate headache, dizziness, feeling of pressure/congestion in the nape of the neck/head are earliest AEs shown in a single dose studies (**#795, 629, 633, 796, 625A**) in all Moex doses 3.75, 7.5, 15 & 30 mg. In study **#629** in subjects with different levels of renal function and study **#636** in pts with hepatic cirrhosis showed a wide range of plasma conc of moexipril and moexiprilat (see Table 3 & 4).

Table 3: Pharmacokinetics with Various Renal Function
Study #629 Moex 15mg 1X

Parameter	Creatinine Clearance (mL/min)			
	> 90	66 - 90	41 - 65	10 - 40
Moexipril	n=4	n=4	n=5	n=5
C_{max} (ng/mL)	46 ± 16	42 ± 11	38 ± 21	40 ± 13
T_{max} (hr)	0.8 ± 0.2	1.0 ± 0.4	1.1 ± 0.3	1.1 ± 0.6
AUC_{0-t} (ng·hr/mL)	60 ± 26	60 ± 13	65 ± 26	72 ± 28
$t_{1/2}$ (hr)	1.1 ± 0.2	1.2 ± 0.1	1.9 ± 0.9	2.2 ± 0.7
TUE (μg)	203 ± 105	152 ± 37	116 ± 71	98 ± 61
Moexiprilat				
C_{max} (ng/mL)	17 ± 10	24 ± 10	18 ± 12	26 ± 18
T_{max} (hr)	1.6 ± 0.3	1.8 ± 0.3	1.9 ± 0.2	2.8 ± 1.6
AUC_{0-t} (ng·hr/mL)	150 ± 57	148 ± 31	166 ± 38	268 ± 152
$t_{1/2}$ (hr)	1.5 ± 0.6	2.9 ± 1.2	5.0 ± 4.1	5.3 ± 3.6
TUE (μg)	531 ± 338	628 ± 122	479 ± 226	621 ± 374

Table 4: Pharmacokinetics in Liver Cirrhosis
Study 636. Moex 15mg 1X

Parameter	Mean ± SD (n=12)	Range
Moexipril		
C_{max} (ng/mL)	154 ± 60	
T_{max} (hr)	0.9 ± 0.3	
AUC_{0-t} (ng·hr/mL)	324 ± 180	
$t_{1/2}$ (hr)	1.7 ± 0.7	
TUE (μg)	469 ± 277	
Moexiprilat		
C_{max} (ng/mL)	16 ± 9	
T_{max} (hr)	2.5 ± 1.9	
AUC_{0-t} (ng·hr/mL)	228 ± 70	
$t_{1/2}$ (hr)	3.5 ± 2.3	
TUE (μg)	439 ± 273	

Cmax and AUC of both moexipril and moexiprilat in cirrhosis pts were 1.5-2 times higher than the normal subjects, but only 1 (pt #09/636) of 12 pts with liver cirrhosis complained of dizziness, lightheadedness with change of BP from 138/92 to 95/48 45 min post-dose. BP returned to baseline in 15 min. This pt showed increase of blood sugar from baseline 6.2 mmol/l to 7.1 mmol/l (normal 3.8-6.2), bilirubin 8.0 mmol/l baseline to 10.1 on Day 4, BUN 4.5 baseline to 6.5 on Day 5. Two additional pts (01/636, 12/626) also increased bilirubin (from 19 to 27 mmol/l; 22 to 32 mmol/l respectively).

In study #629 5 out of 21 pts with kidney dysfunction complained headache: 2 with normal CLcr, 3 with CLcr < 30 ml/min. In study #637 healthy male subjects 18-45 yrs vs. 65-80 yrs showed mild dizziness, dyspepsia was seen in 2/12 elderly subjects but none in 12 younger subjects.

The incidence of common AEs in pooled data below showed a trend increase of AEs in elderly population.

Adverse Experience	Number (%) of Patients < 65 Years: Moexipril (N=625)	< 65 Years: Placebo (N=215)	≥ 65 Years: Moexipril (N=272)	≥ 65 Years: Placebo (N=107)
Total Number With Adverse Experiences	344 (55)	100 (47)	135 (50)	49 (46)
Headache	69 (11)	19 (9)	20 (7)	12 (11)
Upper Respiratory Infection	55 (9)	16 (7)	18 (7)	7 (7)
Cough Increased	43 (7)	4 (2)	20 (7)	6 (6)
Flu Syndrome	30 (5)	1 (<1)	14 (5)	1 (1)
Dizziness	31 (5)	5 (2)	12 (4)	3 (3)
Rhinitis	30 (5)	7 (3)	4 (1)	3 (3)
Diarrhea	25 (4)	2 (1)	8 (3)	3 (3)

Drug interaction pharmacokinetic studies #631 with digoxin, #627 with cimetidine, and #631 with warfarin showed no unusual AE.

ORTHOSTATIC HYPOTENSION

Reduction of BP after the first dose begins around 2 hrs post-dose and peak 3-4 hrs post-dose. In earlier studies BP was measured up to 2 hrs post-dose that the peak effect was missed. Number (%) of pts with ≥ 30 mmHg decrease in standing SBP after the first dose of study drug is shown in Table 5 and each subjects data are shown in Appendix III.

TABLE 5: NUMBER (%) OF PATIENTS WITH ≥ 30 mmHg DECREASE IN TWO-MINUTE STANDING SYSTOLIC BLOOD PRESSURE (SSBP) AFTER FIRST DOSE OF STUDY DRUG

Pl = 9/264 (3.4%)	Moexipril 15/HCTZ 25 = 16/50 (32.0%)
Moexipril 3.75 mg = 7/134 (5.2%)	HCTZ 12.5 mg = 3/48 (6.3%)
Moexipril 7.5 mg = 46/567 (8.1%)	HCTZ 25 mg = 9/149 (6.0%)
Moexipril 15 mg = 45/382 (11.8%)	Verap 180 mg = 1/90 (1.1%)
Moexipril 30 mg = 18/110 (16.4%)	Verap 180 mg/HCTZ 25 mg = 1/52 (1.9%)
Moexipril 60 mg = 21/61 (34.4%)	Captopril 25 mg = 7/54 (12.9%)
Moexipril 3.75/HCTZ 12.5 = 2/44 (4.5%)	Nifedipine 20 mg = 6/51 (11.8%)
Moexipril 7.5/HCTZ 12.5 = 3/46 (6.5%)	Moexipril 3.75/Nif 20 = 6/50 (12.0%)
Moexipril 15/HCTZ 12.5 = 8.47 (17.0%)	Moexipril 7.5/Nif 20 = 13/52 (25.0%)
Moexipril 3.75/HCTZ 25 = 18/50 (36.0%)	Moexipril 15/Nif 20 = 9/50 (18.0%)
Moexipril 7.5/HCTZ 25 = 0/108 (0%)	

However, postural decrease of SBP from sitting to standing were (from Appendix III):

	Plcb	Moex 3.75	Moex 7.5	Moex 15	Moex 30	Moex 60
20-30 mm	1(0.4%)	3(2.2%)	5(0.9%)	1(0.3%)	5(4.5%)	3(4.9%)
> 30 mm Hg	0	1(0.7%)	2(0.4%)	1(0.3%)	1(0.9%)	2(3.3%)

	MX 3.75 + Nif	MX 7.5 + Nif	MX 1.5 + Nif	Nif	HCTZ
20-30 mmHg	1(2.3%)	1(2.2%)	1(2.2%)	1(2.0%)	0
>30 mmHg	0	0	0		1(0.6%)

The degree of orthostatic reduction appear to be dose proportional drug effect.

Study **#651** ambulatory 24 hr BP measurement showed a similar reduction of SBP after 8 wks of Moex treatment as the very first dose (Table 6).

Table 6: ADJUSTED@ MEAN CHANGE (S.E.) FROM BASELINE & BY WEEK AND TWO-HOUR INTERVALS AMBULATORY SYSTOLIC BLOOD PRESSURE (mmHg) COMPARISON OF MoexIPRIL TO PLACEBO Study #651

WEEK 0 (DAY 1, First Dose)

Baseline N	Placebo	Moex 7.5 mg	Moex 15 mg
Hour	14	16	17
0 Sitting	149.3	160.6	156.7
Immed. Stand	148.6	162.4	154.1
2 min. Stand	148.9	161.6	153.1
2	-7.5 (3.95)	1.4 (3.84)	-7.8 (3.72)
2-4	-4.8 (3.42)	2.4 (3.44)	-14.5* (3.34)
4-6	-6.2 (3.14)	-5.8 (3.08)	-22.5*** (2.88)
6-8	-4.6 (3.79)	-8.5 (3.77)	-18.1* (3.62)
8-10	-6.3 (4.12)	-8.1 (3.56)	-19.5* (3.43)
10-12	0.5 (4.18)	-7.2 (4.22)	-13.1 (3.87)
12-14	-6.3 (4.12)	-2.0 (4.32)	-10.4 (4.07)
14-16	0.7 (3.75)	1.8 (3.89)	-7.6 (3.62)
16-18	-3.1 (3.69)	-4.3 (4.01)	-12.6 (3.56)
18-20	-0.3 (3.46)	-4.0 (3.66)	-15.5** (3.36)
20-22	2.0 (4.57)	-11.4 (4.94)	-15.3** (4.21)
22-24	-2.5 (3.39)	-3.8 (3.39)	-12.5 (3.11)

WEEK 8: CHANGE FROM PRE TO POST-LAST DOSE SYSTOLIC BP (mmHg) ADJUSTED@ MEAN CHANGE (S.E.) STUDY #651

Hour	N	Placebo 14	Moex 7.5 mg 16	Moex 15 mg 15
0	sitting	144.5	159.5	146.2
	immediate stand	141.5	158.7	145.6
	2 min. stand	142.7	161.7	146.0
1-2		-4.9 (3.86)	-3.4 (3.52)	-15.4 (3.65)
2-4		-6.2 (4.10)	-2.9 (3.80)	-22.2** (3.98)
4-6		-2.6 (4.74)	-12.8 (4.45)	-19.2* (4.48)
6-8		-2.5 (4.49)	-11.3 (4.22)	-15.7 (4.36)
8-10		-1.4 (5.04)	-7.1 (4.74)	-12.9 (4.92)
10-12		6.1 (5.44)	-3.4 (5.14)	-6.3 (5.09)
12-14		1.0 (5.05)	1.0 (5.07)	-3.0 (5.24)
14-16		7.8 (5.81)	6.6 (5.72)	-4.6 (5.79)
16-18		-4.2 (5.24)	-2.7 (5.43)	-8.3 (5.26)
18-20		4.1 (5.74)	-1.4 (6.10)	-5.6 (5.54)
20-22		-2.9 (3.67)	-3.9 (3.42)	-7.8 (3.30)
22-24		-4.2 (3.91)	0.9 (3.55)	-11.1 (3.79)

@ Mean change from baseline adjusted by analysis of covariance.
* p≤0.050, ** p≤0.010 *** p≤0.001 (significantly different from placebo mean change).

In Study #651 Moex 7.5 QD dosing has very little BP effect 4-10 hr post dose in chronic therapy and hypotensive effect is seen only with Moex 15 mg QD in this small sample of study (Table 7). Treatment with Moex 15 QD has wide peak/through ratio after the 1st dose and it became smaller with chronic dosing.

Antihypertensive effect may diminish toward the end of the 24h dosing interval in some pts specially with Moex 7.5 mg dose and such pts may be given as BID dosing.

TABLE MEAN (Study #651) (S.E.) Sitting Blood Pressure (mmHg)

	Systolic BP			Diastolic BP		
Week	Placebo	Moex 7.5 mg	Moex 15 mg	Placebo	Moex 7.5 mg	Moex 15 mg
N	17	16	18	17	16	18
Baseline*						
(0, Hr. 0)	149.3 (4.17)	160.6 (3.45)	156.7 (3.02)	105.6 (1.16)	103.3 (1.36)	104.2 (1.43)
0, Hr. 1	154.2 (4.24)	155.0 (3.84)	147.6 (3.62)	101.2 (1.88)	102.9 (2.02)	98.1 (1.96)
0, Hr. 2	151.0 (4.29)	152.1 (3.88)	139.0 (3.57)	98.4 (1.54)	101.5 (2.14)	94.5 (1.97)
2, Hr. 0	147.4 (3.63)	156.1 (3.81)	150.9 (3.82)	101.4 (1.32)	99.2 (2.38)	98.2 (2.11)
4, Hr. 0	147.3 (3.88)	156.6 (4.28)	146.6 (3.84)	97.0 (2.44)	101.0 (1.96)	97.4 (2.68)
6, Hr. 0	150.4 (4.74)	158.8 (4.69)	146.1 (3.13)	100.5 (1.80)	102.1 (2.26)	99.0 (2.48)
8, Hr. 0	144.5 (4.69)	159.5 (3.75)	146.2 (3.95)	97.3 (2.29)	102.8 (1.57)	99.4 (1.95)
Endpoint #	148.4 (4.97)	159.5 (3.75)	147.9 (3.82)	99.0 (2.32)	102.8 (1.57)	101.1 (2.11)

* Baseline = Auscultatory BP measurement obtained at Week 0 (Hour 0).
# Last predose (Hour 0) measurement during the double-blind period.

Out of 248 pts whose standing SBP dropped ≥ 30 mmHg from supine/sitting SBP but only 10 had symptoms (Table 8) but unlikely those complaints are due to orthostatic hypotension.

Table 8. PATIENTS WITH SYMPTOMATIC HYPOTENSION
BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Study Treatment Group	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
623/MX 30	13132	144	106 (4)	-38	126	-20	76	80	+4	Headaches
622/MX 15	4103	200	110 (2)	-90	130	-70	76	80	+4	Headaches
622/MX 15	759	182	140 (2)	-42	162	-20	82	82	0	Headaches
										Fatigue
638/MX[illegible]	6401	184	142 (3)	-42	156.7	-14.7	64	88	+24	Dizziness
45										
MX[illegible]Z	4217	160	120 (2)	-40	127.3	-7.3	76	80	+10	Dizziness
3.75										Flushing
										Headaches
										Sweating
644/MX[illegible]Z	4016	150	115 (3)	-35	113.9	+1	80	90	+10	Dizziness
										Sweating
644 MX[illegible]Z	1106	125	94 (3)	-31	105.7	-11.7	100	84	-16	Headache
15										Hypotension
MX[illegible]Z	4122	133	96 (4)	-37	96.7	-0.7	126	95	-31	Flushing
45										
MX[illegible]Z	4338	168	120 (2)	-48	128.7	-8.7	78	94	+16	Dizziness
3.75										Flushing
648/Captopril 25	7032	147	117 (1)	-30	119.3	-2.3	76	64	-12	Fatigue

Severe orthostatic reduction of SBP was seen 2 pts with Moex 60mg, -56, -45 mmHg respectively, however, neither one had complaint. Only 3 pts with reduction of SBP from sitting to standing SBP ≥ 20 mmHg had symptoms (headache 2; dyspnea/fatigue 1) and these are unlikely due to orthostatic hypotension.

The max. decrease of standing SBP was -90 mmHg in 1 pt who complained headache, the next was -81 mmHg in 1 pt, -(60 ± 5) mmHg in 13 pts and they did not have complaints. There was slight increase of HR in most pts (≥ 20 bpm increase 14; ≥ 20 bpm decrease 4 pts). There appeared to be no relation to the degree of reduction of standing SBP to change of HR or symptoms.

UPPER RESPIRATORY SYSTEM RELATED SYMPTOMS

One of the common ACE-inhibitor related AE, eg. cough, upper respiratory infection, flu like symptom, pharyngitis,were observed 1/4 of pts with Moex alone or Moex + HCTZ treatment groups (see Table 2). These symptoms usually occurs with chronic treatment (≥ 3 mos) and but caused for D/C of Moex Rx 16/1254 (1.3%), Moex + HCTZ 5/344 (1.5%). See DISCONTINUATION section.

ANGIOEDEMA

Transient angioedema/face edema was reported in 5 pts with chronic Moex treatment. One of them Moex was discontinued due to angioedema.

#6438 - 46 Y/Wh/M experienced angioedema after wk 21 Moex 15/30 mg. Angioedema lasted 1 day and resolved after treatment with prednisone. The event was not considered serious by the investigator and did not result in study drug discontinuation. The pt continued receiving Moex 30 mg daily for 2 yrs without recurrence of the angioedema

#6249 - 43 Y/Bl/M with a Hx of facial swelling associated with ingestion of seafood and monosodium glutamate experienced two episodes of moderate swelling of the upper lip, at Day 5 and Wk 4 after commencing Moex 7.5 mg + HCTZ. Both episodes lasted approximately 14 hrs and resolved without treatment. The investigator thought drug-relationship was highly probable and d/ced drug after the second episode.

#6450 - 54 Y/Bl/F experienced severe tongue edema at wk 14 of exposure to Moex 7.5/15/30 + HCTZ. The swelling lasted 8 hrs and was treated with diphenhydramine. The relationship to drug was considered possible. Drug was discontinued then but the reason given was lack of effectiveness.

#4134 - 64 Y/Wh/M who had been previously treated with captopril for 5 1/2 years developed severe facial edema after 7 days of treatment with Moex 3.75. It was considered probably not drug related (an intercurrent event) by the investigator. The pat was treated with diphenhydramine and the facial edema disappeared after 4 days despite continued treatment

with Moex. The pt completed the double-blind treatment period, receiving 4 more months of Moex and reported no further recurrences of the facial edema.

#7080 - 41 Y/Wh/F had a Hx of allergy and was also receiving astemizole. After 13 days of Moex 7.5, she developed tingling and numbness of both arms along with a rash lasting 2 hrs and mild swelling of the upper lip lasting 2 days. The investigator felt all events were possibly related to astemizole and Moex. Astemizole was d/ced the following day. The lip swelling recurred 5 days later, lasting for 30-40 min. A pruritic eczematous rash developed 3 wks later and was present intermittently until the completion of the double-blind study approx 8 wks later.

HYPERKALEMIA AND KIDNEY DYSFUNCTION

There are slight increase of mean serum potassium level during chronic Moex therapy (See Table 7).

Table 7: MEAN POTASSIUM VALUES (mmol/l)

Controlled Studies

	Baseline	Endpoint*
HCTZ	3.77	3.45
Moexipril	3.92	4.03
Moexipril + HCTZ	3.81	3.56

Uncontrolled Studies

	Baseline	Endpoint*
Moexipril	3.94	3.91
Moexipril+HCTZ	3.45	3.88

Combined Studies

	Baseline	Endpoint*
HCTZ	3.85	3.96
Moexipril	3.67	3.72
Moexipril + HCTZ	4.11	4.11

* Endpoint is last postbaseline value

Although there was no significant changes in mean values of serum K, BUN or creatinine, a significant increases of serum K, BUN or creatinine values reported in some pts who were treated with Moex alone especially in chronic studies (at wk 6 or wk 8).

Since most of pts were treated with Moex 7.5 or 15 mg, abnormal serum K or creatinine were associated with these dosage groups. However, these abnormalities were seen in few pts with Moex 3.75 mg.

Increase of serum K ≥ 5.4 mEq/l from normal baseline was seen in 32 pts, 9 of them were associated increase of BUN or creatinine [#6012 (Study wk 8), 7064 (wk 2), 8246 (wk 12), 8119 (wk 6), 8263 (wk 18), 8058 (wk 24), 8163 (wk 6), 9019 (wk 4), 9253 (wk 8)] and 6 pts associated with proteinuria [7064 (wk 2), 8076 (wk 12), 8145 (wk 6), 8263 (wk 18), 8051 (wk 7), 8058 (wk 24)]. Two pts (8035, 8144) K was 5.9, 2 pts (330, 600) K was 6.4 and 1 pt (9016) K was 5.8 mEq/l. The last pt (9016) was d/ced Moex due to increase of K.

Increase of serum creatinine ≥ 40% above their baseline value regardless of whether or not the baseline value was above or the normal range, 14 pts with Moex alone group [(#6082 (wk 2), 6418 (wk 6), 6087 (wk 6), 6325 (wk 6), 7449 (wk 8), 9062 (wk 12, 24), 7110 (wk 4), 9102 (wk 8), 9106 (wk 2, 4, 8), 9338 (wk 2, 4), 9107 (wk 4), 328 (wk 34, 47), 6180 OL (wk 100), 7290 OL (wk 28)]; 4 pts in Moex + HCTZ group [6077 (wk 2 & 4), 6517 (wk 2), 4140 (wk 2 & 4), 5014 (wk 8)]; 2 pts in placebo group; 2 pts HCTZ alone group; 2 pts in captopril group.

Two pts d/ced the study due to high serum K and/or creatinine: **#640/7064** 71/F, Moex 15 mg. Baseline creatinine was 137 μ mol/l went up to 164 at Day 15, 160 at Day 29; **#646/8089**, 29 Y/M with a kidney transplant in 1987, CLcreatinine 35 ml/min, urine protein + 1 at baseline. He showed deterioration of kidney function at Day 6 on Moex & improved with D/C of Moex for 18 days.

		K mEq/l	BUN mg/dl	Cr mg/dl
Day	1	5.1	51	3.1
	6	5.7	61	3.5
	10	6.0	65	3.1
Off Day	1	5.2	58	2.7
Day	18	4.6	34	2.3

Abnormal urinalysis (proteinuria n=22, WBC 24, RBC 17, cast 21 pts) was seen mostly in long term treatment period (Wk10), but a few exhibited at Wk 8 samples.

CLINICAL LABORATORY TEST

The incidence of significant abnormal clinical values who had within normal range at baseline but at least one value for a variable outside normal range while receiving study drug is shown Table 8.

Table 8: INCIDENCES OF ABNORMAL VALUES FROM NORMAL.
Number (%) of pts

		Moex	Moex + HCTZ	HCTZ	Placebo
Potassium	(hi)	49(4%)	8(2%)	4(2%)	7(2%)
Calcium	(hi)	21(2%)	5(1%)	3(2%)	1(0%)
	(lo)	19(2%)	10(3%)	14(8%)	13(4%)
BUN	(hi)	41(4%)	7(4%)	1(1%)	6(2%)
Creatinine	(hi)	33(3%)	14(4%)	13(8%)	8(3%)
Glucose	(hi)	133(14%)	44(15%)	20(14%)	29(11%)
	(lo)	45(5%)	17(6%)	9(6%)	0(0%)
Total protein	(hi)	34(3%)	17(5%)	9(6%)	3(1%)
Uric acid	(hi)	106(10%)	47(16%)	46(30%)	21(8%)
T. Bilirubin	(hi)	34(3%)	15(4%)	5(3%)	6(2%)
SGOT	(hi)	31(3%)	14(4%)	12(7%)	10(3%)
SGPT	(hi)	59(5%)	23(7%)	19(11%)	15(5%)
T. Cholesterol	(hi)	184(29%)	57(31%)	28(24%)	39(22%)
Triglyceride	(hi)	172(21%)	75(18%)	38(31%)	41(20%)
Urine protein	(+)	140(14%)	52(18%)	32(21%)	45(17%)
Urin glucose	(+)	50(4%)	7(2%)	5(3%)	8(3%)

A few pts d/ced Moex due to abnormal lab data. One pt due to hypochronic anemia (GI bleeding), 1 pt due to neutropenia (#7080, WBC count was low $3x10^3$ at baseline and during Mx treatment), 1 pt (#7064) due to increased creatinine, 1 pt (#8089) due to kidney function deterioration (see above), 1 pt (#13409) due to hyperkalemia, dehydration, increased BUN and uremia, 3 pts due to abnormal liver function (#8014 on Moex and switched to placebo withdraw, and found increased SGOT/SGPT 294/134 due to acute hepatitis A and AIDS; #6003 on wk 9; 300/241 at wk 9; #6266 165/255 at wk 25.

INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS are shown in Appendix II and summarized Table 9.

Table 9. NUMBER (%) OF PTS WITH AEs LEADING TO DISCONTINUATION

	Controlled Studies*	Combined Studies**	Duration of study
Moex	54/1254 (4.3)	88/1745 (5.0)	8 wk - 2 yr
Mx + HCTZ	14/344 (4.1)	33/544 (6.1)	8 wk - 2 yr
HCTZ	11/197 (5.6)	11/197 (5.6)	8 wk
Placebo	10/360 (2.8)	10/360 (2.8)	8 or 12 wk
Nifedipine		4/51 (7.8)	4 or 12 wk
Nif + MX	7/152 (4.6)	7/152 (4.6)	8 wk
Capopril		2/54 (3.7)	12 wk
Verapamil		7/90 (7.8)	24 wk
Verap + HCTZ		5/52 (9.6)	12 wk

* Protocols Included: 622(DB), 623(DB), 638(DB), 642(DB), 643(DB), 644(DB), 645(DB), 647(DB), 648(DB), 649(DB), 651(DB).

** Protocols Included: 618(OL), 622(DB), 623(DB), 624(OL), 638(DB&OL), 540(DB&OL), 641(OL), 642(DB), 643(DB), 644(DB), 645(DB), 647(DB), 648(DB), 649(DB), 651(DB).

Relevant cases related Moex AEs to discontinue the study:

Hypotension:

#164 - 44 Y/M, Moex 15. At Day 8 BP was 98/70. D/ced same day.

#7234 - 73 Y/M, Moex 7.5. 2 hrs post first dose BP from 169/97 to 115/70, no symptom.

#7246 - 68 Y/F, Moex 15. 2 hrs post first dose BP from 143/99 to 97/70, postural dizziness

Postural Hypotensive Symptom

#2171 - 45 Y/M, Moex 60. At Day 30 for 1 day at home. No BP was measured.

#4248 - 54 Y/M, Moex + HCTZ 25. At Day 2 at home. D/ced Rx and dizziness resolved by Day 8.

Angioedema/Face Edema

#6249 - 44 Y/Bl/M, two episodes of angioedema at Day 5 and Wk 4 which lasted for 8 hrs. Edema disappeared spontaneously.

#6450 - 54 Y/Bl/F, severe tongue edema at wk 4.

Syncope

#7115 - 64 Y/M, Moex 7.5. Day 2, pt complained severe Rt-side headache, syncope for 4 min, speech disturbance at Day 11, another severe headache at Day 14. D/ced Moex. Day 15 ECG showed PVCs. Hx of similar episode 2 yrs ago while drinking cold beer. No BP was measured during these episodes. Unlikely Moex related.

#13409 - 69 Y/M, Moex 60mg BID + HCTZ. At Wk 17 he was in dehydration, uremia, increased BUN and serum K. At Wk 22 he had syncope (duration ?) and Moex d/ced.

Cough

#10413 - 51 Y/M, Moex 60. Cough onset Wk 4, and d/ced at Wk 6.

#8010 - 60 Y/M, Moex 15. Cough Day 6, d/ced Wk 8.

#756 - 64 Y/F, Mx 7.5. Cough Wk 7, d/ced Wk 8.

#5902 - 61 Y/F, Moex 3.75. Cough Wk 7, d/ced Wk 10.

#15201 - 46 Y/F, Moex 30. Cough Wk 12, d/ced Wk 14.

#6134 - 58 Y/M, Moex 7.5. Cough Wk 8, d/ced Wk 11.

#6141 - 57 Y/F, Moex 7.5. Cough Wk 13, d/ced Wk 16.

#6418 - 42 Y/F, Moex 15. Cough Wk 7, d/ced Wk 13.

#6419 - 50 Y/M, Moex 15. Cough Wk 7, d/ced Wk 13.

#7235 - 72 Y/F, Moex 7.5. Cough Wk 17, d/ced Wk 24.

#7240 - 76 Y/F, Moex 7.5. Cough Wk 12, d/ced Wk 15.

#7267 - 67 Y/F, Moex 7.5. Cough Wk 13, d/ced Wk 14.

#7422 - 65 Y/F, Moex 7.5. Cough Day 12, d/ced Wk 24.

#6355 - 65 Y/M, Moex 30. Cough Wk 7, d/ced Wk 45.

#7077 - 67 Y/F, Moex 15. Cough Wk 3, d/ced Wk 8.

#7149 - 41 Y/M, Moex 7.5. Cough Wk 3, d/ced Wk 8.

#6188 - 63 Y/M, Moex 30. Cough Wk 13, d/ced Wk 19.

#4301 - 60 Y/F, Moex 3.75 + HCTZ. Cough Day 3, d/ced Wk 9.

#6126 - 63 Y/F, Moex 7.5 + HCTZ. Cough Wk 2, d/ced Wk 9.

#6127 - 61 Y/M, Moex 1.5 + HCTZ. Cough Wk 13, d/ced Wk 46.

#6493 - 65 Y/F, Moex ? + HCTZ. Cough Wk 21, d/ced Wk 32.

#7256 - 65 Y/F, Moex 7.5 + HCTZ. Cough Wk 23, d/ced Wk 28.

Upper re piratory AEs diminished or resolved in 2 days (#6355) to 2 wks (#8075, 8080, 8095, 8017) after D/C of Moex.

Pts who had AEs that began during Moex Rx & switch over to placebo (**study #643**) are listed Table 10 to evaluate duration of Moex AEs after discontinuation of Moex.

Table 10: DURATION OF ADVERSE EVENTS THAT BEGAN DURING MOEX TREATMENT AND CONTINUED INTO THE WITHDRAWAL PERIOD STUDY #643

Patient No.	Adverse Event (COSTART Term)	Day* of Onset	Duration (Days)	Dose of Moexipril at Onset	Day* of Withdrawal Period	Last Day of Contact*	Duration of AE During Withdrawal Period (Days)
8075	Cough Increased	16	Ongoing	7.5 mg	84	100	>17
8075	Pharyngitis	16	Ongoing	7.5 mg	84	100	>17
8078	Rash	49	Ongoing	15 mg	85	172	>88
8080	Flu Syndrome	81	16	7.5 mg	86	--	12
8145	Nervousness	61	Ongoing	15 mg	85	169	>85
8136	Bone Disorder	73	39	7.5 mg	84	--	29
8042	Back Pain	79	90	7.5 mg	83	--	87
8114	Peripheral Edema	85	15	7.5 mg	86	--	15
8119	Hematuria	81	93	15 mg	84	--	91
8257	Anxiety	15	Ongoing	15 mg	86	170	>85
8257	Headache	15	Ongoing	15 mg	86	170	>85
8213	Abscess	84	30	7.5 mg	86	--	29
8214	Arterial Abnormality	29	Ongoing	15 mg	85	124	>40
8221	Flu Syndrome	80	9	15 mg	83	--	7
8090	Tenosynovitis	43	111	7.5 mg	91	--	64
8095	Cough Increased	80	12	7.5 mg	85	--	8
8095	Headache	80	12	7.5 mg	85	--	8
8095	Rhinitis	80	12	7.5 mg	85	--	8
8053	Tenosynovitis	83	Ongoing	7.5 mg	85	204	>120
8054	Sinusitis	27	101	15 mg	84	--	45
8054	Cough Increased	70	42	15 mg	84	--	29
8017	Cough Increased	72	27	7.5 mg	85	--	15
8017	Rhinitis	72	27	7.5 mg	85	--	15
8022	Upper Respiratory Infection	47	63	7.5 mg	85	--	26
8025	Insomnia	7	Ongoing	15 mg	79	100	>22
8025	Fatigue	21	Ongoing	15 mg	79	100	>22

*If duration of adverse event was ongoing, day of last contact is provide
*Relative to first dose of moexipril.

DEATHS: There were 10 deaths shown in Table 11

Table 11: DEATHS

Study	Patient No.	Diagnosis	Drug (mg)	Relationship to Study Drug
Control: GHBA-644	1075[a]	Myocardial infarction	HCTZ 25	None
GHBA-649	5530[a]	CVA	NR40	None
Uncontrolled: GHBA-618	17811	Myocardial infarction	Moex 3.75 10 days	None
GHBA-638-OL	6146[b]	Ventricular rupture due to AMI	Moex 15 14 mos.	None
Ongoing:	6219[b]	Congestive heart failure	Moex 30 + HCTZ 12.5 21 mos.	None
GHBA-640OL	7309	Pancreatic cancer	Moex. 7.5 5 mos.	None

Source Data: Individual Study Reports.
Moex = moexipril. NR = Nifedipine retard.
[a] Died during the HCTZ run-in period and was not randomized to receive the study drug.
[b] Died during the second year of the ongoing study.

None of the deaths appeared related to the drug treatment.

OVERALL SUMMARY AND CONCLUSIONS

From the experience in over 2200 hypertensive pts treated with Moex (n=1745) or Moex + HCTZ (n=544) in 40 clinical studies up to 2 yrs are reviewed. The submitted safety data showed: Moex

- Is generally well tolerated.
- Is comparable to placebo in the overall incidence of AEs and AE leading to treatment discontinuation except with respiratory tract symptoms such as cough, flu syndrome, during chronic Moex treatment.
- May be associated, in a small percentage of pts, with AEs directly related to BP reduction (trend on dose proportional) such as hypotension and dizziness, especially

when used with a diuretic.

- Has not demonstrated a potential for causing AEs different from those previously associated with other angiotensin-converting enzyme (ACE) inhibitors. In a direct comparison, Moex was comparable to captopril in the overall incidence of AEs.

- Small sample studies have not demonstrated a potential for causing adverse interactions when administered in combination with a calcium channel blocker (nifedipine), digoxin, cimetidine or warferin.

- Does not show evidence that new emergent AEs will develop during prolonged administration (up to 2 years).

- Has generally not demonstrated a relationship between dose and the incidence of AEs. AEs related neurotoxicity (headache, dizziness, fatigue etc) occur early phase and AEs related with respiratory tract symptoms and nephrotoxicity occur with chronic treatment (usually > 2 mos.)

- May be associated with a transient angioedema, as reported with other angiotensin-converting enzyme inhibitors, in a small percentage (0.2%) of pts.

- Has been associated with mild proteinuria in a very small percentage of pts, but not with massive proteinuria or the nephrotic syndrome.

- Had not demonstrated a relationship between age, sex, or race and the incidence of adverse experiences. However, there are a trend of increase AEs in elderly.

- Has not demonstrated a detrimental effect on physical, psychological, or sexual activity.

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cc.
HFD-110
HFD-110/CSO
HFD-110/AKarkowsky
HFD-110/SRodin
HFD-110/SChun
kb/7/30/93

TA. 2 Appendix I

SELECTED STUDY AND PATIENT/SUBJECTS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTENSION CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
A. CLINICAL PHARMACOLOGY STUDIES										
1. Human Pharmacokinetics and Bioavailability Studies										
Pilot or Background Studies										
GHBA-628	Houston (United Kingdom)	Open	Healthy Male Subjects	34 - 53	9/0/0	9/0	4 5 4 4	(*C)MX 5 mg intravenous (*C)MX 15 mg oral solution (*C)MX 15 mg oral solution MX 15 mg (C)	1 d 1 d 1 d, 1 d 4 d	75 60 50 0
PHAKI 750	Welser (Germany)	Open	Healthy Male Subjects	22 - 34	5/0/0	5/0	5	MX 30 mg (C)	1 d	0
CL-4662	Huang et al (USA)	Gas Chroma-tography	Human Plasma	NA	NA	NA	NA	MX intravenous Moexiprilat intravenous	NA	NA
CL-3758	Warner-Lambert (USA)	Gas Chroma-tography	Human Plasma	NA	NA	NA	NA	MX Moexiprilat	NA	NA
CL-3754	Chang et al (USA)	Radio-immuno-assay	Human Plasma	NA	NA	NA	NA	Moexiprilat	NA	NA
Bioavailability/Bioequivalence Studies										
PHAKI 794	Strobel (Germany)	Open, crossover single-dose	Healthy Male Subjects	19 - 39	37/0/0	37/0	37 37	MX 30 mg (T) MX 30 mg (C)	1 d 1 d	16 16
PHAKI 792	Strobel (Germany)	Open, crossover single-dose	Healthy Male Subjects	18 - 39	30/0/0	30/0	30 30	MX 30 mg (T) MX 30 mg (C)	1 d 1 d	30 37
PHAKI 758	Strobel (Germany)	Open, crossover, single-dose	Healthy Male Subjects	19 - 40	12/0/0	12/0	12 12 12	MX 30 mg (C) MX 30 mg Solution MX 30 mg (T)	1 d 1 d 1 d	33 42 33

NA = Not applicable

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SELECTED STUDY AND PATIENT/S :TS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTENSION CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
A. CLINICAL PHARMACOLOGY STUDIES										
1. Human Pharmacokinetics and Bioavailability Studies										
Bioavailability/Bioequivalence Studies (Cont'd)										
PHAKI 754/756	Strobel (Germany)	Open, crossover, single-dose	Healthy Male Subjects	22 - 39	13/0/0	13/0	12 13	MX 30 mg (T) MX 30 mg (C)	1 d 1 d	0 8
PHAKI 759	Strobel (Germany)	Open, crossover single-dose	Healthy Male Subjects	18 - 39	14/0/0	14/0	12 14 12	MX 30 mg (T) MX 30 mg (T) MX 30 mg (C)	3d 3d 3d	75 64 67
PHAKI 791	Strobel (Germany)	Open, crossover single-dose	Healthy Male Subjects	20 - 39	13/0/0	13/0	13 13 12	MX 30 mg (T) MX 30 mg (T) MX 30 mg (C)	1 d 1 d 1 d	62 38 50
PHAKI 751	Weber (Germany)	Open, crossover single-dose	Healthy Male Subjects	19 - 40	21/0/0	21/0	21 20	HCTZ 25 mg (C) HCTZ 25 mg (T)	1 d 1 d	0 0
Pharmacokinetic Studies										
Dose Dependent Kinetics										
PHAKI 795	Strobel (Germany)	Open, crossover, single-dose	Healthy Male Subjects	19 - 39	24/0/0	24/0	24 24 24 24	MX 3.75 mg Solution MX 7.5 mg Solution MX 15 mg Solution MX 30 mg Solution	1 d 1 d 1 d 1 d	17 17 25 13
Hypertensive Patients										
925-3,4,6 (CL-4010)	Lewis et al (USA)	Open, single-dose	Mild to Moderate Hypertension (SDBP 95-115)	21 - 72	10/15/0	17/8	1 1 2 2 2 2 3 2 10	MX 1 mg (C) MX 1 mg, 2 mg (C) MX 2 mg, 4 mg (C) MX 4 mg, 7.5 mg (C) MX 7.5 mg, 15 mg (C) MX 15 mg, 30 mg (C) MX 30 mg, 60 mg (C) MX 60 mg (C) MX 60 mg, 120 mg (C)	1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d 1 d, 1 d	0 0 0 50 50 50 33 50 50

TA 2

SELECTED STUDY AND PATIENT/S CTS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTENSION CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/WO[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
A. CLINICAL PHARMACOLOGY STUDIES										
1. Human Pharmacokinetics and Bioavailability Studies										
Pharmacokinetic Studies										
Hypertensive Patients (Cont'd)										
GHBA-621 (1394)	Flamenbaum (USA)	DB, placebo control, parallel, single-dose	Mild to Moderate Hypertension (SDBP 95-114)	26 - 70	21/5/4	20/10	10 4 4 4 4 4	Placebo (C) MX 3.75 mg (C) MX 7.5 mg (C) MX 15 mg (C) MX 30 mg (C) MX 60 mg (C)	1 d 1 d 1 d 1 d 1 d 1 d	40 25 25 25 100 25
Influence of Age										
GHBA-637	Doane (USA)	Open	Healthy Male Subjects, 18-45 years and 65-80 years	19 - 80	22/0/2	24/0	12 12	MX 15 mg (C) MX 15 mg (C)	5 d 5 d	0 8
Influence of Certain Disease States										
GHBA-629	Oldenbrock et al (Netherlands and United Kingdom)	Open, single-dose	Healthy bjects or Mild Hypertension, and Normal to Severe Renal Insufficiency	25 - 70	Not Available	20/1	21	MX 15 mg (C)	1 d	24
GHBA-636	James and Morgan (United Kingdom)	Open, single-dose	Hepatic Cirrhosis	35 - 66	12/0/0	5/7	12	MX 15 mg (C)	1 d	8
Drug Interaction										
GHBA-625R	Salmon (Ireland)	Open, crossover	Healthy Male Subjects	25 - 44	12/0/0	12/0	12 12 12	MX 30 mg (C) HCTZ 25 mg (T) MX 30 mg (C) + HCTZ 25 mg (T)	1 d 1 d 1 d	17 17 17

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SELECTED STUDY AND PATIENT/S CTS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTEN..ON CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Ra..d	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
A. CLINICAL PHARMACOLOGY STUDIES										
1. Human Pharmacokinetics and Bioavailability Studies										
Pharmacokinetic Studies										
Drug Interaction (Cont'd)										
GHBA-626	Salmon (Ireland)	Open, crossover	Healthy Male Subjects	21 - 40	12/0/0	12/0	12	MX 30 mg (C)	1 d	0
							12	Digoxin 1 mg (T)	1 d	17
							12	Digoxin 0.25 mg (T)	8 d	17
							12	MX 30 mg (C) + Digoxin 0.25 mg (T)	1 d	0
GHBA-627	Salmon (Ireland)	Open, crossover	Healthy Male Subjects	24 - 40	15/0/0	15/0	14	Cimetidine 1200 mg (T) + MX 30 mg (C)	1 d	14
							13	MX 30 mg (C)	1 d	23
							15	Cimetidine 1200 mg (T)	7 d	13
GHBA-631	De Schepper (Belgium)	Open, crossover	Healthy Male Subjects	19 - 24	Not Available	10/0	10	Warfarin 50 mg (T)	1 d	40
							10	MX 15 mg (C) + Warfarin 50 mg (T)	1 d	20
							10	MX 15 mg (C)	5 d	10
GHBA-633	Salmon (Ireland)	Open, crossover, single-dose	Healthy Male Subjects	21 - 43	Not Available	13/0	12	MX 15 mg (C)	1 d	42
							13	Nifedipine Retard 20 mg (T)	1 d	23
							11	MX 15 mg (C) + Nifedipine Retard 20 mg (T)	1 d	45
Food Interaction										
PHAKI 796	Strobel (Germany)	Open, crossover, single-dose	Healthy Male Subjects	21 - 40	24/0/0	24/0	24	MX 15 mg (T)	2 d	12.5
GHBA-617 (1471)	Mamelok (USA)	Open, crossover, single-dose	Healthy Male Subjects	23 - 62	Not Available	12/0	12	MX 30 mg (C)	2 d	50

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SELECTED STUDY AND PATIENT/SUBJECTS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTENSION CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
A. CLINICAL PHARMACOLOGY STUDIES										
1. Human Pharmacokinetics and Bioavailability Studies										
Pharmacokinetic Studies										
Kinetics Over Time										
925-2 (CL-3753)	Colburn et al (USA)	DB, placebo control, parallel	Healthy Subjects	26 - 48	Not Available	12/4	4 4 4 4	Placebo (C) CI-925 30 mg (C) CI-925 60 mg (C) CI-925 120 mg (C)	15 d 15 d 15 d 15 d	NA
Other In Vivo Studies										
GHBA-619 (1578)	Weidler (USA)	Open, crossover, single-dose	Healthy Male Subjects	18 - 33	9/2/1	12/0	12 12 12	MX 30 mg Fast Release (C) MX 30 mg Medium Release (C) MX 30 mg Slow Release (C)	1 d 1 d 1 d	17 8 8
GHBA-625A (Safety Data Only)	Dupont (Belgium)	Open, crossover	Healthy Male Subjects	20 - 33	NA	15/0	12 12 15	MX 30 mg (C) HCTZ 25 mg (T) MX 30 mg (C) + HCTZ 25 mg (T)	1 d 1 d 1 d	17 0 60
In Vitro Studies										
CL-4420	Chan et al (USA)	Plasma protein binding	Human Plasma	NA	NA	NA	NA	MX Moexiprilat	NA	NA
2. Dose Range/Dose Response Studies										
925-1 (CL-3743)	Latts et al (USA)	DB, placebo control, single-dose	Healthy Subjects	20 - 54	16/0/0	14/2	16 2 2 2 2 2 1 1 2 2	Placebo (C) MX 1 mg (C), 1 mg liquid MX 2 mg (C), 2 mg liquid MX 4 mg (C), 4 mg liquid MX 7.5 mg (C), 7.5 mg liquid MX 15 mg (C), 15 mg liquid MX 30 mg (C), 30 mg liquid MX 30 mg (C) MX 60 mg (C), 60 mg liquid MX 120 mg (C), 120 mg liquid	1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d, 1 d 1 d 1 d, 1 d 1 d, 1 d	31 25 (all capsules) 27 (all liquid)

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SELECTED STUDY AND PATIENT/S. CTS CHARACTERISTICS IN THE
MOEXIPRIL FOR HYPERTEN..ON CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
A. CLINICAL PHARMACOLOGY STUDIES 2. Dose Range/Dose Response Studies (Cont'd)										
925-3,4,6 (CL-4010)	Lewis et al (USA)	Open, single-dose	Mild to Moderate Hypertension (SDBP 95-115)	21 - 72	10/15/0	17/8	1	MX 1 mg (C)	1 d	0
							1	MX 1 mg, 2 mg (C)	1 d, 1 d	0
							2	MX 2 mg, 4 mg (C)	1 d, 1 d	0
							2	MX 4 mg, 7.5 mg (C)	1 d, 1 d	50
							2	MX 7.5 mg, 15 mg (C)	1 d, 1 d	50
							2	MX 15 mg, 30 mg (C)	1 d, 1 d	50
							3	MX 30 mg, 60 mg (C)	1 d, 1 d	33
							2	MX 60 mg (C)	1 d	50
							10	MX 60 mg, 120 mg (C)	1 d, 1 d	50
GHBA-621 (1394)	Flamenbaum (USA)	DB, placebo control, parallel, single-dose	Mild to Moderate Hypertension (SDBP 95-114)	26 - 70	21/5/4	20/10	10	Placebo (C)	1 d	40
							4	MX 3.75 mg (C)	1 d	25
							4	MX 7.5 mg (C)	1 d	25
							4	MX 15 mg (C)	1 d	25
							4	MX 30 mg (C)	1 d	100
							4	MX 60 mg (C)	1 d	25
GHBA-623 (1426)	Bardy et al (USA)	DB, placebo control, parallel	Mild to Moderate Hypertension (SDBP 95-114)	25 - 77	202/105/14	209/112	65	Placebo (C)	6 wks	35
							65	MX 7.5 mg (C)	6 wks	43
							65	MX 15 mg (C)	6 wks	43
							65	MX 30 mg (C)	6 wks	46
							61	MX 60 mg (C)	6 wks	48
GHBA-638 DB	Angelo et al (USA)	DB, placebo control, parallel	Mild to Moderate Hypertension (SDBP 95-114)	24 - 84	300/53/60	256/157	45	Placebo (C)	8 wks	47
							49	MX 3.75 mg (C)	8 wks	35
							42	MX 7.5 mg (C)	8 wks	48
							47	MX 15 mg (C)	8 wks	40
							45	MX 30 mg (C)	8 wks	44
							48	HCTZ 12.5 mg (C)	8 wks	46
							44	MX 3.75 mg (C) + HCTZ 12.5 mg (C)	8 wks	43
							46	MX 7.5 mg (C) + HCTZ 12.5 mg (C)	8 wks	48
							47	MX 15 mg (C) + HCTZ 12.5 mg (C)	8 wks	47

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SELECTED STUDY AND PATIENT/S CTS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTEN..ON CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
A. CLINICAL PHARMACOLOGY STUDIES										
2. Dose Range/Dose Response Studies (Cont'd)										
GHBA-641	Hamilton et al (USA)	Open, dose titration	Moderate-Severe Hypertension (SDBP 100-114)	37 - 67	18/3/2	21/2	23	MX 7.5, 15, 30 mg (C) (titrated) + HCTZ 12.5 mg	8 wks	70
3. Special Studies										
GHBA-651	Kaihlanen et al (USA)	DB, placebo control, parallel	Mild to Moderate Hypertension (SDBP 95-114)	30 - 77	36/9/6	43/8	17 16 18	Placebo (C) MX 7.5 mg (C) MX 15 mg (C)	8 wks 8 wks 8 wks	18 63 50
GHBA-646	Angelo et al (USA)	DB, placebo control, dose titration	Mild to Moderate Hypertension (SDBP 95-114) and Impaired Renal Function (Ccr 25 -65 ml/min)	29 - 73	7/7/4	11/7	10 8	MX 3.75, 7.5, 15 mg (C) (Titrated) Placebo (C)	8 wks 8 wks	40 25
B. CONTROLLED CLINICAL STUDIES										
1. Once Daily Dosing										
GHBA-638 DB	Angelo et al (USA)	DB, placebo control, parallel	Mild to Moderate Hypertension (SDBP 95-114)	24 - 84	300/53/60	256/157	45 49 42 47 45 48 44 46 47	Placebo (C) MX 3.75 mg (C) MX 7.5 mg (C) MX 15 mg (C) MX 30 mg (C) HCTZ 12.5 mg (C) MX 3.75 mg (C)+ HCTZ 12.5 mg (C) MX 7.5 mg (C) + HCTZ 12.5 mg (C) MX 15 mg (C) + HCTZ 12.5 mg (C)	8 wks 8 wks 8 wks 8 wks 8 wks 8 wks 8 wks 8 wks 8 wks	47 35 48 40 44 46 43 48 47

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SELECTED STUDY AND PATIENT/S CTS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTENSION CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
B. CONTROLLED CLINICAL STUDIES										
1. Once Daily Dosing (Cont'd)										
GHBA-642	Azorr et al (USA)	DB, placebo control parallel	Mild to Moderate Hypertension (SDBP 95-114)	25 - 87	161/34/5	132/68	51	Placebo (C)	12 wks	61
							51	MX 7.5 mg (C)	12 wks	65
							47	MX 15 mg (C)	12 wks	64
							51	HCTZ 25 mg (C)	12 wks	53
GHBA-651	Kaihlanen et al (USA)	DB, placebo control parallel	Mild to Moderate Hypertension (SDBP 95-114)	30 - 77	36/9/6	43/8	17	Placebo (C)	8 wks	18
							16	MX 7.5 mg (C)	8 wks	[illegible]
							18	MX 15 mg (C)	8 wks	50
GHBA-643	Adamson et al (USA)	DB, placebo control, parallel, withdrawal	Mild to Moderate Hypertension (SDBP 95-114)	23 - 78	178/22/23 151/17/22	149/126 74/64		Treatment:		
							55/49	MX 7.5 mg (C)/Placebo (C)	24 wks	58/51
							57/48	MX 7.5 mg (C)/MX 7.5 mg (C)	24 wks	54/46
							57/47	MX 15 mg (C)/Placebo (C)	24 wks	65/38
							54/46	MX 15 mg (C)/MX 15 mg (C)	24 wks	70/52
GHBA-640	Anderton et al (Finland, Sweden, United Kingdom)	DB, placebo control, parallel	Mild to Moderate Hypertension, (SDBP 95-114) in Elderly Patients (65-80 years)	65 - 80	201/0/0	108/93	48	Placebo (C)	8 wks	35
							50	MX 7.5 mg (C)	8 wks	30
							53	MX 15 mg (C)	8 wks	28
							50	HCTZ 25 mg (C)	8 wks	28
GHBA-644	Dickstein et al (Finland, The Netherlands, Norway, United Kingdom)	DB, placebo control, parallel	Moderate to Severe Hypertension (SDBP 95-114)	25 - 74	199/1/0	128/71	48	Placebo + HCTZ 25mg (C)	8 wks	29
							50	MX 3.75mg (C) + HCTZ 25 mg (C)	8 wks	32
							52	MX 7.5 mg (C) + HCTZ 25 mg (C)	8 wks	37
							50	MX 15 mg (C) + HCTZ 25 mg (C)	8 wks	40
GHBA-623 (1426)	Bardy et al (USA)	DB, placebo control, parallel	Mild to Moderate Hypertension (SDBP 95-114)	25 - 77	202/105/14	209/112	65	Placebo (C)	6 wks	35
							65	MX 7.5 mg (C)	6 wks	43
							65	MX 15 mg (C)	6 wks	43
							65	MX 30 mg (C)	6 wks	46
							61	MX 60 mg (C)	6 wks	48

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SELECTED STUDY AND PATIENT/S CTS CHARACTERISTICS IN THE MOEXIPRIL FOR HYPERTENSION CLINICAL PROGRAM

Company: Schwarz-Pharma Name of Drug: Moexipril

Study No.	Investigator (Country)[a]	Trial Design[b]	Diagnosis[c]	Age Range[d]	Number of Patients/Subjects[e] W/B/O[f]	M/F[g]	Reg.[h]	Drug/Daily Dose (mg)[i]	Duration[j]	AE %[k]
2. Twice Daily Dosing										
GHBA-622 (1425)	Flamenbaum et al (USA)	DB, placebo control, parallel	Mild to Moderate Hypertension (SDBP 95-114)	25 - 75	158/31/14	154/49	39 41 44 38 41	Placebo (C) Placebo, MX 3.75 mg (C) MX 3.75 mg, 7.5 mg (C) MX 7.5 mg, 15 mg (C) MX 15 mg, 30 mg (C)	8 wks 3,5 wks 3,5 wks 3,5 wks 3,5 wks	56 46 50 45 51
C. UNCONTROLLED CLINICAL STUDIES 1. Short-Term Studies										
GHBA-641	Hamilton et al (USA)	Open, dose titration	Moderate-Severe Hypertension (SDBP 100-114)	37 - 67	18/3/2	21/2	23	MX 7.5, 15, 30 mg (C) (titrated) + HCTZ 12.5 mg	8 wks	70
GHBA-618 (1534)	Bialow et al (USA)	Open, dose titration	Mild to Moderate Hypertension (SDBP 95-114)	29 - 81	80/8/3	58/33	91	MX 3.75, 7.5, 15, 30, 60, 120 mg (C) (titrated)	4 mos	43
2. Long Term Studies										
GHBA-638 OL	Barona et al (USA)	Open, titrated	Mild to Moderate Hypertension (SDBP 95-114)	30 - 84	211/22/48	179/102	281	MX 7.5, 15, 30 mg (C), MX 15 mg (C) + HCTZ 12.5 mg, MX 30 mg (C) + HCTZ 12.5 mg (titrated)	12 mos	69
GHBA-624 (1454)	Black et al (USA)	Open, titrated	Mild to Moderate Hypertension (SDBP 95-114)	25 - 76	147/15/8	108/62	170	MX 3.75, 7.5, 15, 30, 60, 120 mg (C) QD or BID (titrated)	13 mos	63
GHBA-640 OL (1 yr)	Anderton et al (Finland, Sweden, United Kingdom)	Open, titrated	Mild to Moderate Hypertension (SDBP 95-114) in Elderly Patients (65-80 years)	65 - 80	171/0/0	91/80	171	MX 7.5, 15 mg, MX 7.5 mg + HCTZ 25 mg, MX 15 mg + HCTZ 25 mg (C) (titrated)	12 mos	48

[a] Investigator
The name and of the principal investigator. In multicenter studies, the name and country of t principal investigator by alphabetical order is shown.

[b] Trial Design
Various descriptions of trial design are listed such as: Double-Blind (DB)

[c] Diagnosis
The diagnosis of the patients/subjects who participated in the study.

[d] Age Range
The youngest to the oldest age of patients/subjects in years at time of study entry

[e] Patients/Subjects
The total number of patients/subjects who entered the "active" treatment phase of the study.

[f] W/B/O
Number of patients/subjects by race. W = White, B = Black, O = Other.

[g] M/F
Number of male (M) and female (F) patients/subjects participating in a study.

[h] Reg.
Regimen: The number of patients/subjects randomized to receive a particular drug regimen in a study. Some studies are not complete; estimated numbers from these studies are underlined.

[i] Drug/Daily Dose (mg)
The generic name of each drug (specified by the study) that a patient/subject receives following baseline washout, followed by the total daily dose in milligrams (mg). The dosage form of Moexipril (MX) is indicated: (C) = capsules and (T) = tablets.

[j] Duration
The maximum number of days (d), weeks (wks), or months (mos) that a patient/subject could have received an indicated regimen.

[k] AE%
The percentage of patients/subjects who had an adverse experience (AE while receiving a particular regimen). Patients in crossover studies could be counted once for each treatment received.

APPENDIX II.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPORTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

PLACEBO ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)	Mean Duration of AE (Days)
Total # of Patients	360	360	360	-			-
HEADACHE	40(11.1)	3(0.8)		29	1	140	13
UPPER RESPIRATORY INFECTION	26(7.2)			54	1	164	22
PAIN	16(4.4)	1(0.3)		37	1	165	45
RHINITIS	14(3.9)			22	1	96	19
BACK PAIN	11(3.1)	1(0.3)		66	2	169	17
COUGH INCREASED	11(3.1)			55	1	104	26
DIZZINESS	9(2.5)	2(0.6)		58	3	139	28
SINUSITIS	9(2.5)			46	7	143	80
PERIPHERAL EDEMA	8(2.2)			43	1	121	37
CHEST PAIN	6(1.7)			63	9	161	2
URINARY FREQUENCY	6(1.7)			17	1	45	24
ANXIETY	5(1.4)			81	1	161	9
DIARRHEA	5(1.4)			51	20	93	8
DYSPEPSIA	5(1.4)			25	5	41	17
FATIGUE	5(1.4)			17	2	33	35
NAUSEA	5(1.4)			20	7	42	21
VERTIGO	5(1.4)			20	1	32	53
BRONCHITIS	4(1.1)			103	57	147	17
FLU SYNDROME	4(1.1)			71	25	131	10
INJURY	4(1.1)			58	1	123	4
RASH	4(1.1)			54	22	91	29

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

PLACEBO ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
ABDOMINAL PAIN	3(0.8)			38	2	93
ASTHMA	3(0.8)			6	1	11
DYSPNEA	3(0.8)			11	6	15
EPISTAXIS	3(0.8)			29	11	55
EYE DISORDER	3(0.8)			58	17	106
GOUT	3(0.8)			56	13	140
HYPERLIPEMIA	3(0.8)			63	1	113
NECK PAIN	3(0.8)			42	12	97
PHARYNGITIS	3(0.8)			35	11	104
PYURIA	3(0.8)			30	1	56
SGOT INCREASED	3(0.8)	1(0.3)	1(0.3)	127	85	169
SGPT INCREASED	3(0.8)	1(0.3)	1(0.3)	127	85	169
BILIRUBINEMIA	2(0.6)			122	75	169
CONJUNCTIVITIS	2(0.6)			63	27	99
ECCHYMOSIS	2(0.6)			45	36	49
HYPERGLYCEMIA	2(0.6)			35	1	85
HYPERURICEMIA	2(0.6)			1	1	1
HYPESTHESIA	2(0.6)			75	7	142
IMPOTENCE	2(0.6)	1(0.3)		50	1	139
INFECTION	2(0.6)			38	33	42
INSOMNIA	2(0.6)	1(0.3)		27	10	43
NERVOUSNESS	2(0.6)			28	22	33
PALPITATION	2(0.6)			56	41	70
PRURITUS	2(0.6)			10	1	22

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPORTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

PLACEBO ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
VOICE ALTERATION	2(0.6)			49	12	86
VOMITING	2(0.6)			35	7	62
ABNORMAL VISION	1(0.3)			62	62	62
ALOPECIA	1(0.3)			38	38	38
AMNESIA	1(0.3)			1	1	1
ARTHRITIS	1(0.3)			1	1	1
ASTHENIA	1(0.3)			23	23	23
AV BLOCK FIRST DEGREE	1(0.3)			30	30	30
BILIARY PAIN	1(0.3)			10	10	10
BUNDLE BRANCH BLOCK	1(0.3)			87	87	87
BURSITIS	1(0.3)			96	96	96
CARCINOMA	1(0.3)	1(0.3)	1(0.3)	154	154	154
CARDIOVASCULAR DISORDER	1(0.3)			103	103	103
CATARACT NOS	1(0.3)		1(0.3)	1	1	1
CELLULITIS	1(0.3)			64	64	64
CONGESTIVE HEART FAILURE	1(0.3)	1(0.3)	1(0.3)	37	37	37
CONSTIPATION	1(0.3)			19	19	19
CONTACT DERMATITIS	1(0.3)			35	35	35
DIPLOPIA	1(0.3)			25	25	25
ECZEMA	1(0.3)			23	12	34
ELECTROCARDIOGRAM ABNORMAL	1(0.3)			21	21	21
EMOTIONAL LABILITY	1(0.3)			12	9	15
FLATULENCE	1(0.3)			15	15	15
FLUSHING	1(0.3)			145	145	145

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

PLACEBO ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
GASTROENTERITIS	1(0.3)			115	115	115
GLYCOSURIA	1(0.3)			34	34	34
HEMATURIA	1(0.3)			29	29	29
HEMORRHAGE	1(0.3)		1(0.3)	38	38	38
HERPES SIMPLEX	1(0.3)			56	56	56
HERPES ZOSTER	1(0.3)			7	7	7
HYPERCHOLESTEREMIA	1(0.3)			50	50	50
HYPOKINESIA	1(0.3)			24	24	24
INCREASED APPETITE	1(0.3)			33	33	33
KIDNEY PAIN	1(0.3)			68	68	68
LAB TEST ABNORMAL	1(0.3)		2(0.6)	88	88	88
LEUKOCYTOSIS	1(0.3)			1	1	1
LEUKOPENIA	1(0.3)			1	1	1
LYMPHADENOPATHY	1(0.3)			109	109	109
MYOCARDIAL INFARCT	1(0.3)	1(0.3)	1(0.3)	50	50	50
NEUROPATHY	1(0.3)			99	99	99
PARESTHESIA	1(0.3)			169	169	169
PERIODONTAL ABSCESS	1(0.3)			119	119	119
POSTURAL DIZZINESS	1(0.3)			12	12	12
SOMNOLENCE	1(0.3)			2	2	2
STRIDOR	1(0.3)			14	14	14
TENOSYNOVITIS	1(0.3)			160	160	160
TOOTH DISORDER	1(0.3)			15	15	15
URINARY TRACT INFECTION	1(0.3)			29	29	29

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

PLACEBO ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
URTICARIA	1(0.3)			166	166	166
UTERINE FIBROIDS ENLARGED	1(0.3)		1(0.3)	127	127	127
VESICULOBULLOUS RASH	1(0.3)			17	17	17
VITREOUS DISORDER	1(0.3)			67	67	67

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPORTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

HCTZ ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)	Mean Duration of AE (Days)
Total # of Patients	197	197	197	-			-
HEADACHE	17(8.6)	1(0.5)		22	1	65	37
HYPERURICEMIA	11(5.6)			39	1	86	0
SGPT INCREASED	7(3.6)			36	1	86	0
UPPER RESPIRATORY INFECTION	7(3.6)			40	10	78	19
DIZZINESS	6(3.0)	1(0.5)		21	2	51	20
PAIN	6(3.0)		1(0.5)	32	16	51	150
BACK PAIN	4(2.0)		1(0.5)	31	2	52	23
HYPOKALEMIA	4(2.0)			18	1	29	0
INFECTION	4(2.0)			52	29	70	6
CREATININE INCREASED	3(1.5)	2(1.0)		33	15	57	0
FLATULENCE	3(1.5)	1(0.5)		23	4	42	13
HYPERCHOLESTEREMIA	3(1.5)			57	24	85	0
HYPERGLYCEMIA	3(1.5)	1(0.5)		25	15	30	0
HYPERLIPEMIA	3(1.5)			41	1	86	0
LEUKOPENIA	3(1.5)			1	1	1	0
PRURITUS	3(1.5)			23	8	45	253
RASH	3(1.5)			36	16	51	88
ALBUMINURIA	2(1.0)			50	1	85	0
ANEMIA	2(1.0)			1	1	1	
BONE DISORDER	2(1.0)	1(0.5)		41	4	77	0
BRONCHITIS	2(1.0)			32	4	59	18 28

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

HCTZ ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
BUN INCREASED	2(1.0)			58	30	86
CHEST PAIN	2(1.0)		1(0.5)	12	6	23
COUGH INCREASED	2(1.0)			27	5	49
DIARRHEA	2(1.0)			42	15	84
DYSPNEA	2(1.0)	1(0.5)	1(0.5)	27	4	49
EPISTAXIS	2(1.0)			44	38	50
FATIGUE	2(1.0)			32	28	36
GOUT	2(1.0)			31	14	48
HYPOCHROMIC ANEMIA	2(1.0)			1	1	1
MYALGIA	2(1.0)			32	15	49
PHARYNGITIS	2(1.0)			14	12	15
PYURIA	2(1.0)			1	1	1
RHINITIS	2(1.0)			20	11	28
SGOT INCREASED	2(1.0)			19	1	36
SINUSITIS	2(1.0)			43	42	44
ABNORMAL VISION	1(0.5)			65	65	65
ACNE	1(0.5)			38	38	38
ALOPECIA	1(0.5)			8	8	8
ANXIETY	1(0.5)			4	4	4
ARRHYTHMIA	1(0.5)			3	3	3
ARTHROSIS	1(0.5)			29	29	29
ASTHENIA	1(0.5)			1	1	1
ATRIAL FIBRILLATION	1(0.5)	1(0.5)	1(0.5)	3	3	3
BUNDLE BRANCH BLOCK	1(0.5)			1	1	1

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

HCTZ ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
CARDIOVASCULAR DISORDER	1(0.5)			1	1	1
CEREBROVASCULAR ACCIDENT	1(0.5)		1(0.5)	59	59	59
CHILLS	1(0.5)			15	15	15
CONGESTIVE HEART FAILURE	1(0.5)	1(0.5)		9	9	9
CONJUNCTIVITIS	1(0.5)			40	40	40
CONSTIPATION	1(0.5)			4	4	4
CORONARY ARTERY DISORDER	1(0.5)	1(0.5)	1(0.5)	28	28	28
CREATININE CLEARANCE DECREASED	1(0.5)	1(0.5)		15	15	15
CYSTITIS	1(0.5)			54	54	54
ELECTROCARDIOGRAM ABNORMAL	1(0.5)		1(0.5)	30	30	30
EOSINOPHILIA	1(0.5)			15	15	15
ESOPHAGITIS	1(0.5)			38	38	38
EXTRASYSTOLES	1(0.5)			4	4	4
FLU SYNDROME	1(0.5)			55	55	55
GASTRITIS	1(0.5)			2	2	2
GLYCOSURIA	1(0.5)			57	29	85
HEMATURIA	1(0.5)			32	1	63
HEPATOMEGALY	1(0.5)			9	9	9
HYPERCALCEMIA	1(0.5)			66	66	66
HYPERTONIA	1(0.5)			26	26	26
HYPESTHESIA	1(0.5)			48	48	48
INCREASED APPETITE	1(0.5)			41	41	41
INJURY	1(0.5)			19	19	19
INSOMNIA	1(0.5)			45	45	45

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

HCTZ ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
LARYNGITIS	1(0.5)			25	25	25
LIBIDO DECREASED	1(0.5)			52	52	52
LUNG DISORDER	1(0.5)			9	9	9
NAUSEA	1(0.5)	1(0.5)		15	15	15
NERVOUSNESS	1(0.5)			17	17	17
PALPITATION	1(0.5)			86	86	86
PARESTHESIA	1(0.5)	2(1.0)	2(1.0)	20	20	20
PAROSMIA	1(0.5)			39	39	39
PATHOLOGICAL FRACTURE	1(0.5)			44	44	44
PERIODONTAL ABSCESS	1(0.5)			56	56	56
PLEURAL DISORDER	1(0.5)	1(0.5)	1(0.5)	51	51	51
PNEUMONIA	1(0.5)			8	8	8
POLYURIA	1(0.5)			13	13	13
POSTURAL DIZZINESS	1(0.5)			2	2	2
PROSTATIC DISORDER	1(0.5)			32	1	63
SLEEP DISORDER	1(0.5)			25	25	25
ST DEPRESSED	1(0.5)			1	1	1
ST ELEVATED	1(0.5)	1(0.5)	1(0.5)	3	3	3
TACHYCARDIA	1(0.5)			49	49	49
THROMBOCYTOPENIA	1(0.5)			1	1	1
URINARY TRACT INFECTION	1(0.5)			41	41	41
VENTRICULAR EXTRASYSTOLES	1(0.5)			1	1	1
VOMITING	1(0.5)			49	49	49

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

APPENDIX I.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)	Mean Duration of AE (Days)
Total # of Patients	1745	1745	1745	-			-
HEADACHE	224(12.8)	8(0.5)		60	1	711	33
UPPER RESPIRATORY INFECTION	175(10.0)			98	1	608	22
COUGH INCREASED	146(8.4)	14(0.8)	1(0.1)	83	1	706	67
PAIN	104(6.0)	2(0.1)		89	1	550	79
RHINITIS	99(5.7)	2(0.1)		91	1	698	29
DIZZINESS	98(5.6)	6(0.3)		62	1	527	55
FLU SYNDROME	71(4.1)			85	2	691	60
DIARRHEA	70(4.0)	1(0.1)		69	1	705	14
FATIGUE	70(4.0)	3(0.2)		68	1	582	22
PHARYNGITIS	60(3.4)	2(0.1)		100	1	594	29
BACK PAIN	51(2.9)	1(0.1)		147	1	711	71
SINUSITIS	50(2.9)			102	1	583	49
CHEST PAIN	41(2.3)	7(0.4)	5(0.3)	103	1	494	52
DYSPEPSIA	41(2.3)	2(0.1)		86	1	535	55
ABDOMINAL PAIN	39(2.2)	1(0.1)	4(0.2)	110	1	524	45
NAUSEA	39(2.2)	1(0.1)		108	1	638	55
RASH	39(2.2)	4(0.2)		68	1	527	20
BRONCHITIS	38(2.2)			126	1	597	12
PERIPHERAL EDEMA	38(2.2)			63	1	314	64
INJURY	33(1.9)	1(0.1)	3(0.2)	134	1	628	47
INSOMNIA	28(1.6)	2(0.1)		103	1	705	

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
NERVOUSNESS	26(1.5)	2(0.1)		71	1	530
FLUSHING	25(1.4)	3(0.2)		81	1	420
MYALGIA	25(1.4)			58	1	266
ASTHENIA	24(1.4)	3(0.2)		94	1	459
HYPERTONIA	24(1.4)			115	1	660
SOMNOLENCE	24(1.4)	5(0.3)		30	1	142
PARESTHESIA	23(1.3)	1(0.1)		140	1	631
VOMITING	23(1.3)			95	15	314
INFECTION	20(1.1)	1(0.1)		165	6	688
URINARY TRACT INFECTION	20(1.1)			157	1	674
ARTHRITIS	18(1.0)			150	1	572
ELECTROCARDIOGRAM ABNORMAL	17(1.0)	2(0.1)		133	1	717
EPISTAXIS	16(0.9)	1(0.1)		51	2	277
HEMATURIA	16(0.9)			52	1	170
HYPESTHESIA	14(0.8)			68	1	216
SGPT INCREASED	14(0.8)	1(0.1)		143	1	708
URINARY FREQUENCY	14(0.8)			44	1	144
CONSTIPATION	13(0.7)	1(0.1)		48	7	222
FEVER	13(0.7)			129	16	705
PALPITATION	13(0.7)	2(0.1)		157	1	652
DYSPNEA	12(0.7)	2(0.1)	1(0.1)	74	1	389
HYPERLIPEMIA	12(0.7)			228	38	710
DEPRESSION	11(0.6)	1(0.1)		186	3	705
HYPERKALEMIA	11(0.6)			73	1	173

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
NECK PAIN	11(0.6)	1(0.1)		75	1	325
PRURITUS	11(0.6)	1(0.1)		[illegible]	1	228
SKIN DISORDER	11(0.6)			154	4	551
TINNITUS	11(0.6)	1(0.1)		26	1	54
ANXIETY	10(0.6)	2(0.1)		52	3	147
PYURIA	10(0.6)			168	1	737
SWEATING	10(0.6)	1(0.1)		102	2	727
TENOSYNOVITIS	10(0.6)			93	1	281
VENTRICULAR EXTRASYSTOLES	10(0.6)	1(0.1)		109	1	337
VERTIGO	10(0.6)	1(0.1)		115	19	420
ABNORMAL VISION	9(0.5)			89	1	660
EAR PAIN	9(0.5)			95	15	331
ECCHYMOSIS	9(0.5)			135	16	686
MALAISE	9(0.5)	1(0.1)		100	3	606
ARTHRALGIA	8(0.5)			117	1	464
CONJUNCTIVITIS	8(0.5)			68	15	161
FLATULENCE	8(0.5)	1(0.1)		55	1	175
HYPERGLYCEMIA	8(0.5)			128	1	737
HYPERURICEMIA	8(0.5)			128	1	701
SGOT INCREASED	8(0.5)	1(0.1)		89	1	376
ALBUMINURIA	7(0.4)			242	1	715
POSTURAL DIZZINESS	7(0.4)	1(0.1)		91	1	202
TACHYCARDIA	7(0.4)	1(0.1)		26	1	63
ALLERGIC REACTION	6(0.3)			65	1	139

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPRCTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
ASTHMA	6(0.3)	1(0.1)		79	42	190
CARDIOVASCULAR DISORDER	6(0.3)	2(0.1)	1(0.1)	57	1	105
CREATININE INCREASED	6(0.3)	1(0.1)		121	1	701
DRY MOUTH	6(0.3)			86	2	212
EAR DISORDER	6(0.3)			100	5	331
EDEMA	6(0.3)			41	1	94
EYE PAIN	6(0.3)			112	17	373
FACE EDEMA	6(0.3)	1(0.1)		35	8	73
HYPERCHOLESTEREMIA	6(0.3)			179	38	373
LIBIDO DECREASED	6(0.3)			192	1	705
MELENA	6(0.3)			167	23	527
OTITIS MEDIA	6(0.3)			135	32	334
PNEUMONIA	6(0.3)			197	43	500
ACNE	5(0.3)			40	3	99
ANOREXIA	5(0.3)	2(0.1)		37	1	92
BONE DISORDER	5(0.3)			92	41	163
CYST	5(0.3)			298	8	507
GENERALIZED EDEMA	5(0.3)			26	1	60
GOUT	5(0.3)			75	1	210
HYPOCHROMIC ANEMIA	5(0.3)	1(0.1)		68	1	197
HYPOTENSION	5(0.3)	3(0.2)		49	1	163
LEUKOCYTOSIS	5(0.3)			130	1	707
NEOPLASM	5(0.3)		2(0.1)	271	1	715
TOOTH DISORDER	5(0.3)			64	15	110

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
ANGINA PECTORIS	4(0.2)	2(0.1)		217	58	522
CYSTITIS	4(0.2)			116	25	242
DRY SKIN	4(0.2)			13	1	46
GASTRITIS	4(0.2)		1(0.1)	154	87	345
GASTROENTERITIS	4(0.2)			202	18	467
HERPES ZOSTER	4(0.2)			212	1	538
HYPOKALEMIA	4(0.2)			81	38	169
IMPOTENCE	4(0.2)			36	1	77
LUNG DISORDER	4(0.2)			80	18	233
PERIODONTAL ABSCESS	4(0.2)			28	13	67
PHOTOSENSITIVITY REACTION	4(0.2)			176	1	573
PROSTATIC DISORDER	4(0.2)			90	3	194
SUBCUTANEOUS NODULE	4(0.2)			176	1	441
TREMOR	4(0.2)			49	16	74
ABNORMAL DREAMS	3(0.2)	2(0.1)		98	82	123
ABSCESS	3(0.2)			78	53	98
ANEMIA	3(0.2)	1(0.1)		14	1	51
BUNDLE BRANCH BLOCK	3(0.2)			718	702	736
CHILLS	3(0.2)			67	45	104
COLITIS	3(0.2)	1(0.1)	1(0.1)	294	79	683
CONFUSION	3(0.2)			201	3	525
CONTACT DERMATITIS	3(0.2)			51	43	59
EMOTIONAL LABILITY	3(0.2)			20	2	46
EYE DISORDER	3(0.2)			232	43	542

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
EYE HEMORRHAGE	3(0.2)			187	8	388
HERPES SIMPLEX	3(0.2)			67	6	222
JOINT DISORDER	3(0.2)			93	41	141
LARYNGITIS	3(0.2)			90	39	137
LEUKOPENIA	3(0.2)	1(0.1)		32	1	52
MYOCARDIAL INFARCT	3(0.2)	2(0.1)	2(0.1)	48	10	81
PERIPHERAL VASCULAR DISORDER	3(0.2)		1(0.1)	63	38	84
RECTAL DISORDER	3(0.2)			37	8	75
SINUS BRADYCARDIA	3(0.2)			255	1	707
SKIN BENIGN NEOPLASM	3(0.2)			54	1	127
SYNCOPE	3(0.2)	1(0.1)		169	2	463
TASTE PERVERSION	3(0.2)			29	21	40
THROMBOCYTOPENIA	3(0.2)	1(0.1)		34	1	57
VAGINAL HEMORRHAGE	3(0.2)			243	5	497
ALOPECIA	2(0.1)			133	11	372
ARTERIAL ANOMALY	2(0.1)			46	29	62
ATRIAL FIBRILLATION	2(0.1)	1(0.1)	1(0.1)	532	358	706
BREAST NEOPLASM	2(0.1)			24	6	42
BURSITIS	2(0.1)			225	92	291
CALCIUM CRYSTALLURIA	2(0.1)			169	168	169
CARCINOMA	2(0.1)	1(0.1)	2(0.1)	257	7	507
CELLULITIS	2(0.1)			50	16	84
CHOLECYSTITIS	2(0.1)		?(.1)	239	21	457
CHOLELITHIASIS	2(0.1)		1(0.1)	95	21	168

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
CREATININE CLEARANCE DECREASED	2(0.1)	1(0.1)		22	15	29
DEATH	2(0.1)	2(0.1)	1(0.1)	207	10	403
DYSMENORRHEA	2(0.1)			125	81	168
DYSURIA	2(0.1)			15	4	25
FURUNCULOSIS	2(0.1)			35	18	51
GASTROINTESTINAL CARCINOMA	2(0.1)	1(0.1)	1(0.1)	207	76	338
HEMORRHAGE	2(0.1)	1(0.1)		70	1	139
HYPOGLYCEMIA	2(0.1)			113	56	169
HYPOKINESIA	2(0.1)			8	4	12
MACULOPAPULAR RASH	2(0.1)			60	10	109
MENOPAUSE	2(0.1)			69	44	93
MIGRAINE	2(0.1)			14	2	26
MONILIASIS	2(0.1)			236	11	461
MYOCARDIAL ISCHEMIA	2(0.1)			26	1	62
NAUSEA AND VOMITING	2(0.1)			218	105	330
NECK RIGIDITY	2(0.1)			50	14	70
NEUROPATHY	2(0.1)	1(0.1)		105	39	170
OTITIS EXTERNA	2(0.1)			313	295	331
PAROSMIA	2(0.1)			40	36	43
RECTAL HEMORRHAGE	2(0.1)			278	56	500
SUPRAVENTRICULAR EXTRASYSTOLES	2(0.1)			128	85	171
T INVERTED	2(0.1)			53	50	56
TASTE LOSS	2(0.1)			10	2	20
THROMBOPHLEBITIS	2(0.1)		1(0.1)	78	64	92

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
VAGINITIS	2(0.1)			234	3	464
WEIGHT LOSS	2(0.1)	1(0.1)		88	84	92
ABNORMAL EJACULATION	1(0.1)			45	45	45
ABNORMAL GAIT	1(0.1)			47	47	47
AMNESIA	1(0.1)			117	117	117
ANAPHYLACTOID REACTION	1(0.1)			102	93	111
ANGIOEDEMA	1(0.1)			208	208	208
ARTHROSIS	1(0.1)			69	69	69
AV BLOCK FIRST DEGREE	1(0.1)			15	1	29
BRADYCARDIA	1(0.1)			49	49	49
BREAST CARCINOMA	1(0.1)	1(0.1)	1(0.1)	365	365	365
BREAST PAIN	1(0.1)			489	489	489
BUN INCREASED	1(0.1)			701	701	701
CATARACT NOS	1(0.1)			394	394	394
CEREBRAL ISCHEMIA	1(0.1)			60	60	60
CEREBROVASCULAR ACCIDENT	1(0.1)		1(0.1)	31	28	34
CERVIX NEOPLASM	1(0.1)			110	110	110
CHEILITIS	1(0.1)			28	27	29
COAGULATION TIME INCREASED	1(0.1)			145	145	145
CORNEAL LESION	1(0.1)			10	1	18
DEAFNESS	1(0.1)			169	169	169
DEHYDRATION	1(0.1)			205	205	205
DIPLOPIA	1(0.1)			36	36	36
DYSPHAGIA	1(0.1)			165	165	165

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

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TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
ECZEMA	1(0.1)			25	22	27
ENDOCRINE DISORDER	1(0.1)			99	99	99
EPIDIDYMITIS	1(0.1)			110	110	110
ESOPHAGITIS	1(0.1)			7	7	7
FACIAL PARALYSIS	1(0.1)	1(0.1)		23	23	23
FUNGAL DERMATITIS	1(0.1)			56	56	56
GASTROINTESTINAL DISORDER	1(0.1)			372	372	372
GINGIVITIS	1(0.1)			45	45	45
GLOBULIN INCREASED	1(0.1)			42	40	43
GLYCOSURIA	1(0.1)			16	16	16
HERNIA	1(0.1)			153	153	153
HOSTILITY	1(0.1)			32	17	46
HYPERCALCEMIA	1(0.1)			109	44	174
HYPERVENTILATION	1(0.1)			3	3	3
HYPOCALCEMIA	1(0.1)			66	66	66
HYPOGLYCEMIC REACTION	1(0.1)		1(0.1)	234	234	234
HYPONATREMIA	1(0.1)			86	86	86
HYPOPROTEINEMIA	1(0.1)			1	1	1
INCOORDINATION	1(0.1)			72	72	72
LAB TEST ABNORMAL	1(0.1)			186	186	186
LEUKORRHEA	1(0.1)			161	161	161
LYMPHOCYTOSIS	1(0.1)			44	44	44
MENORRHAGIA	1(0.1)		2(0.1)	199	160	238
MOUTH ULCERATION	1(0.1)			1	1	1

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

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TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
MYOPATHY —	1(0.1)			2	2	2
MYOSITIS —	1(0.1)			654	654	654
NAIL DISORDER	1(0.1)			1	1	1
NEURALGIA	1(0.1)			29	29	29
NOCTURIA	1(0.1)			59	59	59
OLIGURIA	1(0.1)			192	192	192
PANCREATITIS	1(0.1)		1(0.1)	457	457	457
PATHOLOGICAL FRACTURE	1(0.1)			93	92	93
PELVIC PAIN	1(0.1)			72	72	72
POLYURIA	1(0.1)			45	43	46
PROCTITIS	1(0.1)			31	31	31
RETINAL DETACHMENT	1(0.1)			51	51	51
RETINAL DISORDER	1(0.1)			83	83	83
RETINAL VASCULAR DISORDER	1(0.1)			56	56	56
SKIN CARCINOMA	1(0.1)		1(0.1)	394	394	394
SKIN NODULE	1(0.1)			20	20	20
SKIN ULCER	1(0.1)			82	82	82
SPEECH DISORDER	1(0.1)	1(0.1)		2	2	2
ST DEPRESSED	1(0.1)			161	161	161
SUPRAVENTRICULAR TACHYCARDIA	1(0.1)			157	157	157
TENESMUS	1(0.1)			76	76	76
THINKING ABNORMAL	1(0.1)	1(0.1)		4	1	7
THIRST	1(0.1)			58	58	58
THROMBOSIS	1(0.1)			668	668	668

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

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TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL ALONE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
URINARY CASTS	1(0.1)			85	85	85
URINARY TRACT DISORDER	1(0.1)			81	81	81
URINATION IMPAIRED	1(0.1)			44	44	44
UTERINE DISORDER	1(0.1)		1(0.1)	275	275	275
UTERINE FIBROIDS ENLARGED	1(0.1)			214	214	214
VAGINAL MONILIASIS	1(0.1)			153	153	153
VISUAL FIELD DEFECT	1(0.1)			517	517	517
VOICE ALTERATION	1(0.1)			2	2	2
VULVOVAGINITIS	1(0.1)			107	107	107

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET, OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)	Mean Duration of AE (Days)
Total # of Patients	544	544	544	-			-
HEADACHE	47(8.6)			100	1	479	18
COUGH INCREASED	43(7.9)	5(0.9)		152	1	673	49
UPPER RESPIRATORY INFECTION	39(7.2)			210	20	673	13
DIZZINESS	32(5.9)	2(0.4)		132	1	559	32
FLU SYNDROME	32(5.9)			196	3	659	7
PAIN	29(5.3)	1(0.2)		200	2	607	49
DIARRHEA	22(4.0)	1(0.2)		99	2	449	6
FATIGUE	22(4.0)	1(0.2)		64	1	337	59
HYPERURICEMIA	19(3.5)			73	1	330	0
PHARYNGITIS	18(3.3)			255	9	614	7
RHINITIS	17(3.1)			147	1	544	40
SINUSITIS	17(3.1)			182	3	497	48
BACK PAIN	15(2.8)		1(0.2)	273	2	622	27
NAUSEA	14(2.6)	2(0.4)		211	4	497	30
ABDOMINAL PAIN	12(2.2)	1(0.2)	1(0.2)	178	2	651	38
INFECTION	12(2.2)		1(0.2)	286	18	734	26
DYSPEPSIA	11(2.0)			146	13	382	64
ELECTROCARDIOGRAM ABNORMAL	11(2.0)			283	1	717	0
HYPERGLYCEMIA	11(2.0)	1(0.2)	1(0.2)	127	1	525	0
FEVER	10(1.8)			124	2	491	5
HYPOKALEMIA	9(1.7)			20	1	63	

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
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* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
PERIPHERAL EDEMA	9(1.7)			231	2	701
ANEMIA	8(1.5)	1(0.2)		136	1	438
CHEST PAIN	8(1.5)	1(0.2)	1(0.2)	221	2	475
FLUSHING	8(1.5)			8	1	41
HYPERTONIA	8(1.5)			167	7	684
INSOMNIA	8(1.5)	1(0.2)		147	2	610
POSTURAL DIZZINESS	8(1.5)			147	3	631
PYURIA	8(1.5)			60	1	211
HYPOCHROMIC ANEMIA	7(1.3)	1(0.2)		129	1	355
SGPT INCREASED	7(1.3)	2(0.4)	1(0.2)	112	1	326
SOMNOLENCE	7(1.3)	1(0.2)		68	3	276
URINARY FREQUENCY	7(1.3)			28	2	56
CONJUNCTIVITIS	6(1.1)			161	26	453
DRY MOUTH	6(1.1)	2(0.4)		35	2	128
HYPERLIPEMIA	6(1.1)			130	1	694
IMPOTENCE	6(1.1)	3(0.6)		82	2	309
INJURY	6(1.1)			316	43	585
POSTURAL HYPOTENSION	6(1.1)	1(0.2)	1(0.2)	101	2	342
RASH	6(1.1)			238	48	699
BILIRUBINEMIA	5(0.9)		1(0.2)	211	1	720
BRONCHITIS	5(0.9)			136	11	249
HEMATURIA	5(0.9)			176	15	376
SGOT INCREASED	5(0.9)	1(0.2)	1(0.2)	83	1	177
SYNCOPE	5(0.9)		2(0.4)	27	2	61

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPORTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
VERTIGO	5(0.9)			240	42	483
VOMITING	5(0.9)	1(0.2)		109	22	260
ALBUMINURIA	4(0.7)			22	1	43
ANXIETY	4(0.7)			215	36	315
ASTHENIA	4(0.7)			31	21	41
AV BLOCK FIRST DEGREE	4(0.7)			57	56	58
ERYTHROCYTES ABNORMAL	4(0.7)	1(0.2)		53	15	148
GASTRITIS	4(0.7)			194	4	416
GOUT	4(0.7)			156	124	196
HERNIA	4(0.7)			148	1	306
HYPERCHOLESTEREMIA	4(0.7)			192	1	694
LEUKOPENIA	4(0.7)			86	1	323
MYALGIA	4(0.7)			316	41	619
NERVOUSNESS	4(0.7)			36	2	81
ALLERGIC REACTION	3(0.6)			205	20	378
ARTHRALGIA	3(0.6)			25	12	55
BUN INCREASED	3(0.6)	1(0.2)		35	15	61
CARDIOVASCULAR DISORDER	3(0.6)			73	42	119
CONSTIPATION	3(0.6)			214	8	469
CREATININE INCREASED	3(0.6)	1(0.2)		31	15	62
CYST	3(0.6)			466	216	630
EPISTAXIS	3(0.6)			123	38	177
FLATULENCE	3(0.6)	1(0.2)		150	5	413
GINGIVITIS	3(0.6)			213	18	348

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

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TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
HYPOTENSION	3(0.6)			184	1	459
MYOCARDIAL INFARCT	3(0.6)	1(0.2)	1(0.2)	235	51	329
NEURITIS	3(0.6)			233	37	624
PALPITATION	3(0.6)			235	109	328
PARESTHESIA	3(0.6)			11	5	17
PRURITUS	3(0.6)			78	10	113
SWEATING	3(0.6)			12	1	35
URINARY TRACT INFECTION	3(0.6)			283	13	655
ANOREXIA	2(0.4)			22	8	36
ARRHYTHMIA	2(0.4)	1(0.2)	1(0.2)	400	323	476
ARTHRITIS	2(0.4)			183	63	303
CATARACT NOS	2(0.4)			210	99	320
CHILLS	2(0.4)			348	196	499
CHOLELITHIASIS	2(0.4)	1(0.2)	1(0.2)	225	144	306
CONTACT DERMATITIS	2(0.4)			353	342	363
DEPRESSION	2(0.4)			41	29	52
EAR DISORDER	2(0.4)			376	175	576
ECCHYMOSIS	2(0.4)			202	29	376
ESOPHAGITIS	2(0.4)			225	112	337
EYE HEMORRHAGE	2(0.4)			97	42	152
GLYCOSURIA	2(0.4)			375	1	749
HEMOLYSIS	2(0.4)			29	15	43
HERPES SIMPLEX	2(0.4)			45	10	80
LAB TEST ABNORMAL	2(0.4)			424	148	699

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

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TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
LIBIDO DECREASED	2(0.4)			525	421	628
LYMPHADENOPATHY	2(0.4)			31	18	44
NECK PAIN	2(0.4)			329	325	332
OTITIS MEDIA	2(0.4)			456	409	502
PATHOLOGICAL FRACTURE	2(0.4)			458	301	615
PERIODONTAL ABSCESS	2(0.4)			401	327	459
PNEUMONIA	2(0.4)		1(0.2)	261	184	338
POLYURIA	2(0.4)			205	119	290
PROSTATIC DISORDER	2(0.4)	1(0.2)		135	18	252
RECTAL DISORDER	2(0.4)			234	168	287
RETINAL DISORDER	2(0.4)			50	42	57
SINUS BRADYCARDIA	2(0.4)			57	56	57
TACHYCARDIA	2(0.4)			592	476	708
THIRST	2(0.4)			19	1	36
TOOTH DISORDER	2(0.4)			16	3	28
VAGINAL HEMORRHAGE	2(0.4)		1(0.2)	342	172	512
VENTRICULAR EXTRASYSTOLES	2(0.4)			206	42	372
ACNE	1(0.2)			15	15	15
ALOPECIA	1(0.2)			388	388	388
ASTHMA	1(0.2)	1(0.2)		166	166	166
ATAXIA	1(0.2)			100	100	100
ATRIAL FIBRILLATION	1(0.2)	1(0.2)	1(0.2)	323	323	323
BONE DISORDER	1(0.2)			30	30	30
BREAST CARCINOMA	1(0.2)		1(0.2)	98	98	98

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

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TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
BREAST ENLARGEMENT	1(0.2)			126	126	126
BREAST NEOPLASM	1(0.2)	1(0.2)		153	153	153
BREAST PAIN	1(0.2)			126	126	126
BURSITIS	1(0.2)			173	173	173
CARCINOMA	1(0.2)	1(0.2)	1(0.2)	142	142	142
CARCINOMA OF LUNG	1(0.2)	1(0.2)	1(0.2)	472	472	472
COLITIS	1(0.2)			22	22	22
CYSTITIS	1(0.2)			18	18	18
DEHYDRATION	1(0.2)			116	116	116
DRY SKIN	1(0.2)			10	10	10
DYSPHAGIA	1(0.2)			213	187	239
DYSPNEA	1(0.2)			2	2	2
DYSURIA	1(0.2)			153	153	153
EAR PAIN	1(0.2)			128	128	128
ECZEMA	1(0.2)			167	167	167
EMOTIONAL LABILITY	1(0.2)			31	31	31
ENZYMATIC ABNORMALITY	1(0.2)			57	57	57
ERUCTATION	1(0.2)			24	24	24
EYE DISORDER	1(0.2)			1	1	1
FURUNCULOSIS	1(0.2)			56	56	56
GASTROENTERITIS	1(0.2)			170	170	170
GLOSSITIS	1(0.2)			4	4	4
GOITER	1(0.2)			699	699	699
HEMORRHAGE	1(0.2)		1(0.2)	305	305	305

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
HERPES ZOSTER	1(0.2)			423	423	423
HYPERKALEMIA	1(0.2)			1	1	1
HYPOCHLOREMIA	1(0.2)			29	29	29
HYPOMAGNESIA	1(0.2)			55	55	55
HYPONATREMIA	1(0.2)			29	29	29
INCREASED APPETITE	1(0.2)			33	33	33
JAUNDICE	1(0.2)		1(0.2)	141	141	141
LEUKORRHEA	1(0.2)			11	11	11
LUNG DISORDER	1(0.2)			263	263	263
LYMPHOCYTOSIS	1(0.2)			8	1	15
MACULOPAPULAR RASH	1(0.2)			44	44	44
MELENA	1(0.2)			214	214	214
MIGRAINE	1(0.2)			372	372	372
MONILIASIS	1(0.2)			541	541	541
MYOCARDIAL ISCHEMIA	1(0.2)			1	1	1
NAIL DISORDER	1(0.2)			324	324	324
NECK RIGIDITY	1(0.2)			79	79	79
NEOPLASM	1(0.2)		1(0.2)	455	455	455
NEURALGIA	1(0.2)			284	284	284
NOCTURIA	1(0.2)			2	2	2
PERSONALITY DISORDER	1(0.2)	1(0.2)		51	51	51
PHOTOSENSITIVITY REACTION	1(0.2)			354	354	354
PYELONEPHRITIS	1(0.2)	1(0.2)	1(0.2)	7	7	7
QT INTERVAL PROLONGED	1(0.2)			57	57	57

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + HCTZ

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
RECTAL HEMORRHAGE	1(0.2)			37	37	37
RETINAL DEGENERATION	1(0.2)			409	409	409
RETINAL VASCULAR DISORDER	1(0.2)			56	56	56
SCROTAL EDEMA	1(0.2)			362	362	362
SKIN CARCINOMA	1(0.2)	1(0.2)	1(0.2)	407	407	407
SUBCUTANEOUS NODULE	1(0.2)			302	302	302
T INVERTED	1(0.2)			1	1	1
TENOSYNOVITIS	1(0.2)			198	198	198
THYROID DISORDER	1(0.2)	1(0.2)	1(0.2)	17	17	17
TINNITUS	1(0.2)			45	45	45
TONGUE EDEMA	1(0.2)			155	155	155
TOOTH CARIES	1(0.2)			155	155	155
URINARY CASTS	1(0.2)			139	139	139
URINARY RETENTION	1(0.2)			41	41	41
URINARY TRACT DISORDER	1(0.2)			308	303	313
URTICARIA	1(0.2)			514	514	514
UTERINE DISORDER	1(0.2)		1(0.2)	30	30	30
VAGINITIS	1(0.2)			56	56	56
VASCULAR ANOMALY	1(0.2)			56	56	56
VOCAL CORD PARALYSIS	1(0.2)	1(0.2)		58	58	58
VOICE ALTERATION	1(0.2)			41	41	41

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPORTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + NIFEDIPINE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)	Mean Duration of AE (Days)
Total of Patients	152	152	152	-			-
DIZZINESS	5(3.3)			14	4	31	22
HEADACHE	5(3.3)	2(1.3)		7	1	23	15
COUGH INCREASED	4(2.6)			17	1	31	8
PAIN	4(2.6)	1(0.7)		8	1	11	22
PERIPHERAL EDEMA	4(2.6)	2(1.3)		12	1	26	28
SGOT INCREASED	4(2.6)			18	1	29	0
SGPT INCREASED	4(2.6)			14	1	27	0
UPPER RESPIRATORY INFECTION	4(2.6)			34	24	48	6
BRONCHITIS	3(2.0)			37	22	48	8
FLU SYNDROME	3(2.0)			39	22	70	4
FLUSHING	3(2.0)	1(0.7)		2	1	4	22
PHARYNGITIS	3(2.0)			37	29	44	7
SINUSITIS	3(2.0)			26	1	52	-11
NERVOUSNESS	2(1.3)			31	29	32	21
TACHYCARDIA	2(1.3)			40	29	51	2
ANXIETY	1(0.7)			44	44	44	13
ARTHRITIS	1(0.7)			14	14	14	4
ATRIAL ARRHYTHMIA	1(0.7)	1(0.7)		1	1	1	0
BACK PAIN	1(0.7)			77	77	77	0
CARDIOVASCULAR DISORDER	1(0.7)			15	1	29	0
CEREBRAL HEMORRHAGE	1(0.7)	1(0.7)	1(0.7)	6	6	6	

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + NIFEDIPINE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
CHILLS	1(0.7)	1(0.7)		2	2	2
CONVULSION	1(0.7)			50	50	50
CYST	1(0.7)			1	1	1
DEATH	1(0.7)	1(0.7)	1(0.7)	7	7	7
DRY MOUTH	1(0.7)			3	3	3
DYSPEPSIA	1(0.7)			11	11	11
DYSPNEA	1(0.7)			12	12	12
ECZEMA	1(0.7)			24	24	24
EDEMA	1(0.7)			3	3	3
ELECTROCARDIOGRAM ABNORMAL	1(0.7)			29	1	56
FATIGUE	1(0.7)			31	31	31
FLATULENCE	1(0.7)			8	8	8
GASTRITIS	1(0.7)			35	35	35
GLYCOSURIA	1(0.7)			71	71	71
HEMATURIA	1(0.7)	1(0.7)	1(0.7)	1	1	1
HYPERKALEMIA	1(0.7)	1(0.7)		15	15	15
HYPERLIPEMIA	1(0.7)			15	15	15
HYPERTONIA	1(0.7)			30	30	30
HYPOKALEMIA	1(0.7)			1	1	1
INFECTION	1(0.7)			22	22	22
INJURY	1(0.7)			12	12	12
LEUKOPENIA	1(0.7)			57	57	57
LIBIDO DECREASED	1(0.7)			2	2	2
MYALGIA	1(0.7)			31	31	31

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

MOEXIPRIL + NIFEDIPINE

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
NEURALGIA	1(0.7)			14	14	14
RASH	1(0.7)			1	1	1
RETINAL DISORDER	1(0.7)			60	60	60
RHINITIS	1(0.7)			62	62	62
SOMNOLENCE	1(0.7)			2	2	2
THROMBOCYTOPENIA	1(0.7)			1	1	1
THROMBOPHLEBITIS	1(0.7)		1(0.7)	40	40	40
URTICARIA	1(0.7)			26	26	26

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

CAPTOPRIL

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)	Mean Duration of AE (Days)
Total # of Patients	54	54	54	-			-
DIZZINESS	7(13.0)			19	1	81	9
HEADACHE	7(13.0)			32	4	87	6
COUGH INCREASED	6(11.1)			19	2	66	33
FATIGUE	6(11.1)			19	1	63	9
UPPER RESPIRATORY INFECTION	5(9.3)			59	12	89	9
FLUSHING	3(5.6)			1	1	1	1
HEMATURIA	3(5.6)			28	1	56	0
NERVOUSNESS	3(5.6)			50	15	72	29
PHARYNGITIS	3(5.6)			59	43	68	3
PYURIA	3(5.6)			29	1	57	0
SOMNOLENCE	3(5.6)			28	2	73	4
ABNORMAL VISION	2(3.7)			69	60	77	5
ALBUMINURIA	2(3.7)			30	1	59	0
BACK PAIN	2(3.7)			24	22	26	33
ELECTROCARDIOGRAM ABNORMAL	2(3.7)			12	1	23	0
HYPERGLYCEMIA	2(3.7)			20	1	57	0
PAIN	2(3.7)			58	35	81	3
ABDOMINAL PAIN	1(1.9)			43	43	43	3
ABNORMAL DREAMS	1(1.9)			52	31	72	
ALLERGIC REACTION	1(1.9)			51	51	51	
AV BLOCK FIRST DEGREE	1(1.9)			1	1	1	

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPORTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

CAPTOPRIL

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
AV BLOCK SECOND DEGREE	1(1.9)	2(3.7)	2(3.7)	2	1	2
DEPRESSION	1(1.9)			22	22	22
DRY MOUTH	1(1.9)			2	2	2
EPISTAXIS	1(1.9)			28	28	28
FEVER	1(1.9)			4	4	4
FLU SYNDROME	1(1.9)			57	57	57
GLYCOSURIA	1(1.9)			71	57	85
GOUT	1(1.9)			25	25	25
HEMORRHAGE	1(1.9)			16	16	16
HYPOKALEMIA	1(1.9)			33	29	36
INSOMNIA	1(1.9)			44	44	44
LARYNGITIS	1(1.9)			72	72	72
LEUKOPENIA	1(1.9)			64	57	71
MACULOPAPULAR RASH	1(1.9)			1	1	1
NOCTURIA	1(1.9)			77	77	77
PALPITATION	1(1.9)			49	49	49
PARANOID REACTION	1(1.9)			72	72	72
PATHOLOGICAL FRACTURE	1(1.9)			81	81	81
PERIODONTAL ABSCESS	1(1.9)			20	20	20
PERIPHERAL EDEMA	1(1.9)			31	31	31
PROSTATIC CARCINOMA	1(1.9)	1(1.9)	1(1.9)	57	57	57
RASH	1(1.9)			1	1	1
RECTAL DISORDER	1(1.9)			54	54	54
RHINITIS	1(1.9)			27	27	27

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)

* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

TABLE 11A

MEAN TIME OF ONSET OF ALL REPROTED ADVERSE EXPERIENCES (AE)
AND INCIDENCE OF DISCONTINUATIONS AND SERIOUS EVENTS

CAPTOPRIL

Adverse Experience	Number (%) of Patients with AE	Number (%) of Patients Discontinued for AE	Number (%) of Patients had Serious AE	Mean Time To Onset of AE * (Days)	Minimum (Days)	Maximum (Days)
SGOT INCREASED	1(1.9)			29	29	29
SGPT INCREASED	1(1.9)			29	29	29
SINUSITIS	1(1.9)			25	25	25
THROMBOCYTOPENIA	1(1.9)			55	55	55
URINARY FREQUENCY	1(1.9)			1	1	1
URINARY TRACT INFECTION	1(1.9)			56	56	56

Protocols Included: 618(OL) 622(DB) 623(DB) 624(OL) 638(DB&OL) 640(DB&OL) 641(OL)
642(DB) 643(DB) 644(DB) 645(DB) 647(DB) 648(DB) 649(DB) 651(DB)
* Onset time is time from start of study, regardless of any other treatment which may have been received previously.

APPENDIX III

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 623										
Placebo	10407	152	122 (1)	-30	122	0	74	74	0	none
Placebo	2368	172	139 (4)	-33	148	-9	80	102	+22	none
Placebo	2131	208	152 (6)	-56	174	-22	80	74	-6	none
7.5 mg	15235	184	116 (6)	-68	118	-2	76	68	-8	none
7.5 mg	12834	160	120 (0.5)	-40	130	-10	76	72	-4	none
7.5 mg	2966	184	136 (4)	-48	154	-18	68	80	+12	none
7.5 mg	13102	156	120 (6)	-36	122	-2	66	92	+26	none
7.5 mg	13140	162	126 (6)	-36	132	-6	74	88	+14	none
7.5 mg	2334	182	152 (4)	-30	154	-2	64	78	+14	none
7.5 mg	2363	154	116 (60)	-38	143	-27	82	100	+18	none
7.5 mg	11039	186	138 (4)	-48	130	-18	80	89	+9	none
15 mg	14307	170	112 (1)	-58	160	-48	88	80	-8	none
15 mg	15237	182	126 (6)	-56	134	-8	69	78	+9	none
15 mg	12836	142	110 (4)	-32	122	-12	80	76	-4	none
15 mg	2968	174	144 (0.5)	-30	146	-2	76	76	0	none
15 mg	14040	160	120 (6)	-40	118	+2	64	76	+12	none
15 mg	3170	162	130 (4)	-32	128	+2	78	88	+10	none
15 mg	13105	144	104 (4)	-40	110	-6	76	100	+24	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 625 cont'd.										
15 mg	2333	188	130 (4)	-58	132	-2	86	86	0	none
15 mg	11038	164	130 (4)	-34	128	+2	73	80	+7	none
15 mg	2731	148	108 (4)	-40	128	-20	70	80	+10	none
15 mg	2136	172	136 (4)	-36	150	-14	76	84	+8	none
15 mg	2169	172	126 (4)	-46	130	-4	68	80	+12	none
15 mg	15532	140	116 (4)	-24	124	-8	76	84	+8	none
30 mg	2567	166	132 (1)	-34	154	-22	92	100	+8	none
30 mg	13402	144	114 (6)	-30	142	-28	80	84	+4	none
30 mg	13407	174	116 (4)	-58	120	-4	80	96	+14	none
30 mg	13411	154	120 (6)	-34	142	-22	96	88	-8	none
30 mg	13703	164	130 (1)	-34	140	-10	84	72	-12	none
30 mg	15236	194	146 (6)	-48	142	+4	81	82	+1	none
30 mg	14907	159	124 (1)	-35	138	-14	92	88	-4	none
30 mg	14035	180	150 (1)	-30	160	-10	76	76	0	none
30 mg	11602	174	140 (4)	-34	174	-34	66	70	+4	none
30 mg	13132	144	106 (4)	-38	126	-20	76	80	+4	headache
30 mg	13139	156	122 (4)	-34	128	-6	72	90	+8	none
30 mg	11040	148	110 (6)	-38	126	-16	97	95	-2	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 623 cont'd.										
60 mg	14634	152	122 (6)	-30	120	+2	80	76	-4	none
60 mg	2564	144	104 (6)	-40	118	-14	84	100	+16	none
60 mg	2568	144	106 (4)	-38	108	-2	96	104	+8	none
60 mg	13406	150	98 (6)	-52	124	-26	80	88	+8	none
60 mg	13423	136	98 (4)	-38	114	-16	72	76	+4	none
60 mg	13432	150	120 (4)	-30	138	-18	88	86	-2	none
60 mg	14309	152	108 (6)	-44	102	+6	80	80	0	none
60 mg	13706	160	114 (1)	-46	134	-20	64	56	-8	none
60 mg	15233	172	122 (4)	-50	124	-2	66	64	-2	none
60 mg	14908	156	112 (4)	-44	114	-2	70	75	+5	none
60 mg	10410	170	140 (0.5)	-30	136	+4	78	74	-4	none
60 mg	12832	162	100 (6)	-62	156	-56	60	84	+24	none
60 mg	12503	154	116 (1)	-38	128	-12	76	80	+4	none
60 mg	12535	134	100 (4)	-34	110	-10	76	64	-12	none
60 mg	3161	140	92 (4)	-48	100	-8	88	88	0	none
60 mg	13135	148	100 (4)	-48	108	-8	68	88	+20	none
60 mg	13138	144	106 (6)	-38	154	-48	72	74	+2	none
60 mg	2366	152	120 (4)	-32	126	-6	70	66	-4	none
60 mg	2137	172	128 (4)	-44	136	-8	78	84	+6	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

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BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 623 cont'd										
60 mg	10104	140	110 (4)	-30	138	-28	76	86	+10	none
60 mg	15539	186	140 (6)	-46	138	+2	92	84	-8	none
Study 649										
Nifedipine 20	9020	160	124 (2)	-36	126.7	-2.7	66	64	-2	none
Nifedipine 20	9025	156	122 (1)	-34	138.7	-16.7	78	74	-4	none
Nifedipine 20	9029	158	114 (2)	-44	126.7	-12.7	84	84	0	none
Nifedipine 20	9340	173	135 (2)	-38	139.3	-4.3	76	72	-4	none
Nifedipine 20	9230	178	140 (1)	-38	158.7	-18.7	96	94	-2	none
Nifedipine 20	9152	146	100 (1)	-46	122.7	-22.7	94	102	+8	none
3.75 mg + Nif	9140	138	104 (1)	-34	124.7	-20.7	88	104	+16	none
3.75 mg + Nif	9049	180	136 (2)	-44	134.0	+2.0	76	78	+2	none
3.75 mg + Nif	9082	172	114 (2)	-58	120.7	-6.7	100	112	+12	none
3.75 mg + Nif	9088	158	124 (1)	-34	148.0	-24	92	120	+16	none
3.75 mg + Nif	9154	170	132 (1)	-38	134.7	-2.7	70	74	+4	none
3.75 mg + Nif	9160	178	142 (1)	-36	146.7	-4.7	68	82	+14	none
7.5 mg + Nif	9327	160	120 (2)	-40	122.7	-2.7	118	108	-10	none
7.5 mg + Nif	9102	170	140 (1)	-30	150.0	-10.0	84	86	+2	none
7.5 mg + Nif	9193	150	112 (2)	-38	110.0	+2.0	68	76	+8	none
7.5 mg + Nif	9177	190	150 (1)	-40	154.7	-4.7	72	80	+8	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 649 cont'd										
7.5 mg + Nif	9134	176	146 (1)	-30	160.7	-14.7	90	90	0	none
7.5 mg + Nif	9141	190	150 (1)	-40	179.3	-29.3	100	118	+18	none
7.5 mg + Nif	9027	189	138 (2)	-51	139.7	-1.7	82	80	-2	none
7.5 mg + Nif	9033	152	120 (1)	-32	121.3	-1.3	80	80	0	none
7.5 mg + Nif	9344	168	138 (2)	-30	138.7	-0.7	93	80	-13	none
7.5 mg + Nif	9240	176	116 (2)	-60	125.3	-9.3	58	72	+14	none
7.5 mg + Nif	9147	166	134 (2)	-32	140.7	-6.7	62	76	+14	none
7.5 mg + Nif	9153	160	118 (2)	-42	131.3	-13.3	106	100	-6	none
7.5 mg + Nif	9162	170	140 (2)	-30	146.0	-6.0	80	100	+20	none
15 mg + Nif	9116	202	164 (2)	-38	170.7	-6.7	110	92	-18	none
15 mg + Nif	9022	186	156 (2)	-30	163.3	-7.3	80	88	+8	none
15 mg + Nif	9136	132	100 (1)	-32	124.0	-24.0	100	116	+16	none
15 mg + Nif	9026	185	150 (2)	-35	162.3	-12.3	74	74	0	none
15 mg + Nif	9081	174	138 (2)	-36	142.7	-4.7	104	120	+16	none
15 mg + Nif	9149	152	116 (2)	-36	111.3	+4.7	82	76	-6	none
15 mg + Nif	9253	150	115 (2)	-35	113.7	+1.3	70	74	+4	none
15 mg + Nif	9161	167	136 (2)	-31	142.0	-6	67	64	-3	none
15 mg + Nif	9167	152	115 (2)	-37	123.7	-8.7	72	88	+16	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 651										
Placebo	8010	170	140 (2)	-31	140	0	70	82	+12	none
7.5 mg	8075	177	142 (2)	-35	149	-7	88	84	-4	none
7.5 mg	8055	191	155 (2)	-36	149	+6	90	83	-7	none
15 mg	8028	168	128 (2)	-40	124	+4	104	108	+4	none
15 mg	8037	147	111 (2)	-36	130	-19	100	106	+6	none
15 mg	8051	151	106 (2)	-45	112	-6	88	88	0	none
Study 643										
7.5 mg	8136	140	110 (2)	-30	110.0	0	58	52	-6	none
7.5 mg	8073	190	159 (2)	-31	160.0	-1.0	72	72	0	none
7.5 mg	8047	173	123 (2)	-50	134.7	-11.7	82	80	-2	none
15 mg	8247	149	119 (2)	-30	131.3	-12.3	76	70	-6	none
Study 647										
Verapamil 180 mg + HCTZ 25 mg	7112	150	113.0 (2)	-37.0	132.7	-19.7	74	76	+2	none
Study 642										
Placebo	7110	188	155 (2)	-33	166.0	-11	74	72	-2	none
Placebo	7043	153	122 (2)	-31	129.3	-7.3	76	84	+8	none
HCTZ 25 mg	7108	165	135 (2)	-30	148.0	-13	88	80	+8	none
7.5 mg	7169	187	155 (2)	-32	138.7	+16.3	72	72	0	none

* The patients were receiving moexipril unless otherwise indicated.
** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 642 cont'd.										
15 mg	7158	172	132 (2)	-40	132.0	0	72	50	-22	none
15 mg	7168	171	115 (2)	-56	127.3	-12.3	80	96	+16	none
15 mg	7033	163	131 (2)	-32	142.0	-11.0	70	74	+4	none
Study 648										
7.5 mg	7018	170	133 (2)	-37	136	-3	68	72	+4	none
7.5 mg	7110	150	120 (2)	-30	120	0	78	72	-6	none
7.5 mg	7122	171	137 (1)	-34	144	-7	70	80	+10	none
7.5 mg	7157	173	134 (2)	-39	141.3	-7.3	84	68	-16	none
7.5 mg	7174	172	118 (2)	-54	130.7	-12.7	68	88	+20	none
Captopril 25 mg	7017	156	118 (2)	-38	128.0	-10	88	80	-8	none
Captopril 25 mg	7032	147	117 (1)	-30	119.3	-2.3	76	64	-12	Fatigue
Captopril 25 mg	7047	179	146 (2)	-33	148.7	-2.7	82	84	+2	none
Captopril 25 mg	7117	173	142 (2)	-31	153.3	-11.3	90	80	-10	none
Captopril 25 mg	7128	145	102 (1)	-43	106.7	-4.7	98	88	-10	none
Captopril 25 mg	7173	168	132 (2)	-36	142.7	-10.7	84	92	+8	none
Captopril 25 mg	7201	160	121 (2)	-39	133.3	-12.3	72	76	+4	none
Study 645										
7.5 mg	9013	159	119 (2)	-40	138.7	-19.7	72	80	+8	none
7.5 mg	9067	170	131 (2)	-39	130.0	+1	62	64	+2	none
7.5 mg	9068	153	111 (2)	-42	109.3	+1.7	84	100	+16	none

* The patients were receiving moexipril unless otherwise indicated.
** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 645 cont'd										
7.5 mg	9118	159	122 (2)	-37	122.0	0	73	74	+1	none
7.5 mg	9201	163	133 (2)	-30	140.7	-7.7	71	63	-8	none
7.5 mg	9150	149	115 (2)	-34	116.7	-1.7	62	60	-2	none
7.5 mg	9160	169	139 (2)	-30	128.7	+10.3	78	82	+4	none
7.5 mg	9166	169	131 (2)	-38	127.3	+3.7	90	104	+14	none
Verapamil 180 mg	9176	180	171 (2)	-9	160.7	+10.3	76	74	-2	none
Study 640										
Placebo	7227	200	170 (4)	-30	170.7	-0.7	80	88	+8	none
HCTZ 25 mg	7023	193	154 (2)	-39	153.3	+0.7	86	84	-2	none
HCTZ 25 mg	7216	193	154 (2)	-39	142.0	+12.0	68	64	-4	none
HCTZ 25 mg	7230	183	133 (3)	-50	149.3	-16.3	98	96	-4	none
HCTZ 25 mg	7283	202	166.5 (2)	-35.5	161.3	+5.2	80	88	+8	none
HCTZ 25 mg	7298	177	139 (4)	-38	181.7	-42.7	96	96	0	none
HCTZ 25 mg	7453	165	134.5 (3)	-30.5	151.0	-16.5	82	86	+4	none
7.5 mg	7204	183	133 (4)	-50	142.0	-9.0	95	86	-10	none
7.5 mg	7211	161	125 (2)	-36	133.3	-8.3	90	100	+10	none
7.5 mg	7212	197	158 (4)	-39	169.3	-11.3	80	80	0	none
7.5 mg	7221	164.5	130 (4)	-34.5	150.7	-20.7	76	70	-6	none
7.5 mg	7229	186	140 (2)	-46	164.3	-21.3	100	88	-12	none
7.5 mg	7233	194	160 (2)	-34	195.3	-35.3	62	56	-6	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 640 cont'd										
7.5 mg	7274	157	119 (4)	-38	124.0	-5.0	74	84	+10	none
7.5 mg	7277	166	100 (4)	-66	112.7	-12.7	100	108	+8	none
7.5 mg	7286	160	126 (2)	-34	128.0	-2.0	82	80	-2	none
7.5 mg	7295	215	167 (3)	-46	164.0	+3	90	70	-20	none
7.5 mg	7449	178	128.5 (3)	-49.5	153.3	-24.8	72	69	-3	none
15 mg	7009	162	130 (3)	-32	132.0	-2.0	76	76	0	none
15 mg	7060	180	147 (4)	-33	151.3	-4.3	64	90	+26	none
15 mg	7201	190	153 (3)	-37	146.7	+6.3	58	70	+12	none
15 mg	7203	189	129 (3)	-60	142.0	-13.0	64	100	+36	none
15 mg	7223	148	112.5 (4)	-35.5	115.0	-2.5	74	78	+4	none
15 mg	7239	161	120 (2)	-41	115.3	+4.7	90	96	+6	none
15 mg	7262	195	165 (3)	-30	180.7	-15.7	72	58	-14	none
15 mg	7265	173	132 (3)	-41	144.0	-12.0	80	86	+6	none
15 mg	7281	158	125 (4)	-33	129.3	-4.3	90	84	-6	none
15 mg	7293	155	111 (4)	-44	123.3	-12.3	--	80	--	none
15 mg	7301	179	139 (4)	-40	141.3	-2.3	82	86	+4	none
15 mg	7305	199	155 (3)	-44	160.0	-5.0	60	60	0	none
15 mg	7307	194	113 (3)	-81	125.3	-12.3	76	80	+4	none
15 mg	7451	168.5	111.5 (3)	-57	121.0	-9.5	75	78	+3	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 644										
HCTZ 25 mg	4327	160	130 (3)	-30	137.3	-7.3	76	68	-8	none
HCTZ 25 mg	4336	180	150 (2)	-30	144.7	+5.3	64	68	+4	none
3.75 + HCTZ	4071	196	152 (1)	-44	174.0	-22	90	84	-6	none
3.75 + HCTZ	4250	156	118 (2)	-38	123.3	[illegible]	72	76	+4	none
3.75 + HCTZ	4331	220	190 (4)	-30	210.0	-20	76	76	0	none
3.75 + HCTZ	4358	200	170 (2)	-30	180.0	-10	96	80	-16	none
3.75 + HCTZ	4049	170	115 (4)	-55	116.7	-1.7	104	84	-16	none
3.75 + HCTZ	4056	165	120 (4)	-45	125.0	-5	100	88	-12	none
3.75 + HCTZ	4112	183	150 (4)	-33	156.0	-6	72	83	+11	none
3.75 + HCTZ	4117	158	113 (4)	-45	116.0	-3	92	81	-11	none
3.75 + HCTZ	4137	190	160 (3)	-30	180.0	-20	72	76	+4	none
3.75 + HCTZ	4212	168	123 (2)	-45	129.3	-6.3	74	78	+4	none
3.75 + HCTZ	4217	160	120 (2)	-40	127.3	-7.3	70	80	+10	Dizziness, Flushing, Headache, Sweating
3.75 + HCTZ	4221	180	145 (2)	-35	139.0	+6	70	70	0	none
3.75 + HCTZ	4228	150	118 (1)	-32	126.7	-8.7	80	74	-6	none
3.75 + HCTZ	4271	170	118 (3)	-52	117.0	+1	70	68	-2	none
3.75 + HCTZ	4329	160	130 (2)	-30	132.7	-2.7	76	76	0	none
3.75 + HCTZ	4335	140	110 (4)	-30	110.7	-0.7	98	78	-20	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 644 cont'd.										
3.75 + HCTZ	4338	168	120 (2)	-48	128.7	-8.7	78	84	+6	Dizziness, Flushing
3.75 + HCTZ	4359	180	140 (3)	-40	140.0	0	76	72	-4	none
15 + HCTZ	4016	150	115 (3)	-35	114.0	+1	80	90	+10	Dizziness, Sweating
15 + HCTZ	4018	190	152 (4)	-38	162.3	-10.3	82	78	-4	none
15 + HCTZ	4030	164	130 (3)	-34	136.7	-6.7	86	82	-4	none
15 + HCTZ	4061	180	140 (3)	-40	155.0	-15	90	112	+22	none
15 + HCTZ	4065	180	150 (1)	-30	166.7	-16.7	72	66	-6	none
15 + HCTZ	4103	194	141 (3)	-53	186.0	-4.3	60	57	-3	none
15 + HCTZ	4106	125	94 (3)	-31	105.7	-11.7	100	84	-16	Headache, Hypotension
15 + HCTZ	4122	133	96 (4)	-37	96.7	-0.7	126	95	-31	Flushing
15 + HCTZ	4203	150	120 (3)	-30	127.7	-7.7	70	68	-2	none
15 + HCTZ	4231	148	100 (3)	-48	106.0	-6	70	74	+4	none
15 + HCTZ	4251	160	124 (3)	-36	124.7	-0.7	80	100	+20	none
15 + HCTZ	4272	138	108 (3)	-30	107.7	+0.3	74	78	+4	none
15 + HCTZ	4328	186	135 (4)	-51	135.3	-0.3	76	78	+2	none
15 + HCTZ	4330	160	125 (3)	-35	116.7	+8.3	60	66	+6	none
15 + HCTZ	4360	142	110 (2)	-32	111.3	-1.3	72	68	-4	none
15 + HCTZ	4403	180	120 (3)	-60	129.3	-9.3	92	80	-12	none

* The patients were receiving moexipril unless otherwise indicated.

** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 622										
Placebo	327	190	160 (2)	-30	160	0	84	76	-8	none
3.75 mg	558	186	142 (2)	-44	166	-24	80	92	+12	none
3.75 mg	561	156	120 (2)	-36	140	-20	80	104	+24	none
3.75 mg	5631	195	150 (2)	-45	164	-14	76	70	-6	none
3.75 mg	7464	182	152 (2)	-30	178	-26	92	88	-4	none
3.75 mg	726	196	162 (2)	-34	174	-12	68	76	+8	none
3.75 mg	757	172	134 (2)	-38	170	-36	84	84	0	none
3.75 mg	5902	168	128 (2)	-40	138	-10	88	88	0	none
7.5 mg***	4403	142	110 (2)	-32	120	-10	68	74	+6	none
7.5 mg***	6871	186	150 (2)	-36	180	-30	68	68	0	none
7.5 mg***	8061	140	106 (2)	-34	100	+6	78	84	5	Fatigue
7.5 mg	5602	153	112 (2)	-41	126	-14	62	63	+1	none
7.5 mg***	4731	150	120 (2)	-30	140	-20	72	72	0	none
15 mg	4103	200	110 (2)	-90	130	-20	76	80	+4	Headache
15 mg***	7465	144	112 (2)	-32	120	-8	80	66	-14	none
15 mg	227	170	130 (2)	-40	166	-36	88	100	+12	none
15 mg***	6861	172	120 (2)	-52	134	-14	68	64	-4	none
15 mg	6265	165	124 (2)	-41	124	0	88	102	+14	none
15 mg	729	190	133 (2)	-57	140	-7	66	70	+4	none
15 mg	759	182	140 (2)	-42	162	-22	82	82	0	Dyspnea/ Fatigue

* The patients were receiving moexipril unless otherwise indicated.
** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.
*** Titrated to dose

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BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 622 cont'd.										
30 mg***	6265	153	122 (2)	-31	130	-8	80	84	+4	none
30 mg***	5961	134	92 (2)	-42	104	-12	80	86	+6	none
Study 638										
Placebo	6156	184	154 (3)	-30	159.3	-5.3	76	74	-2	none
HCTZ 12.5	6014	160	124 (3)	-36	123.3	+0.7	60	64	+4	none
HCTZ 12.5	6021	160	128 (3)	-32	133.3	-9.3	74	66	-8	none
HCTZ 12.5	6081	162	132 (3)	-30	148.7	-16.7	78	78	0	none
7.5 mg	6213	172	142 (3)	-30	146.7	-4.7	68	72	+4	none
7.5 mg	6046	180	140 (3)	40	157.3	-17.3	68	68	0	none
7.5 mg	6424	200	168 (3)	-32	165.3	+2.7	96	84	-12	none
15 mg	6189	168	134 (3)	-34	125.3	+9.0	72	72	0	none
15 mg	6356	160	112 (3)	-48	125.3	-13.3	90	82	-8	none
15 mg	6209	154	118 (3)	-36	122	-4.0	76	72	-4	none
15 mg	6443	160	112 (3)	-48	121.3	-9.3	84	72	-12	none
15 mg	6375	172	132 (3)	-40	122.7	+9.3	96	88	-8	none
30 mg	6002	160	126 (3)	-34	130.7	-4.7	72	64	-8	none
30 mg	6201	150	118 (3)	-32	143.3	-25.3	80	74	-6	none
30 mg	6211	158	126 (3)	-32	122.7	+3.3	84	76	-8	none
30 mg	6435	150	90 (3)	-60	100.7	-10.7	70	80	+10	none
3.75 + HCTZ	6268	160	130 (3)	-30	142	-12	76	64	-12	none
3.75 + HCTZ	6177	164	130 (3)	-34	130	0	70	72	+2	none

* The patients were receiving moexipril unless otherwise indicated.
** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.
*** Titrated to dose

BASELINE AND MAXIMAL CHANGE IN TWO-MINUTE STANDING SYSTOLIC
BLOOD PRESSURE (mmHg) UP TO SIX HOURS POST-INITIAL DOSE
IN PATIENTS WHO EXPERIENCED ≥ 30 mmHg REDUCTION

Treatment Group*	Patient #	Systolic BP - 2 min. standing (mmHg)			Sitting Systolic BP (mmHg)**		Pulse - 2 min standing (bpm)			Symptoms
		0 hour	Postdose (Hr)	Change	Hour of Drop	Change	Hour (0)	Hour of Drop	Change	
Study 638 cont'd.										
7.5 + HCTZ	6001	180	140 (3)	-40	140	0	82	76	-6	none
7.5 + HCTZ	6401	184	142 (3)	-42	156.7	-14.7	64	88	+24	Dizziness
7.5 + HCTZ	6091	186	130 (3)	-56	137.3	-7.3	76	76	0	none
15 + HCTZ	6118	160	128 (3)	-32	118.7	+9.3	60	80	+20	none
15 + HCTZ	6295	178	144 (3)	-34	140.0	+4	72	70	-2	none
15 + HCTZ	6255	136	102 (3)	-34	101.3	+7	72	74	+2	none
15 + HCTZ	6203	186	144 (3)	-42	138	+6	78	78	0	none
15 + HCTZ	6252	166	124 (3)	-42	130.7	-6.7	67	76	+9	none
15 + HCTZ	6501	142	112 (3)	-30	129.3	-13.3	71	79	+8	none
15 + HCTZ	6185	148	110 (3)	-38	114.7	-4.7	72	68	-4	none
15 + HCTZ	6437	160	110 (3)	-50	106.7	+3.3	60	70	+10	none

* The patients were receiving moexipril unless otherwise indicated.
** For studies 622 and 623 supine systolic blood pressure was measured instead of sitting systolic blood pressure.
*** Titrated to dose

OCT 2 7 1993

Steven M. Rodin, M.D.

Food and Drug Administration — Division of Cardio-Renal Drug Products, HFD-110

Addendum #2 to Medical Review of NDA Efficacy data

1 General information

NDA #:	20-312
Drug:	moexipril (Schwarz Pharma)
Proposed indication:	treatment of essential hypertension
Date of original review:	3 August 1993
this addendum last revised:	27 October 1993

2. Onset of acute effect

The sponsor has corrected their original communication with the subsequent statement that several studies did indeed measure first dose effects under fasting conditions. This corrected information was incorporated into the discussion of peak-trough differences [as rendered on page 2 of Addendum #1 to my NDA review dated 9/29/93]. It remains to clarify that observations of the time of onset of acute antihypertensive effects [described on pages 7, 24, 32, and 47 of my NDA review dated 8/3/93] were obtained after first doses, and were not confounded by the effects of prior food ingestion.

Steven Rodin, MD — 10/27/93

Steven M. Rodin, MD — Date

cc: AKarkowsky/HFD-110; SChun/HFD-110; KBongiovanni/HFD-110; division file/HFD-110
*** no copy to MO**

Steven M. Rodin, M.D.

Food and Drug Administration — Division of Cardio-Renal Drug Products, HFD-110

SEP 29 1993

Addendum #1 to Medical Review of NDA Efficacy data

1 General information

NDA #:	20-312
Drug:	moexipril (Schwarz Pharma)
Proposed indication:	treatment of essential hypertension
Date of original review:	3 August 1993
Date of latest data submission:	22 September 1993
this addendum last revised:	29 September 1993

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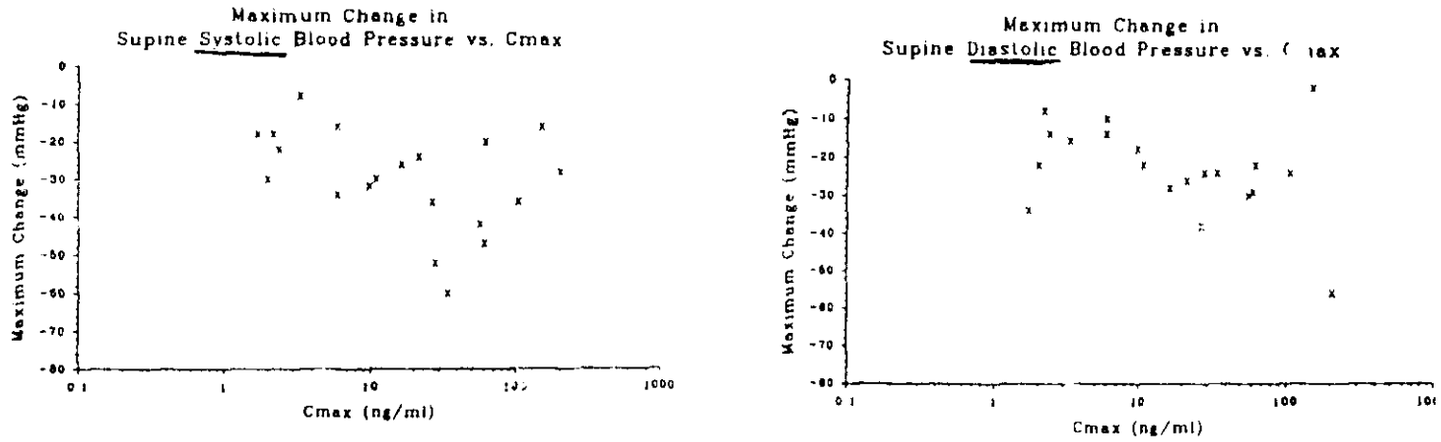
3. Peak-trough difference in antihypertensive effect

It had previously been underscored that the mean peak antihypertensive effects observed in the clinical trials may have underestimated the effect of the proposed-for-market formulation. With none of the steady-state observations in the trials was it known with certainty whether or not patients had fasted prior to dosing. The to-be-marketed formulation (which is very similar to the formulation used in two of the efficacy trials (638, and 640)) exhibited a food interaction whereby the mean C_{max} for moexipril and moexiprilat was reduced by 40 and 21%, respectively. Thus in a worst case scenario where all the trial patients are assumed to have fed themselves just prior to dosing[1], the mean C_{max} for moexiprilat in these trials would have underestimated (by roughly 20%) the levels to be expected during administration of drug under fasting conditions (those being the conditions reasonably proposed for administration of the marketed product).

It remains unclear whether the C_{max}-peak BP response relationship is sufficiently steep (over the range of proposed doses) such that a 20% increase in C_{max} would be of clinical importance. The more recently submitted data do not add substantial insights into this issue. In response to my inquiry about this relationship, the sponsor referred to PK-PD data (study 621) which was widely scattered, and not clearly demonstrative of a relationship between plasma moexiprilat concentration and antihypertensive response to moexipril at doses of 3.75 to 60 mg/d (see below).

Table 1:

Maximal BP change vs C_{max} (study 621)



[source: photocopy of tables in attachment 3 of submission dated 9/22/93]

Fasting, placebo-controlled monotherapy data are available, but these represent *first dose* peak antihypertensive effects (studies 621, 638, 640, 642, 649, and 651). In these studies, mean peak (placebo-corrected) diastolic BP changes generally did not exceed -7 mm Hg (except for the highly variable results of study 621 (standard deviations as high as 22.6 mm Hg) where mean diastolic BP changes were as large as -15.9 mm Hg) [for those who are inclined to rely on these study 621 data, it is noted that the large mean response is not accounted for by dissimilar racial demographics, or by explicit selection of ACE inhibitor-responsive subjects[1]. From all of these fasting data, only limited inferences can be drawn about steady-state because the long terminal half life of moexiprilat makes it plausible that C_{max} may be significantly higher at steady-state than it is following a first dose.

[1]the actual proportion who did so was not characterized.

4. Clinical pharmacology studies

The clinical pharmacology studies were small, and less adequately designed than the previously reviewed clinical trials; hence they provide a less definitive assessment of the anti-hypertensive action of moexipril. Except for *study 621* (which was discussed in the preceding section of this addendum), the mean results of these studies were not discordant with those of the clinical trials.

In study 925-1 there were no clinically significant mean BP effects (as expected) in the normotensive subjects evaluated. In *study 925-3*, moexipril at doses of 4-120 mg/d achieved mean changes in supine diastolic BP of -4.3 to -13.7 mm Hg at 4 hours post-dose, and -0.8 to and -11.0 mm Hg at 24 hours post-dose. *Study 641* also did not demonstrate discordant mean antihypertensive effects. In this open-label study moexipril (at once-daily doses titrated of 7.5-30 mg in addition to hydrochlorothiazide 50 mg/d) was associated with a mean change from pre-treatment sitting diastolic (sitD) BP of -11.6 mm Hg.

Study 646 was a placebo-controlled, double-blind, randomized evaluation of 18 patients with hypertension and impaired renal function (creatinine clearance of 25-65 ml/min). Moexipril, at a once-daily dose titrated as needed from 3.75 to 15 mg, changed pre-treatment mean sitDBP by -7.3 mm Hg at 24 hours post-dose (placebo-corrected), and yet by only 3.1 mm Hg at 2 hours post-dose. Two of 10 moexipril-treated patients maintained a sitDBP of 90 mm Hg while on the 3.75 mg/d dose for the duration of the study.

5. Study 624

It is now clear that study 624 was discontinued early for administrative reasons (the previous sponsor decided to discontinue development of moexipril). The sponsor has not submitted sufficient information about the stability of concomitant diuretic doses to draw any unambiguous conclusions about the the longterm persistence of moexipril effect in this trial.

6. Additional trials submitted since the original NDA submission

The mean results of these additional clinical trials were not discordant with those of the previously reviewed clinical trials.

Study 649 was a placebo-controlled, combination drug, double-blind, parallel-group study which randomized 203 hypertensive subjects to receive fixed, once-daily doses of placebo, or moexipril (3.75, 7.5, or 15 mg) as therapy which was sequentially added to controlled-release nifedipine (40 mg/d) for 8 weeks. Moexipril at 3.75, 7.5, and 15 mg/d produced additional changes in mean sitDBP (in addition to those associated with nifedipine monotherapy) of -1.1, -4.1, and -3.8 mm Hg, respectively (placebo-corrected). No definitive conclusions about the additivity of effects can be made because no moexipril monotherapy arm was included. The added effect of moexipril was approximately the same as that observed with moexipril monotherapy in other studies.

Study 645 was a positive-controlled, double-blind, parallel-group study which randomized 178 subjects (patients with mild-to-moderate essential hypertension) to receive sustained release verapamil (180-240 mg/d), or moexipril (7.5-15 mg/d) for 24 weeks. At the end of the study moexipril was associated with a mean change from pre-treatment sitDBP of -9.7 mm Hg, and verapamil was associated with a mean change of -10.6 mm Hg (neither mean result is placebo-corrected).

6. Additional trials submitted since the original NDA submission [continued]

Study 647 was a positive-controlled, double-blind, parallel-group study which randomized 108 subjects (patients who remained hypertensive despite hydrochlorothiazide (HCTZ) 25 mg/d monotherapy) to receive verapamil (180-240 mg/d), or moexipril (7.5-15 mg/d) in addition to the HCTZ background therapy for 12 weeks. After 12 weeks moexipril and verapamil were associated with additional changes in mean sitDBP of -10.7 and -11.2 mm Hg, respectively (relative to those associated with HCTZ monotherapy).

Study 648 was a positive-controlled, double-blind, parallel-group study which randomized 159 hypertensive patients to receive captopril (50-100 mg/d), or moexipril (7.5-15 mg/d) for 12 weeks. At the end of the study moexipril was associated with a mean change from pre-treatment sitDBP of -11.8 mm Hg, and captopril was associated with a mean change of -12.2 mm Hg (24 hours post-dose, not placebo-corrected).

7. Proposed product labelling

a. On page 12 of the proposed product label (sponsor's draft dated 4/28/93) the sponsor makes general assertions regarding the additivity of effects of moexipril and concomitant thiazide diuretics, or calcium channel blockers when in fact only one agent in each of these classes was investigated as a co-therapy (hydrochlorothiazide and nifedipine, respectively). This language is unjustifiably broad.

b. On page 37 of the proposed product label (sponsor's draft dated 4/28/93) the sponsor recommends an initial moexipril dose of 3.75 mg/d and a maximum dose of 15 mg/d in populations with renal insufficiency. However, in study 646, when patients of this type were uptitrated (as needed) to once-daily moexipril doses of 15 mg, neither the mean peak nor trough changes from pre-treatment sitDBP were excessive [see page 3 of this addendum]. Thus there is no support in the *efficacy* data for the sponsor's implied claim that doses higher than 15 mg/d are not more clinically useful in renal insufficiency. My colleague's reviews of the kinetic (study 629) and/or safety data may, however, offer support for this claim.

Steven Rodin, MD 9/24/93

Steven M. Rodin, MD Date

cc: AKarkowsky/HFD-110; SChun/HFD-110; KBongiovanni/HFD-110; division file/HFD-110
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K BONAGURA MI

Steven M. Rodin, M.D.
Medical Officer

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Medical Review of NDA Efficacy data

1 General information

AUG 3 1993

NDA #:	**20-312**
Drug:	**moexipril hydrochloride**
Sponsor:	Schwarz Pharma (via Besselaar Associates)
Proposed indication:	oral treatment of systemic arterial hypertension
Pharmacologic type:	angiotensin converting enzyme inhibitor
Dosage:	3.75 to 60 mg/d p.o.
NDA classification:	1S
Date of NDA submission:	21 December 1992
Latest data submission:	12 July 1993
Reviewer:	Steven M. Rodin, M.D.
Review last revised:	3 August 1993

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3 Chemistry

Moexipril hydrochloride is a prodrug formally named 2-[2-[[(1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxypropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, hydrochloride (S,S,S). It is activated by hydrolysis of the ethylester to moexiprilat, an angiotensin converting enzyme (ACE) inhibitor. See the chemist's review for a detailed discussion of chemistry.

4 Preclinical Pharmacology

See the pharmacologist's review for a detailed discussion of pre-clinical pharmacology. Briefly, chronic oral treatment with moexipril caused dose-dependent decreases in arterial blood pressure (BP) in both renal hypertensive and spontaneously hypertensive rats. The drug selectively inhibited the vasopressor responses to angiotensin I without altering the hemodynamic effects of angiotensin II, norepinephrine, epinephrine, or acetylcholine. Moexipril was also observed to potentiate the hypotensive effects of bradykinin (an action attributable to kininase II inhibition).

5 Clinical Pharmacokinetics

See the Biopharmaceutical review for detailed discussions of clinical pharmacokinetics. A few of the salient assertions made by the sponsor are summarized here, however these kinetic data have not been critically evaluated by this reviewer.

The absolute bioavailability of moexipril was estimated to be 22% [study GHBA 628, vol 52, pg 41]. Following absorption, moexipril is hydrolyzed to moexiprilat, a pharmacologically active ACE inhibitor. Moexipril is highly bound to human plasma protein (about 90%), and moexiprilat is moderately protein bound (about 72%) [study CL 4420, vol 107, pg 433]. Unchanged moexipril is eliminated mainly in the urine and moexiprilat is eliminated in both the urine and feces [study GHBA 628, vol 52, pg 41]. The kinetics of moexipril were reported to be linear after single doses ranging from 3.75 to 30 mg [study PHAKI 795, vol 71, pg 1]. The effective elimination half-lives of moexipril and moexiprilat were reported to be 1 to 2 hours, and 6 to 10 hours, respectively [study PHAKI 794, vol 56, pg 1]. Following oral administration of moexipril, peak plasma concentrations of moexipril were reached between 0.75 and 1.5 hours [study PHAKI 794, vol 56, pg 1], and peak plasma concentrations of moexiprilat were reached between 1 and 2 hours [study PHAKI 794, vol 56, pg 1].

The to-be-marketed formulation of moexipril exhibits a food interaction which appreciably reduces the AUC and C_{max} for both parent and moexiprilat [study PHAKI 796, vol 99, pg 1]. Food was associated with a 24 hour mean AUC for moexipril and moexiprilat which was 43% and 46% of that observed in the fasted state, respectively. In the fed state, mean C_{max} for moexipril and moexiprilat was 40%, and 21% of that observed in the fasted state, respectively.

In hepatic insufficiency [study GHBA 636, vol 80, pg 1] the AUC for moexipril was increased and peak moexiprilat levels were diminished. In these patients the AUC for moexiprilat was larger than in healthy subjects and moexiprilat's elimination half-life was prolonged. In patients with renal insufficiency, the elimination half-lives of moexipril and moexiprilat were increased (approximately 2 and 4-fold, respectively) [study GHBA 629, vol 76, pg 1]. The kinetics of moexipril and moexiprilat were reported to be uninfluenced by age [study GHBA 637, vol 73, pg 1].

5 Clinical Pharmacokinetics [continued]

Bioequivalence of formulations:

The majority of the clinical efficacy trials (studies 642, 651, 643, 640, 638, and 644) used a capsule formulated by Schwarz Pharma, whereas studies 622 and 623 utilized a different capsule formulated by Syntex. The available pharmaceutical data does not establish the bioequivalency of these formulations, however the efficacy results of studies 622 and 623 are not critical for the evaluation of approvability.

6 Clinical Pharmacology

One aspect of the clinical pharmacology of this drug, that is the heartrate effect, was well studied in the clinical efficacy trials. The results of an analysis of pooled, placebo-controlled monotherapy trials involving once-daily dosing are shown below:

Table 1:

Mean change from pre-treatment Heartrate in beats/min
(pooled, placebo-corrected trough data)

	Daily Moex Dose				
N/arm	3.75 mg	7.5 mg	15 mg	30 mg	60 mg
49-317	0.1	-0.3	-0.5	-0.3	-1.1

[source: modification of table in attachment 3, addendum dated 6/22/93]

No differences were statistically significant at an alpha level of 0.05. The data are based on adjusted mean changes from pre-treatment baseline in pooled monotherapy trials (studies 623, 638, 640, 642, 643, and 651). Standard errors ranged from 0.46 to 1.16. Trough= 22-26 hours post-dose.

The majority of the clinical pharmacology studies were dose-ranging studies which provide a less definitive assessment of anti-hypertensive dose-response than do the clinical trials reviewed in the next section of this report. A few of the sponsor's salient assertions regarding these studies are summarized here, however these clinical pharmacology data have not been critically evaluated by this reviewer. See Dr. Karkowsky's review for a detailed discussion of these studies.

Study 925-1 was a rising dose study of moexipril in 16 healthy subjects. The percent inhibition of circulating ACE activity was reported to be dose-related, with maximum inhibition ranging from 34.6% for a 7 mg dose to 98.4% for a 120 mg dose. Study 925-3 examined moexipril doses of 4-120 mg in 25 hypertensive patients. Mean antihypertensive effects were reported to be maximal at 4-8 hours after dosing and still observable at 12 hours post-dose. Study 621 evaluated 30 hypertensive patients and reported that moexipril (at doses of 15 or 30 mg) produced mean changes from pre-treatment supine diastolic BP which, at 24 hours post-dosing, were generally greater than those observed with placebo. In open-label study 641, those hypertensive patients who responded to moexipril at 7.5 mg once-daily (added to a background of hydrochlor-othiazide 50 mg/d) were reported to manifest a mean change from pre-treatment diastolic BP of -14.3 mm Hg. Study 646 evaluated 18 patients with hypertensive and impaired renal function. Moexipril at a once-daily dose of 15 mg was reported to reduce supine diastolic BP by -7.3 mm Hg, relative to placebo.

7 Clinical efficacy trials

7.1. Placebo-controlled trials

Efficacy data tables were submitted in both hard copy and in machine-readable form. In some cases the machine-readable versions were imported into this document. With each submission the sponsor attested to the accuracy of the digitized data. For example, they asserted in an addendum dated 4/26/93 that "the tables... formatted in Word Perfect 5.1... are an exact representation of the hard copy of the tables contained in the submissions."

7.1.1 Antihypertensive effect of moexipril monotherapy (study 642)!

SUMMARY

This placebo-controlled, double-blind, parallel-group study randomized 200 subjects (mild-to-moderate essential hypertensive patients of both sexes) to receive fixed, once-daily oral capsule doses of placebo, moexipril (7.5, or 15 mg/d), or hydrochlorothiazide (HCTZ) 25 mg for 12 weeks subsequent to a 1-4 week placebo-exposed pre-treatment period. The objective was to assess the change from pre-treatment BP at 24 hours post-dosing after 12 weeks.

PROTOCOL

▸ **Enrollment criteria**

Enrolled subjects were adults with mild-to-moderate essential hypertension (untreated sitting diastolic BP (sitDBP) between 95 and 114 mm Hg). Women of child-bearing potential (i.e. not post-menopausal, not surgically sterilized, or not using a progestin-only contraceptive) were excluded from enrollment (pregnancy was not explicitly mentioned as an exclusion criterion) as were patients manifesting:

- heart failure, left ventricular hypertrophy, heart block, significant cardiac valvular disease, uncontrolled cardiac dysrhythmia, or myocardial infarction within the previous 12 months
- a history of cerebrovascular accident, or hypertensive encephalopathy
- secondary hypertension, or high-grade hypertensive retinopathy
- hepatic, gastrointestinal, or hematologic dysfunction
- a requirement for drugs known to affect BP
- diabetes mellitus with poor glucose control
- renal insufficiency

▸ **Treatment regimen**

Subsequent to a 1-4 week placebo run-in period, subjects underwent double-blind randomization to placebo or moexipril given as a fixed 7.5, or 15 mg dose in once-daily capsule administrations for 12 weeks (the capsule was the Schwarz Pharma formulation). Patients were not instructed to fast prior to drug ingestion.

Study 642

▸ **Endpoints**

The primary efficacy endpoint was the change from baseline (end of placebo run-in) mean sitDBP measured 22-26 hours post-dose after 12 weeks of double-blind therapy. The mean of 3 replicate BP measures was used at each observation.

▸ **Statistical procedures**

• **Data set analyzed**

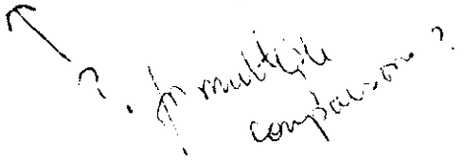
The results of an intent-to-treat analysis (all randomized subjects who received at least one dose) were presented.

• **Handling of missing data**

For the main analysis patients with missing data at a given timepoint were excluded from the mean description of that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

• **Analyses performed**

Data were analyzed by means of a 2-way analysis of covariance (ANCOVA) with the baseline measurement as the covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. Statistical significance was defined as a 2-sided p-value ≤ 0.05.



RESULTS

• **Demographics**:

Pre-treatment mean age, and weight as well as the distribution of sex, and race were comparable among the treatment groups.

• **Disease severity**:

The severity of pre-treatment hypertension was comparable among treatment groups.

[CONTINUED NEXT PAGE]

Study 642

▸ **Antihypertensive effect:**

• **Onset of first-dose effect:**

By 2 hours following a first dose of 15 mg, mean sitDBP was significantly lowered (-3.3 mm Hg, placebo-corrected). The 7.5 mg dose had no significant effect at this, the final timepoint observed on day 1.

• **Onset of significant trough effect:**

Each of the examined doses (7.5, and 15 mg/d) achieved statistically significant trough effects (22-24 hours post-dose) on mean sitDBP by the second treatment week, and these effects were essentially unchanged at week 12 (the final observation point).

• **Extent of steady-state trough effect:**

Table 2:

Mean change in trough *SITTING* BP [systolic/diastolic], in mm Hg (placebo corrected)

			Daily Moex Dose				
trial	*analysis*	*N/arm*	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*	*60 mg*
642	2 wk ITT	47-51	--	-6.2*/-4.1*	-6.1*/-4.5*	--	--
"	6 wk ITT	45-46	--	-6.6*/-3.5*	-5.0/-2.6	--	--
"	12 wk ITT	43-44	--	-4.5/-3.4*	-9.3*/-4.4*	--	--
"	endpoint ITT	47-51	--	-7.1*/-4.8*	-10.7*/-5.2*	--	--

[source: modification of table in attachment 2, addendum dated 3/19/93]

Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). The data are based on adjusted mean changes from pre-treatment baseline. Standard errors ranged from 0.91 to 2.13. Trough= 22-24 hours post-dose; ITT=intent to treat; wk = week. Patients with missing data at a given timepoint were excluded, except for the endpoint analysis in which the last nonmissing double-blind data were carried forward.

Study 642

- **Response in demographic subgroups**

In this report, each review of individual studies will not contain demographic analyses. For such analyses see the overview presented in section 7.2 of this report.

COMMENTS (study 642):

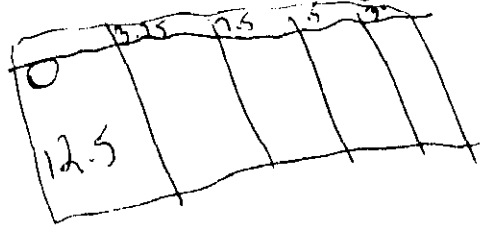
1. The results of this large and well-controlled study provide convincing evidence that moexipril monotherapy (administered as 7.5-15 mg/d once-daily) produces a clinically significant reduction in sitting diastolic BP 24 hours post-dose in mild-to-moderate hypertensive subjects. Moexipril was generally statistically distinguishable from placebo by 2 weeks of therapy.

2. These data did not convincingly distinguish the effectiveness of 15 mg/d from that of 7.5 mg/d moexipril.

7.1.2 Factorial trial with hydrochlorothiazide (study 638)!

SUMMARY:

This placebo-controlled, double-blind, parallel-group, factorial study randomized 413 subjects (patients with mild-to-moderate essential hypertension) to receive fixed, once-daily oral doses of placebo, moexipril monotherapy (3.75, 7.5, 15, or 30 mg/d), hydrochlorothiazide (HCTZ) monotherapy (12.5 mg), or combination therapy (moexipril at each of the three lowest doses in combination with 12.5 mg HCTZ) for 8 weeks, subsequent to a 1-4 week placebo run-in period. The objective was to assess the change from pre-treatment sitDBP at the interdosing interval after 8 weeks.



PROTOCOL:

- **Enrollment criteria:**

Inclusion and exclusion criteria were not substantially different from those described above under study 642.

- **Treatment regimen:**

Following a 1-4 week placebo run-in period, patients were randomized to fixed, once-daily oral doses of placebo, moexipril monotherapy (3.75, 7.5, 15, or 30 mg/d) in capsule (Schwarz Pharma formulation), HCTZ monotherapy (12.5 mg), or combination therapy (moexipril at each of the three lowest doses in combination with 12.5 mg HCTZ) for 8 weeks. Patients were not instructed to fast prior to drug ingestion.

- **Endpoints:**

The primary efficacy endpoint was the change from pre-treatment (end of placebo run-in) sitDBP after 8 weeks. Trough BPs were measured in triplicate at 22-26 hours post-dose.

- **Statistical procedures:**

  - **Data set analyzed:**

The results of an intent-to-treat analysis (all randomized subjects who received ≥1 dose) were presented.

  - **Handling of missing data:**

For the main analysis patients with missing data at a given timepoint were excluded from the mean estimate for that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

Study 638

• **Analyses performed**:

Data were analyzed by means of a 2-way ANCOVA with the pre-treatment (baseline) measurement as the covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. Dose responses were evaluated by fitting linear regression models containing linear and quadratic terms. Statistical significance was defined as a 2-sided p-value $\leq$ 0.05.

RESULTS:

▸ **Treatment group comparability**:

• **Demographics**:

Pretreatment mean age, and weight as well as the distribution of sex, and race were comparable among the treatment groups.

• **Disease severity**:

The severity of pre-treatment sitDBP was comparable among treatment groups (means ranging from 99.8 to 101.9 mm Hg).

Study 638

- **Antihypertensive effect:**

  - **Extent of trough effect with Monotherapy:**

Table 3:

Mean change (mm Hg) in trough SITTING BP [systolic/diastolic], *in the absence of HCTZ* (placebo corrected)

			Daily Moex Dose				
trial	*analysis*	*N/arm*	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*	*60 mg*
638	6 wk ITT	41-48	-0.2/0.4	-3.0/-0.7	-6.3*/-2.2	-7.7*/-4.3*	--
"	8 wk ITT	39-48	-0.2/-1.0	-3.4/-2.7	-4.0/-2.8*	-5.0/-3.2*	--
"	endpoint ITT	42-49	-0.5/-1.1	-4.0/-3.2*	-4.4/-3.1*	-5.3/-3.4*	--

[source: modification of table in attachment 2, addendum dated 3/19/93]

Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). The data are based on adjusted mean changes from pre-treatment baseline. Standard errors ranged from 0.94 to 2.11. Trough= 22-26 hours post-dose; ITT=intent to treat; wk = week.

Study 638

▸ **Antihypertensive effect** [continued]:

• **Trough effect of monotherapy vs combination therapy**:

Table 4:

Mean change in trough SITTING BP [systolic/diastolic] in mm Hg, *after 8 weeks* (placebo-corrected, study 638)

		Daily Moex Dose			
		0 mg	*3.75 mg*	*7.5 mg*	*15 mg*
Daily	*0 mg*	**0.0/0.0**	**-0.2/-1.0**	**-3.4/-2.7**	**-4.0/-2.8***
HCTZ	*12.5 mg*	**-4.9/-2.6**	**-9.3/-6.0**	**-9.7/-6.2**	**-11.0/-4.9**
Dose					

[source: modification of table in attachment 2, addendum dated 3/19/93]

The combination treatment was not statistically compared to placebo. Shown are the results of the week 8 intention to treat analysis. Significant differences between placebo and moexipril monotherapy are denoted by asterisks ($p \leq 0.05$). The data are based on adjusted mean changes from pre-treatment baseline. The sample size per arm was 39-48. Standard errors ranged from 0.94 to 2.11. Trough= 22-26 hours post-dose.

• **Dose response**:

A statistically significant linear dose response was observed with moexipril monotherapy after the first dose, and at week 6. Quadratic effects were also statistically significant in the regression model at these time points. The combination regimens did not demonstrate significant dose response relationships beyond the first day.

▸ **Antihypertensive effect** [continued]:

• **Peak effect of monotherapy vs combination therapy:**

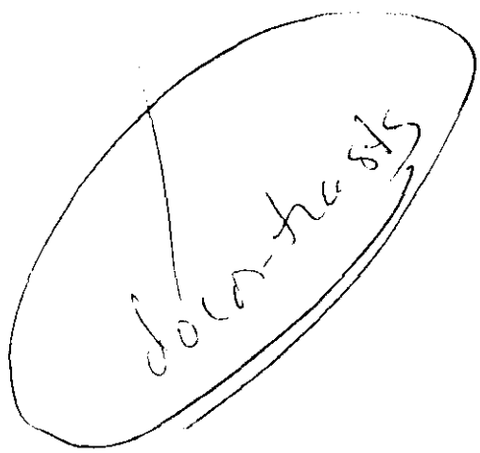
Table 5 [revised]:

Mean change in peak sitting DBP in mm Hg, *after 6 weeks*
(placebo-corrected, study 638)

		Daily Moex Dose				
		0 mg	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*
Daily	*0 mg*	**0.0/0.0**	**-0.8**	**-4.5**	**-5.7**	**-6.8**
HCTZ	*12.5 mg*	**-1.9**	**-7.1**	**-8.9**	**-8.2**	**no data**
Dose						

[source: modification of table J.a., attachment 4, submission dated 3/19/93]

Unlike the previous table of trough data, these are 6 week data. Effects are placebo-corrected mean changes from pre-treatment BP (expressed in mm Hg). Peak was defined as the largest mean change observed with 3 once-hourly observations post-dose. In all cases this peak was observed at 3 hours post-dose.



▸ **Antihypertensive effect** [continued]:

• **Peak effect**:

Table 5:

Mean change in peak sitting DBP *after 6 weeks* (study 638)

metric	Moexipril dose (mg/d) *3.75*	*7.5*	*15*	*30*	*3.75 + HCTZ*	*7.5 + HCTZ*	*15 + HCTZ*
time of peak effect (hr)	**3**	**3**	**3**	**3**	**3**	**3**	**3**
mean change in peak DBP (mm Hg)	**-0.8**	**-4.5**	**-5.7**	**-6.8**	**-7.1**	**-8.9**	**-8.2**

[source: modification of table J.a., attachment 4, submission dated 3/19/93]

Unlike the previous table of trough data, these are 6 week data. Effects are placebo-corrected mean changes from pre-treatment BP (expressed in mm Hg). Peak was defined as the largest mean change observed with 3 once-hourly observations post-dose.

Study 638

• **Ratio of trough-to-peak effect**:

Table 6:

Trough-peak (T-P) ratio of mean effects on sitting DBP *after 6 weeks* (study 638)

		Daily Moex Dose				
		0 mg	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*
Daily HCTZ Dose	*0 mg*	--	**-0.50**	**0.16**	**0.39**	**0.63**
	12.5 mg	**1.68**	**0.76**	**0.67**	**0.66**	--

[source: modification of table J.a., attachment 4, submission dated 3/19/93]

Unlike the trough data shown in Table 4, these are 6 week data. Peak was defined as the largest mean change observed with 3 once-hourly observations post-dose (which in all cases was observed at 3 hours). The negative sign denotes directionally opposite observations at peak vs trough. Trough= 22-26 hours post-dose; HCTZ= hydrochlorothiazide; moex= moexipril.

COMMENTS (study 638):

1. The results of this large and well-controlled study provide convincing evidence that moexipril monotherapy (administered as 15-30 mg/d once-daily for 8 weeks) produces a statistically (and clinically) significant reduction in sitting diastolic BP at 24 hours post-dose patients with mild-to-moderate hypertension. This study also suggests that 7.5 mg/d moexipril is efficacious once-daily monotherapy, that is, a statistically (and clinically) significant mean reduction in sitting diastolic BP was observed in the endpoint analysis, and directionally similar trends were obtained in the main analyses. Moexipril at 3.75 mg once-daily was also shown to be a no-effect dose.

2. These data did not convincingly distinguish the effectiveness of 30 mg/d moexipril from that of 15 or 7.5 mg/d, although antihypertensive response tended to increase monotonically over these doses.

3. For neither once-daily moexipril monotherapy (7.5-30 mg/d), or combination therapy with moexipril (7.5-15 mg/d) and HCTZ (12.5 mg/d), was the mean trough antihypertensive effect obtained at the price of clinically excessive mean diastolic hypotensive effect at peak. However, the possibility of extreme peak effects among outliers is not excluded by these data [the review of safety data should be consulted for inquiries into the frequency of hypotension among individuals]. In addition, caution must be exercised in extrapolating these peak-trough data to the proposed-for-market formulation [see conclusions, page 49].

4. Semi-quantitative assessment of the mean data suggests that the antihypertensive effect of moexipril is approximately additive to the antihypertensive effect of HCTZ.

7.1.3 Placebo-controlled withdrawal study (643)!

SUMMARY:

This double-blind, parallel-group, placebo-controlled withdrawal study randomized 223 subjects (mild-to-moderate essential hypertension patients of both sexes) to receive one of two fixed, once-daily oral doses of moexipril (7.5, or 15 mg/d) for 12 weeks, subsequent to a 1-4 week placebo-treated run-in. Following moexipril treatment, subjects were randomized to either placebo (withdrawal) or to continued moexipril therapy for 12 additional weeks.

PROTOCOL:

▸ **Enrollment criteria:**

Inclusion and exclusion criteria were not substantially different from those described above under study 642.

▸ **Treatment regimen:**

Following a 1-4 week placebo run-in, subjects were randomized to one of two fixed, once-daily oral doses of moexipril (7.5, or 15 mg/d) in capsule (Schwarz Pharma formulation) for 12 weeks. Following moexipril treatment, subjects were allocated either placebo (withdrawal) or continued moexipril therapy for 12 more weeks. The actual randomization to ultimate placebo-withdrawal or to continued moexipril therapy was performed at the start of the study (patients were not re-randomized at the end of the pre-withdrawal, moexipril-treated phase).

Patients were not instructed to fast prior to drug ingestion.

▸ **Endpoints:**

Although not clearly stated, the primary efficacy endpoint appeared to be the change from pre-treatment (placebo phase) sitDBP after 24 weeks of continuous moexipril therapy. BPs were obtained approximately at the interdosing interval (ranging from 22-26 hours post-dose).

▸ **Statistical procedures:**

• **Data set analyzed:**

The results of an intent-to-treat analysis (all randomized subjects who received at least one dose) were presented.

• **Handling of missing data:**

For the main analysis patients with missing data at a given timepoint were excluded from the mean estimate for that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

Study 643

• **Analyses performed:**

Data were analyzed by means of a 2-way ANCOVA with the baseline measurement as the covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. Statistical significance was defined as a 2-sided p-value ≤ 0.05.

RESULTS:

▸ **Treatment group comparability:**

• **Demographics:**

Pre-treatment mean age, and weight as well as the distribution of sex, and race were comparable among the treatment groups.

• **Disease severity:**

Mean pre-treatment sitDBP was not significantly different in the continuously moexipril-treated vs the placebo withdrawn group.

▸ **Antihypertensive effect in *Pre-withdrawal* phase:**

Since randomization to withdrawal or not was performed early in the study, one needs to evaluate whether the group which was ultimately placebo-withdrawn became enriched with moexipril responders (which could plausibly result from a greater number of dropouts secondary to moexipril nonresponsiveness) [see justification for this concern under "Comments" on page 22]. The following table presents evidence against any appreciable group differences in response to moexipril among completers of the pre-withdrawal phase:

Table 7:

Mean trough sitting Diastolic BP (mm Hg) before, and after moexipril exposure (study 643)

Time of observation	Treatment group			
	moex 7.5 mg/d & randomized to withdrawal	*moex 7.5 mg/d & randomized to no withdrawal*	*moex 15 mg/d & randomized to withdrawal*	*moex 15 mg/d & randomized to no withdrawal*
End of placebo baseline	**100.1**	**100.7**	**99.7**	**100.4**
end of week 12 of moexipril-treated phase	**91.5**	**89.5**	**92.3**	**89.1**

[source: modification of table 8, pg 75, vol 134]

▸ **Antihypertensive effect in *Pre-withdrawal* phase** [continued]:

After pooling data from the groups ultimately withdrawn from a given moexipril dose, and data from those not withdrawn, the BP changes (relative to baseline placebo treatment), were as follows:

Table 8:

Mean change from pre-treatment trough SITTING BP [systolic/diastolic], immediately prior to withdrawal, in mm Hg (baseline-corrected):

			moexipril dose (mg/d)				
trial	analysis	N/arm	3.75	7.5	15	30	60
643	12 wk ITT (pre-withdrawal)	93-97	--	-8.3/-8.5	-10.0/-10.3	--	--

[source: modification of tables h & k, pgs 77 & 84, vol 134]

The data pools the groups ultimately withdrawn vs not withdrawn from a given moexipril dose. Statistical significance was not reported. Standard errors ranged from 0.88-2.02. Trough= 22-26 hours post-dose; wk =week.

Study 643

▸ **Antihypertensive effect in *Post-withdrawal* phase:**

The post-withdrawal BP difference between patients withdrawn vs not withdrawn from moexipril are shown below:

Table 9:

Difference between groups (patients withdrawn vs not withdrawn) in mean trough SITTING BP at various times after moexipril withdrawal from one group (corrected for differences manifest at the start of withdrawal) [study 643]

			Daily Moexipril Dose				
trial	analysis	N/arm	3.75 mg	7.5 mg	15 mg	30 mg	60 mg
643	2 wks post withdrawal ITT	46-48	--	-0.9/-3.6*	-4.0/-3.5*	--	--
643	4 wks post withdrawal ITT	45-46	--	-2.1/-3.6*	-5.3/-3.5*	--	--
643	6 wks post withdrawal ITT	42-43	--	-3.1/-4.3*	-2.3/-2.7*	--	--
643	8 wks post withdrawal ITT	42-42	--	-4.6*/-4.6*	-2.1/-1.1	--	--
643	10 wks post withdrawal ITT	40-42	--	-2.8/-5.9*	-4.9/-1.4	--	--
643	12 wks post withdrawal ITT	39-41	--	+0.4/-2.8	-7.7/-1.8*	--	--
643	Endpoint	46-48	--	-2.6/-4.5*	-11.4*/4.7*	--	--

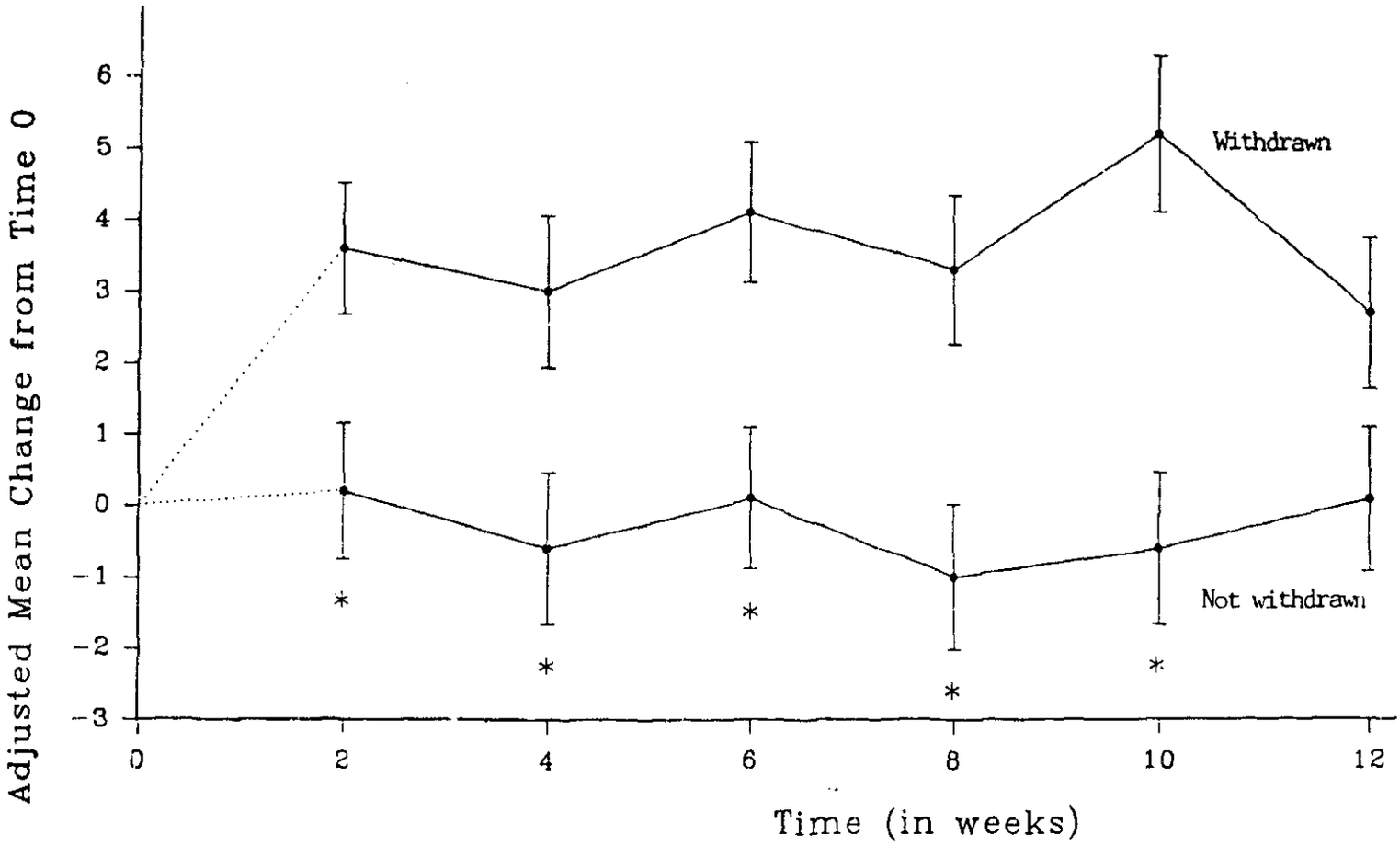
[source: modification of table from attachment 2, submission dated 3/19/93]

Shown are differences (mm Hg) in systolic/diastolic BP in continuously moexipril-treated patients vs placebo-withdrawn patients, at various times after drug withdrawal from the one group (corrected for differences manifest at the start of withdrawal). Negative signs denote where mean post-withdrawal BPs were lower in the continuously moexipril-treated group. Significant differences between groups are denoted by asterisks ($p \leq 0.05$). Standard errors ranged from 0.90-2.19. The "endpoint" analysis carried forward the last nonmissing double-blind data and excluded only patients lacking all double-blind data. Trough= 22-26 hours post-dose; wks =weeks; ITT = intent to treat.

▸ **Antihypertensive effect in *Post-withdrawal* phase** (continued):

Figure 1:

Mean *change* in trough sitting DBP following withdrawal of **7.5 mg/d** moexipril:



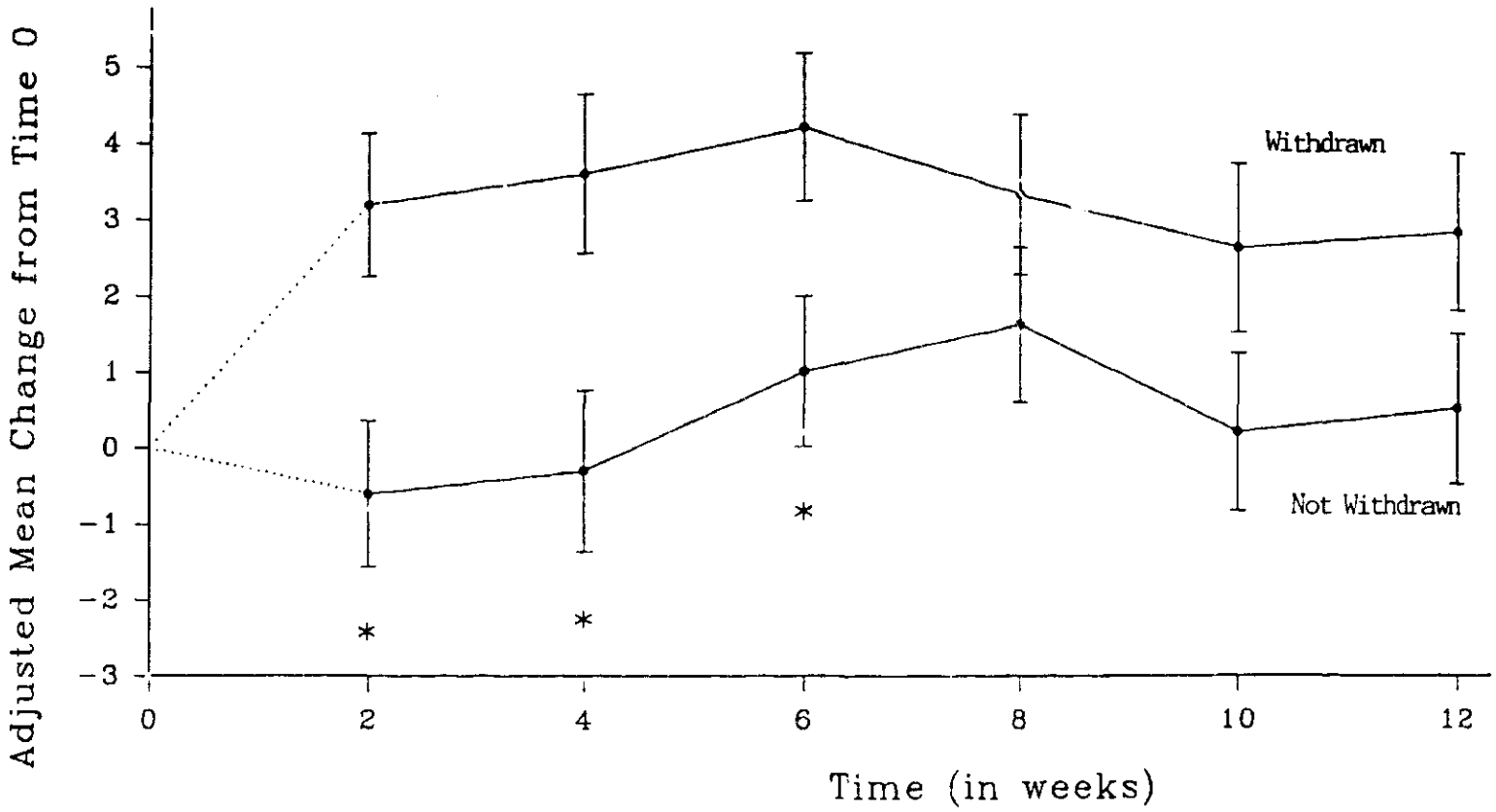
[source: modified photocopy of fig. 1, attachment 3 of submission dated 3/19/93]

At time zero (the start of the withdrawal period), group means were identical. Asterisks denote significant differences between-groups ($p \leq 0.05$). The analysis excluded patients with missing data. Trough measurements were obtained 22-26 hours postdose.

▸ **Antihypertensive effect in *Post-withdrawal* phase** (continued):

Figure 2:

Mean *change* in trough sitting DBP following withdrawal of **15 mg/d** moexipril:



[source: modified photocopy of fig 2, attachment 3 of submission dated 3/19/93]

At time zero (the start of the withdrawal period), although only a nonsignificant difference between groups (1.3 mm Hg) was observed, the analysis accounted for this. Asterisks denote significant differences between-groups ($p \leq 0.05$). Patients with missing data were excluded. Trough measurements were obtained 22-26 hours postdose.

Study 643

▸ **Rebound phenomena:**

The evidence against clinically significant mean rebound tachycardia is as follows:

Table 10:

Mean sitting Heartrate (bpm) prior to treatment, and after moexipril withdrawal (study 643)

Time of observation	*withdrawn from moexipril 7.5 mg/d*	*withdrawn from moexipril 15 mg/d*
End of placebo baseline	71.7	70.3
2 weeks after moex withdrawal	72.7	73.4
4 weeks after moex withdrawal	72.8	75.3
12 weeks after moex withdrawal	72.3	72.5

[source: modification of table 13.4, vol 135, page 153]

The evidence against mean rebound hypertension is as follows:

Table 11:

Mean trough sitting Diastolic BP (mm Hg) prior to, and after withdrawal from moexipril (study 643)

Time of observation	*withdrawn from moexipril 7.5 mg/d*	*withdrawn from moexipril 15 mg/d*
End of placebo baseline	100.1	99.7
2 weeks after moex withdrawal	94.7	93.3
4 weeks after moex withdrawal	93.2	93.7
12 weeks after moex withdrawal	91.5	92.3

[source: modification of table 3.6, page 34, vol 135]

Study 643

COMMENTS (study 643):

a. Study 643 provides convincing evidence of the trough (24 hour post-dose) antihypertensive efficacy of moexipril at once daily doses of 7.5 and 15 mg. During the post-withdrawal phase, statistically significantly lower diastolic BPs were generally observed in continuously drug-treated patients (relative to placebo withdrawn patients) and directionally similar trends were observed with systolic BP.

b. As is always the case with a withdrawal design, it can be argued that the apparent evidence of drug activity may be artefactual, i.e. arising as a result of nothing more than rebound worsening upon drug withdrawal. However, the mean trough sitting diastolic BP data before and after moexipril withdrawal do not support such an argument since they convey no suggestion of rebound hypertension.

c. Although in the main analysis (which excluded patients with missing data) the trough anti-hypertensive activity in the 15 mg/d moexipril group appeared to diminish between 8 and 12 weeks post-withdrawal, this is plausibly an artefact resulting from the means of handling of missing data. When one looks at the 12 week data it is evident that the "endpoint" analysis (which carried foward the last nonmissing data), in contrast to the main analysis, demonstrated significant drug efficacy. This suggests that drug effect was underestimated by the main analysis on the basis of exclusion of a disproportionately greater number of nonresponders from the placebo withdrawn group (which is certainly plausible given the evidence from other studies that this drug is differentiable from placebo).

d. As judged by the mean sitting heartrate data before and after moexipril withdrawal, there was no clinically significant rebound tachycardia after discontinuation of moexipril therapy.

e. Patients were not re-randomized at the end of the moexipril-treated period and thus differential dropout rates could have theoretically resulted in an imbalanced distribution of moexipril-responsive subjects among the groups which entered the withdrawal phase. In such a case, the extent of moexipril effect (as inferred by the post-withdrawal BP difference in the withdrawn vs continuously treated groups) may have been overestimated[1]. However, this does not appear to have been the scenario since there is evidence against any appreciably group difference in antihypertensive response to moexipril during the pre-withdrawal phase.

[1] if the group ...ich was ultimately placebo-withdrawn had a substantially larger proportion of dropouts due to moexipril nonresponsiveness, then at the time of withdrawal this sample would have been enriched with responders (e.g. nonblack patients or users (albeit in violation of protocol) of concomitant diuretic therapies). With such enrichment the mean elevation in BP in the placebo group (post-withdrawal) may have plausibly been higher than it would have been in a less enriched group. The inference drawn from the dissimilar group which was continuously moexipril-treated would then have then been biased towards overestimation of antihypertensive efficacy.

7.1.4 Antihypertensive effect in the elderly (study 640)!

SUMMARY:

This placebo-controlled (and positive-controlled), double-blind, parallel-group study randomized 201 elderly subjects (patients aged 65-80, with mild-to-moderate essential hypertension) to receive fixed, once-daily oral doses of placebo, moexipril (7.5, or 15 mg/d), or HCTZ (25 mg) for 8 weeks, subsequent to a 1-4 week placebo run-in period. The objective was to assess the change from pre-treatment sitDBP at the interdosing interval after 8 weeks.

PROTOCOL:

▸ **Enrollment criteria:**

Inclusion and exclusion criteria were not substantially different from those described above under study 642.

▸ **Treatment regimen:**

Following a 1-4 week placebo run-in, subjects were randomized to fixed, once-daily oral doses of placebo, moexipril (7.5, or 15 mg/d) in capsule (Schwarz Pharma) formulation, or HCTZ (25 mg) for 8 weeks. Patients were not instructed to ~~fast~~ prior to drug ingestion.

▸ **Endpoints:**

The primary efficacy endpoint was the change from pre-treatment (end of placebo run-in) sitDBP after 8 weeks. Trough BPs were measured in triplicate at 22-26 hours post-dose.

▸ **Statistical procedures:**

• **Data set analyzed:**

The results of an intent-to-treat analysis (all randomized subjects who received at least one dose) were presented.

• **Handling of missing data:**

For the main analysis, patients with missing data at a given timepoint were excluded from the mean estimate for that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

• **Analyses performed:**

Data were analyzed by means of a 2-way ANCOVA with the baseline measurement as the covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. Statistical significance was defined as a 2-sided p-value ≤ 0.05.

Study 640

RESULTS:

- **Demographics:**

Pre-treatment mean age, and the distribution of race were comparable among the treatment groups. A somewhat lower proportion of males were randomized to moexipril 7.5 mg vs placebo (69 vs 42%, respectively), and a somewhat higher mean pre-treatment weight was present in the subjects randomized to moexipril 7.5 mg vs. the placebo group (80 vs 73 kg, respectively).

- **Disease severity:**

The severity of pre-treatment sitDBP was comparable among treatment groups (means ranging from 101.6 to 102.5 mm Hg).

- **Antihypertensive effect:**

- **Onset of first-dose effect:**

By 2 hours following a first dose of either 7.5 or 15 mg moexipril, sitDBP was significantly lowered (by 8.5, and 8.9 mm Hg, respectively (placebo-corrected)).

- **Onset of significant trough effect:**

Each of the examined doses (7.5, and 15 mg/d) achieved statistically significant mean trough effects on sitDBP (22-24 hours post-dose) by the second treatment week, and these effects were little changed by week 8 (the last observation point).

Study 640

▸ **Antihypertensive effect** [continued]:

• **Extent of steady-state trough effect**:

Table 12:

Mean mm Hg change in trough *SITTING* BP [systolic/diastolic]) *in elderly patients* (placebo corrected)

trial	*analysis*	*N/arm*	*Daily Moex Dose*				
			3.75 mg	*7.5 mg*	*15 mg*	*30 mg*	*60 mg*
640	2 wk ITT	49-51	--	-6.6*/-5.0*	-9.3*/-5.5*	--	--
"	4 wk ITT	47-50	--	-0.5/-3.7*	-8.8*/-6.3*	--	--
"	6 wk ITT	46-50	--	-2.4/-4.9*	-7.0*/-6.7*	--	--
"	8 wk ITT	46-49	--	-1.3/-5.0*	-6.1/-6.2*	--	--
"	endpoint ITT	49-51	--	-1.0/-4.8*	-5.8/-6.2*	--	--

[source: modification of table in attachment 2, addendum dated 3/19/93]

Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). The data are based on adjusted mean changes from pre-treatment baseline. Standard errors ranged from 0.96 to 2.47. Trough= 22-24 hours post-dose; ITT=intent to treat; wk = week. Patients with missing data at a given timepoint were excluded, except for the endpoint analysis in which the last nonmissing double-blind data were carried forward.

Study 640

- **Antihypertensive effect** [continued]:

  - **Ratio of trough-to-peak effect:**

Table 13:

Trough-peak (T-P) ratio of mean effects on sitDBP (in mm Hg) in elderly patients after 4 weeks

	Moexipril dose (mg/d)	
metric	***7.5***	***15***
time of peak effect (hr)	**3**	**3**
mean change in peak BP	**-6.7**	**-7.7**
mean change in trough BP	**-3.7**	**-6.3**
mean T-P ratio	**0.55**	**0.82**

[source: modification of table g, pg 66, vol 140]

Effects are placebo-corrected mean changes from pre-treatment BP (expressed in mm Hg). Peak= the largest mean change observed with 4 once-hourly observations after dosing. Trough= 22-24 hours post-dose.

COMMENTS (study 640):

1. The results of this large and well-controlled study provide convincing evidence that moexipril monotherapy (administered as 7.5-15 mg/d once-daily for 2-8 weeks) produces a statistically significant (and clinically important) reduction in mean sitting diastolic BP at 24 hours post-dose in elderly, mild-to-moderate hypertensive subjects.

2. The available data (at 4 weeks) suggest that in elderly patients the trough antihypertensive effect of once-daily moexipril (with doses of 7.5-15 mg/d) is not obtained at the price of excessive mean diastolic hypotensive effect at peak. However, these data do not exclude the possibility of extreme peak effects among outliers in this trial. Additionally, caution should be exercised in extrapolating these peak-trough data to the proposed-for-market formulation [see conclusions, page 49]).

3. The imbalanced distribution of sex (a lower proportion of males were randomized to moexipril 7.5 mg than to placebo) was not plausibly a source of bias towards overestimation of drug effect [if anything, given the results of the pooled analysis of response in demographic subsets[2], this may have introduced the opposite bias].

[2]this provided some evidence that mean antihypertensive response to moexipril may tend to be greater in males [see section 7.2 of this review].

7.1.6 Antihypertensive effect of moexipril (study 651)!

SUMMARY:

This placebo-controlled, double-blind, parallel-group study randomized 51 subjects (mild-to-moderate essential hypertension patients of both sexes) to receive fixed, once-daily oral capsule doses of placebo or moexipril (7.5, or 15 mg/d) for 8 weeks, subsequent to a 4 week placebo-exposed pre-treatment period. The objective was to assess the change from pre-treatment BP (via ambulatory BP monitoring (ABPM) and office measurements) after 8 weeks.

PROTOCOL:

▸ **Enrollment criteria:**

Inclusion and exclusion criteria were not substantially different from those described above under study 642. Subjects with sitDBP between 95 and 114 mm Hg and ambulatory diastolic BP measurements ≥ 90 mm Hg for at least 40% of the day at the end of the placebo run-in were qualified for randomization.

▸ **Treatment regimen:**

Subsequent to a 4 week placebo run-in period, subjects underwent double-blind randomization to placebo or moexipril given as a fixed 7.5 or 15 mg dose in once-daily capsule administrations (Schwarz Pharma formulation) for 8 weeks. Patients were not instructed to fast prior to drug ingestion.

▸ **Endpoints:**

The primary efficacy endpoint was the change from baseline (end of placebo run-in) mean ambulatory BP (average obtained during a 24 hour period at the end of week 8). Serial observations of office BP were also obtained (means of 3 replicate measures). Office measurements involved conventional sphygmomanometer-based auscultatory methods, and ABPM procedures utilized Suntech Accutracker II equipment.

The ABPM device monitored BP every 15 minutes during the day and every 30 minutes in the evening. A patient's 24-hour ABPM data were considered valid if 75% of the readings were interpretable (without continuous lapses in data which exceeded 2 hours), and the agreement with sphygmomanometer measures was within 10 mm Hg.

▸ **Statistical procedures:**

• **Data set analyzed:**

The results of an intent-to-treat analysis (all randomized subjects who received at least one dose) were presented.

Study 651

• **Handling of missing data**:

For the main analysis, patients with missing data at a given timepoint were excluded from the mean estimate for that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

• **Analyses performed**:

Data were analyzed by means of a 2-way ANCOVA with the baseline measurement as the covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. Statistical significance was defined as a 2-sided p-value ≤ 0.05.

RESULTS:

▸ **Treatment group comparability**:

• **Demographics**:

Pre-treatment mean age, and weight as well as the distribution of sex and race were comparable among the treatment groups.

• **Disease severity**:

The severity of pre-treatment hypertension was comparable among treatment groups (mean sitDBP ranging from 103-106).

▸ **Antihypertensive effect**:

• **ABPM results**:

Table 14:

Mean change in AMBULATORY BP [systolic/diastolic] (average over 24 hours), in mm Hg (placebo-corrected)

			moexipril dose (mg/d)	
trial	*analysis*	*n/arm*	*7.5*	*15*
651	**wk 8 ABP, ITT**	**14-16**	**-6.5/-2.1**	**-12.9*/-7.4***

[source: modification of tables e & i, pgs 43 & 62, vol 131]

Significant differences from placebo are denoted by asterisks (p≤ 0.05). The data are based on ANCOVA-adjusted mean changes from pre-treatment baseline. Standard errors ranged from 1.60 to 3.01. ABP= ambulatory BP. ITT=intent to treat; wk =week.

Study 651

▸ **Antihypertensive effect:**

• **Office BP results:**

Table 15:

Mean change in trough *SITTING* BP [systolic/diastolic] in mm Hg (placebo-corrected)

				Daily	*Moex*	*Dose*	
trial	*analysis*	*N/arm*	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*	*60 mg*
651	6 wk sit ITT	15-16	--	-0.6/-5.7	-10.7/-8.7	--	--
"	8 wk sit ITT	15-16	--	(+5.0/-8.3*	-5.8/-12.2	--	--

[source: modification of tables 13.3 & 14.3, pgs 107 & 111, vol 132]

Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). The data are based on ANCOVA-adjusted mean changes from pre-treatment baseline. Standard errors ranged from 1.74-3.54. Trough= 24 hours post-dose; sit= sitting posture, ITT=intent to treat; wk =week.

COMMENTS (study 651):

1. This small study provides some supportive evidence of the antihypertensive efficacy of moexipril monotherapy (administered as 7.5-15 mg/d once-daily for 8 weeks). With respect to the office sitDBP determinations, moexipril 7.5 mg/d was statistically distinguishable from placebo, and there was a tendency towards a numerically greater effect of the 15 mg/d dose. Although this study has some contradictory results (the mean systolic BP effect of the lower dose was *hyper*tensive), other larger studies provide adequately conclusive insights into the antihypertensive efficacy of this drug.

7.1.5 Moexipril monotherapy with an alternative formulation (study 623)!

SUMMARY

This placebo-controlled, double-blind, parallel-group study randomized 321 subjects (mild-to-moderate essential hypertension patients of both sexes) to receive fixed, once-daily oral doses of placebo or moexipril (7.5, 15, 30, or 60 mg/d) for 6 weeks subsequent to a placebo-exposed pre-treatment period. The objective was to assess the relationship between dose and the change from pre-treatment BP 24 hours post-dosing after 6 weeks.

This study utilized a moexipril formulation which substantially differed from that used in the other efficacy studies (with the exception of twice-daily dosing study 622). There was no submitted evidence of its bioequivalence, relative to the formulation used in these other studies. In addition, this formulation was substantially modified[3] during the study (after the first 40 patients), and there was no submitted evidence of bioequivalence with the unmodified form.

PROTOCOL

▸ Enrollment criteria

Inclusion and exclusion criteria were not substantially different from those described above under study 642.

▸ Treatment regimen

Qualified subjects underwent double-blind randomization to placebo or moexipril given as a fixed 7.5, 15, 30, or 60 mg dose in once-daily capsule administrations for 6 weeks. Patients were not instructed to fast prior to drug ingestion.

[3]with respect to proportion of inactive ingredients and total capsule weight.

Study 623

▸ **Endpoints**

The primary efficacy endpoint was the change from baseline (end of placebo run-in) mean supine diastolic BP (supDBP) at 24 hours post-dose after 6 weeks of double-blind therapy. Only a single supine BP measurement was used at each observation point.

▸ **Statistical procedures**

• **Data set analyzed**

The results of an intent-to-treat analysis (all randomized subjects who received at least one dose) were presented.

• **Handling of missing data**

For the main analysis, patients with missing data at a given timepoint were excluded from the mean estimate for that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

• **Analyses performed**

Data were analyzed by means of a 2-way ANCOVA with the baseline measurement as a covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. No statistical adjustment was made for testing of multiple response variables. Statistical significance was defined as a 2-sided p-value ≤ 0.05.

RESULTS

▸ **Treatment group comparability**

• **Demographics**

Pre-treatment mean age, height, and weight as well as the distribution of sex, and race were comparable among the treatment groups.

• **Disease severity**

The severity of pre-treatment hypertension was comparable among treatment groups.

▸ **Antihypertensive effect:**

• **Onset of first-dose effect:**

By 4 hours following a first moexipril dose (at 15, 30, and 60 mg), supine BP was significantly lowered, relative to the effect of placebo. For supine systolic and diastolic BP the largest mean antihypertensive effect at 4 hours was -12.2 and -7.2 mm Hg, respectively (placebo-corrected).

• **Onset of significant trough effect:**

Each of the examined moexipril doses achieved statistically significant trough effects on SupDBP by the fourth treatment week, and these effects were essentially unchanged at week 6 (the last observation point).

• **Extent of steady-state trough effect:**

Table 16:

Mean change in trough SUPINE BP [systolic/diastolic], in mm Hg (placebo-corrected)

				Daily Moex Dose			
trial	*analysis*	*N/arm*	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*	*60 mg*
623	6 wk ITT	53-60	--	-6.4*/-2.7	-8.8*/-4.4*	-10.1*/-6.0*	-6.9*/-4.2*
"	endpoint ITT	60-65	--	-4.6/-2.4	-8.0*/-4.1*	-10.0*/-6.2*	-7.1*/-3.7*

[source: modification of table in attachment 2, addendum dated 3/19/93]

Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). The data are based on adjusted mean changes from pre-treatment baseline. Standard errors ranged from 1.1 to 2.15. Trough= 24 hours post-dose; ITT=intent to treat; wk = week.

• **Dose-response**

No significant linear dose-response was observed, with respect to the change from pre-treatment supDBP at 24 hour post-dose after 6 weeks of therapy.

Study 623

▸ **Antihypertensive effect** (continued):

• **Ratio of trough-to-peak effect:**

Table 17:

Trough-to-peak (T-P) ratio of mean effects on SupDBP after 4 weeks (study 623)

	Moexipril dose (mg/d)			
metric	*7.5*	*15*	*30*	*60*
time of peak effect (hr)	**6**	**6**	**6**	**6**
mean change in peak BP (mm Hg)	**-5.9**	**-6.7**	**-10.6**	**-9.3**
mean change in trough BP (mm Hg)	**-3.7**	**-6.1**	**-7.6**	**-5.6**
mean T-P ratio	**0.63**	**0.91**	**0.72**	**0.60**

[source: modification of table g, pg 43, vol 152]

Unlike the previous table, these are 4 week data. Effects are placebo-corrected mean changes from pre-treatment BP (expressed in mm Hg). Peak= the mean change observed at 6 hours post-dose. Trough= 24 hours post-dose; SuD=supine diastolic.

Study 623

COMMENTS (study 623):

a. From the efficacy vantage point this reviewer considers the approveability of moexipril to by no means rest on the results of this study. Thus, although the study utilized a moexipril formulation which substantially differed from that used in other efficacy studies, there is little impetus for requesting supportive bioequivalence data in order to remove the ambiguities involved in interpreting this study.

b. For whatever it is worth, this study probably provides sound evidence [assuming that mean responsiveness was not skewed by excessive responses in the small fraction who received the first version of the drug formulation[4]] that *an alternative formulation of moexipril of unknown bioequivalence* (given as 15-60 mg/d once-daily monotherapy for 6 weeks) produced a clinically significant reduction in supine diastolic BP at trough (24 hours post-dose). This effect appeared to be statistically distinguishable from that of placebo. This study also suggested that 7.5 mg/d of *this formulation* of moexipril was efficacious once-daily monotherapy. A statistically (and clinically) significant mean reduction in supine systolic BP was observed with this dose, as well as a directionally similar trend for supine diastolic BP. The benefit of increasing the dose of a moexipril formulation of undetermined bioequivalence from 30 to 60 mg was not established by this study. The trough antihypertensive efficacy of *this moexipril formulation* (dosed at 7.5-60 mg/d) was not obtained at the price of clinically excessive diastolic hypotensive effect at peak, as indicated by the 4 week mean data (although caution must be exercised in extrapolating these peak-trough data to the proposed-for-market formulation [see conclusions, page 49]).

c. Although only one BP measure was used during each patient observation, this would only be expected to increase the variance of the data, and not to introduce a bias.

[4]an assumption which can be readily validated if the division ultimately attaches a greater regulatory importance to this study than does this reviewer.

7.1.7 Moexipril added to hydrochlorothiazide background therapy (study 644)!

SUMMARY:

This placebo-controlled, double-blind, parallel-group study randomized 200 subjects (patients who remained mildly-to-moderately hypertensive despite HCTZ monotherapy) to receive fixed, once-daily capsule doses of placebo, or moexipril (3.75, 7.5, or 15 mg) in addition to the HCTZ background therapy for 8 weeks. The objective was to assess the change from baseline (end of HCTZ monotherapy run-in) sitDBP at the interdosing interval after 8 weeks.

PROTOCOL:

▸ **Enrollment criteria:**

Inclusion and exclusion criteria were not substantially different from those described above under study 642.

▸ **Treatment regimen:**

Following a 2-4 week long, open-label, HCTZ monotherapy run-in period (utilizing a fixed 25 mg once-daily dose), patients were randomized to receive (in addition to the HCTZ background) fixed, once-daily capsule doses of placebo, or moexipril (3.75, 7.5, or 15 mg) in capsule (Schwarz Pharma formulation) for 8 weeks. Patients were not instructed to fast prior to drug ingestion.

▸ **Endpoints:**

The primary efficacy endpoint was the change from baseline (end of HCTZ monotherapy run-in) sitDBP at the interdosing interval after 8 weeks. Trough BPs were measured in triplicate at 22-26 hours post-dose.

▸ **Statistical procedures:**

• **Data set analyzed:**

The results of an intent-to-treat analysis (all randomized subjects who received ≥1 dose) were presented.

• **Handling of missing data:**

For the main analysis, patients with missing data at a given timepoint were excluded from the mean estimate for that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

Study 644

• **Analyses performed**:

Data were analyzed by means of a 2-way ANCOVA with the baseline measurement as the covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. Dose responses were evaluated by fitting linear regression models containing linear and quadratic terms. Statistical significance was defined as a 2-sided p-value ≤ 0.05.

RESULTS:

▸ **Treatment group comparability**:

• **Demographics**:

Pretreatment mean age, and weight as well as the distribution of sex were comparable among the treatment groups. There was only one black patient in the study sample.

• **Disease severity**:

The severity of baseline (end of HCTZ monotherapy run-in) sitDBP was comparable among treatment groups (means ranging from 100.9 to 102.4 mm Hg).

Study 644

- **Antihypertensive effect:**

  - **Extent of trough effect:**

Table 18:

Mean change (mm Hg) in baseline trough *SITTING BP* [systolic/diastolic] *in the presence of HCTZ* (placebo-corrected)

			Daily Moex Dose				
trial	*analysis*	*N/arm*	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*	*60 mg*
644	6 wk sit ITT	48-49	-6.2*/-3.3*	-11.9*/-5.3*	-12.8*/-5.2*	--	--
"	8 wk sit ITT	46-50	-10.3*/-3.6*	-11.1*/-4.0*	-11.1*/-4.6*	--	--
"	endpoint ITT	49-52	-10.3*/-3.8*	-11.4*/-4.2*	-11.1*/-4.3*	--	--

[source: modification of table in attachment 2, addendum dated 3/19/93]

The data are based on adjusted mean changes from baseline (the end of the HCTZ monotherapy run-in). Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). Standard errors ranged from 0.91 to 1.93. Trough= 22-24 hours post-dose; ITT=intent to treat; wk = week. Patients with missing data at a given timepoint were excluded, except for the endpoint analysis in which the last nonmissing double-blind data were carried forward.

- **Dose-response:**

At weeks 4 and 6, the trough antihypertensive response to moexipril (when added to HCTZ) demonstrated a significant linear relationship to dose ($p \leq 0.02$), but no dose-response was apparent at 8 weeks (at which time 3.75 mg moexipril had effects similar to those of the higher doses).

COMMENTS (study 644):

1. The 3.75 mg once-daily moexipril dose was an effective antihypertensive adjunct in subjects receiving 25 mg/d HCTZ. This contrasts with the ineffectiveness of this moexipril dose when given as monotherapy in study 638. However, the evidence for antihypertensive synergy between 25 mg/d HCTZ and moexipril is equivocal. Although the diuretic may have potentiated the effect of the ACE inhibitor (an effect not inconsistent with ACE inhibitor pharmacology), population differences could have plausibly accounted for the differential responses (the current study, by excluding diuretic nonresponders, plausibly selected for ACE inhibitor responders). Although systolic BP responses to moexipril were higher in this study than they were for comparable monotherapy doses in other studies, diastolic responses to the higher moexipril doses in this study fell approximately in the middle of the range of diastolic responses in the monotherapy studies.

7.1.8 Twice-daily therapy (study 622)!

SUMMARY:

This placebo-controlled, double-blind, parallel-group study randomized 203 subjects (patients with mild-to-moderate essential hypertension) to receive initially fixed oral doses of placebo or moexipril (0[5], 7.5, 15, or 30 mg/d) in twice daily, equally divided dose administrations for 1 week. Forced up-titration then ensued to a double-dose for 5 additional weeks followed by forced down-titration to the original dose for 2 weeks. The objective was to assess the dose-antihypertensive response relationship.

This study utilized a moexipril formulation which substantially differed from that used in the other efficacy studies (with the exception of study 623). There was no submitted evidence of its bioequivalence, relative to the formulation used in these other studies.

PROTOCOL:

- **Enrollment criteria:**

Enrollment criteria did not substantially differ from those described above under study 642.

- **Treatment regimen:**

After a 2 week placebo run-in period, patients were randomized to receive initially fixed oral doses of placebo or moexipril (0, 7.5, 15, or 30 mg/d) in twice daily, equally divided dose capsule administrations for 1 week. Forced up-titration then ensued to a double-dose (7.5[6], 15, 30, or 60 mg/d), administered in the same manner for 5 weeks, followed by forced down-titration to the original dose for 2 weeks. Patients were not instructed to fast prior to drug ingestion.

- **Endpoints:**

The primary efficacy endpoint was the change from pre-treatment mean supDBP at the interdosing interval after 6 weeks. A single trough supine BP was measured without replication at 12 hours post-dose.

- **Statistical procedures:**

  - **Data set analyzed:**

The results of an intent-to-treat analysis (all randomized subjects who received ≥1 dose) were presented.

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[5]this group initially received a placebo because the intended lowest dosage form of moexipril had stability problems.

[6]the moexipril-randomized group which initially received 0 mg/d was up-titrated to 7.5 mg/d.

Study 622

• **Handling of missing data**:

For the main analysis patients with missing data at a given timepoint were excluded from the mean estimate for that timepoint. Alternatively, the "endpoint" analysis carried forward the last nonmissing double-blind data to the end of the study and excluded only patients lacking all double-blind data.

• **Analyses performed**:

Data were analyzed by means of a 2-way ANCOVA with the baseline measurement as the covariate. Comparisons between placebo and moexipril were conducted using the Fisher's least significant difference test. Dose responses were evaluated by fitting linear regression models containing linear and quadratic terms. Statistical significance was defined as a 2-sided p-value ≤ 0.05.

RESULTS:

• **Demographics**:

Pretreatment mean age, and weight as well as the distribution of sex and race were comparable among the treatment groups (ranging from 99.7 to 102 mm Hg).

• **Disease severity**:

Mean pre-treatment supDBP was comparable among treatment groups (ranging from 99.7 to 102 mm Hg).

Study 622

▸ **Antihypertensive effect:**

• **Extent of effect 12 hours post-dose:**

Table 19:

Mean change in *SUPINE* BP [systolic/diastolic], in mm Hg, *12 hour post-dose* [b.i.d. dosing] (placebo-corrected)

trial	*analysis*	*N/arm*	--	*Daily Moex Dose* 3.75 mg b.i.d.	7.5 mg b.i.d.	15 mg b.i.d.	30 mg b.i.d.
622	4 wk b.i.d. ITT	35-38	--	-1.0/-1.7	-7.0*/-5.3*	-13.0*/-4.1*	-9.1*/-6.7*
"	6 wk b.i.d. ITT	34-37	--	-1.5/-0.6	-5.1/-2.0	-10.4*/-0.3	-4.6/-3.5
"	endpoint b.i.d. ITT	38-40	--	-1.0/-1.4	-6.1/-2.9	-11.4*/-2.3	-5.3/-5.2

[source: modification of table in attachment 2, addendum dated 3/19/93]

Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). The data are based on adjusted mean changes from pre-treatment baseline. Standard errors ranged from 1.3 to 2.6. ITT=intent to treat. Patients with missing data at a given timepoint were excluded, except for the endpoint analysis in which the last nonmissing double-blind data were carried forward.

Study 622

▸ **Antihypertensive effect:**

• **Dose-response:**

A statistically significantly linear dose response ($p < 0.05$) was observed among the four moexipril doses at the interdosing interval after 1 and 3 weeks of the uptitrated doses.

COMMENTS (study 622):

1. In this study, moexipril at 7.5-30 mg b.i.d. was statistically superior to placebo in reducing supine diastolic BP *12 hours post-dose* after 4 treatment weeks.

2. When evaluating this putatively once-a-day drug, one could find disconcerting the evidence of nonsuperiority to placebo at 12 hours post-dose on week 6. However, it is plausible that the finding is in large part attributable to the study's design and method of analysis. For example, the main analysis overestimated placebo response by excluding a proportionally larger fraction of placebo patients on the basis of dropping out for inefficacy (10% of placebo-treated vs 3% of moexipril-treated patients[7] [table 1.2, pg 9, vol 163]). The mean response to placebo in the main analysis was not only large, but larger at week 6 than at week 4 (7.8 mm Hg vs 6.3 mean reduction in supDBP, respectively). In addition, the variance in this experiment was not optimally reduced insofar as only one BP measure was utilized per patient observation. Given all of this, the 6 week results of study 622 should not be construed to stand in stark contrast to the bulk of the other efficacy data.

[7]all moexipril doses thus manifested numerically larger responses in the endpoint (carryover) analysis than they did in the main analysis at week 6.

7.2 Efficacy in Demographic Subgroups:

The pooled dataset of once-daily, placebo-controlled monotherapy studies was utilized to evaluate the role of demographic covariates in determining antihypertensive responsiveness.

Table 20:

Placebo-corrected mean change from baseline sitting Diastolic BP (mm Hg) at trough, according to demographic subgroup

		moexipril dose (mg/d)				
Subgroup	measure	3.75	7.5	15	30	60
blacks	n/arm	3	46	40	30	22
	BP change	-16.0/-7.9	-3.1/0.5	-6.4/-2.4	-9.5/-2.6	-4.2/-1.9
nonblacks	n/arm	46	223	231	77	37
	BP change	-3.2/-1.3	-4.5*/-3.8*	-8.5*/-4.9*	-9.7*/-6.2*	-8.0*/-4.0*
males	n/arm	29	160	171	77	41
	BP change	-4.5/-2.4	-5.5*/2.9*	-9.6*/-5.4*	-9.3*/-5.8*	-9.2*/-4.7*
females	n/arm	20	110	97	30	19
	BP change	-3.8/-0.3	-2.3/-3.0	-5.5/-2.6	-9.1/-3.6	-1.6/-0.9
< 65 yrs	n/arm	43	177	170	79	47
	BP change	-3.8/-2.1	-4.3*/-3.0*	-8.3*/-4.1*	-11.2*/-6.0*	-7.3*/-3.7*
≧ 65 yrs	n/arm	6	93	101	28	13
	BP change	-5.2/0.3	-4.0/-3.2*	-7.9*/-5.0*	-3.3/-2.9	-3.2/-2.8

[source: modification of tables in attachment 5, 3/19/93; attachment 2, 6/22/93; attachment 13, 4/26/93, & attachment 4, 7/12/93]

Asterisks denote statistically significant differences from placebo (p≤0.05). The dataset included studies 623, 638, 640, 642, 643, and 651. Trough measures were obtained approximately 24 hours post-dose. Means were adjusted by analysis of covariance. Missing data were carried forward to the final week of each study (which ranged from 6 to 24 weeks in duration).

COMMENTS- Efficacy in Demographic Subgroups:

1. Since the size of the sample exposed to the highest moexipril dose was quite small in some demographic subgroups, study 623 (one of the few sources of these 60 mg/d data) was not excluded from the pooled dataset despite uncertainties about the bioequivalence of the formulation used in that study.

2. The pooled analysis generally reveals evidence of a reduced moexipril responsiveness among black patients, relative to that of nonblack patients. Although the point estimates for the response of the few black patients exposed to 3.75 mg/d moexipril may appear to contradict this conclusion, they are highly uncertain (e.g. the coefficient of variation for diastolic response was 116%). Among blacks, no moexipril dose manifested a mean anti-hypertensive effect which was statistically differentiable from that of placebo (for either systolic or diastolic BP), although directional mean trends towards efficacy were observed in blacks treated with doses ≥15 mg/d.

3. For each of the moexipril doses studied, female patients tended to have smaller mean reductions in BP than did males, abeit for a minority of the dose levels the differences were clinically trivial.

4. Moexipril responsiveness was not clearly demonstrated to be a function of age. Although the mean response to high doses (30-60 mg/d) among older patients (≥ 65 years) was numerically lesser than that manifest among the younger ones, these mean estimates are of questionable certainty (for older patients the sample sizes were 13 and 28 in the 30 and 60 mg/d moexipril groups, respectively).

7.3 Uncontrolled clinical trials:

Several uncontrolled clinical trials were conducted (studies 638 OL, 640 OL, 624, and 618), and the results of some of these shed insights into the longterm persistence of moexipril's antihypertensive efficacy.

7.3.1 Longterm antihypertensive efficacy (638 OL)!

This was an uncontrolled, 2 year, open-label extension of study 638. Hypertensive patients initially received moexipril 7.5 mg once-daily, and were titrated to 15 mg as needed for BP control. HCTZ 12.5 mg/d was then added if supDBP was ≥ 90 mm Hg despite moexipril monotherapy. When HCTZ was added, the moexipril dose was halved, and only doubled again if supDBP was ≥ 90 mm Hg.

Sixteen percent of the subjects dropped out because of declared inefficacy, although these largely represented initial *non*responders as opposed to initial responders who subsequently manifested a loss of response. After stabilizing the mean doses of moexipril (at approximately 20 mg/d) and HCTZ by week 20, those remaining in the trial maintained a relatively stable mean sitting diastolic BP (88-94 mmg Hg) over the subsequent 19 months [source: addendum 7/12/93].

7.3.2 Longterm antihypertensive efficacy in the elderly (640 OL)!

This was an uncontrolled, 2 year, open-label extension of study 640. Elderly hypertensive patients initially received moexipril 7.5 mg once-daily, and were titrated to 15 mg as needed for BP control. HCTZ 25 mg/d was then added if supDBP was ≥ 90 mm Hg (at which time the moexipril dose was reduced to 7.5 mg/d). The moexipril dose was then increased to 15 mg/d if supDBP remained ≥ 90 mm Hg.

In the first year of the open-label study 8% of the subjects dropped out because of declared inefficacy. After stabilizing the mean moexipril dose at approximately 10 mg/d by week 22 (and with only slightly rising mean doses of HCTZ), those remaining in the trial maintained a relatively stable mean sitting diastolic BP (89-93 mm Hg) over the subsequent 7.5 months [source: addendum dated 7/12/93]. The second year data are pending.

7.3 **Uncontrolled clinical trials** [continued]:

7.3.3 Longterm antihypertensive efficacy (study 624)!

This study was discontinued prematurely (for an unspecified reason) by the previous sponsor of this drug's development This was an uncontrolled, open-label extension of studies 622 and 623. Hypertensive patients received titrated doses of moexipril (from 3.75-120 mg daily), and were allowed to use concomitant antihypertensive drugs if moexipril monotherapy did not achieve a supDBP ≤90 mm Hg. The majority of patients were treated for 3-9 months and 19% received concomitant antihypertensive medications.

Since the study was discontinued early, it does not provide an unambiguous assessment of the stability of BP control over time (individual patients may not have been titrated to effective doses, or may not have been treated long enough for any tolerance phenomena to have developed). It was observed that only 0.6% of the subjects dropped out because of declared inefficacy.

Further information, about the reason for stopping the study and the persistence of moexipril effect, is pending.

7.3.4 Open-label dose titration (study 618)!

This was an uncontrolled, open-label evaluation of titrated moexipril doses (3.75-120 mg daily) in hypertensive patients. This study is of little value because there were important protocol violations, and an early termination for administrative reasons. Mean reductions from pre-treatment supDBP were reported to be 6.8 mm Hg.

8 Conclusions: Efficacy

▸ Overview of Efficacy in all Placebo-controlled monotherapy trials

Table 21:

Placebo-corrected mean change from pre-treatment trough BP [systolic/diastolic], in mm Hg

			Daily Moex Dose				
trial	*anal-ysis*	*N/arm*	*3.75 mg*	*7.5 mg*	*15 mg*	*30 mg*	*60 mg*
638	8 wk ITT	39-48	-0.2/-1.0	-3.4/-2.7	-4.0/-2.8*	-5.0/-3.2*	--
642	12 wk ITT	43-44	--	-4.5/-3.4*	-9.3*/-4.4*	--	--
643[8]	12 wk ITT	39-41	--	0.4/-2.8	-7.7/-1.8*	--	--
640[9]	8 wk ITT	46-49	--	-1.3/-5.0*	-6.1/-6.2*	--	--
651	8 wk ITT	15-16	--	+5.0/-8.3*	-5.8/-12.2	--	--
623[+]	6 wk ITT	53-60	--	-6.4*/2.7	-8.8*/-4.4*	-10.1*/-6.0*	-6.9*/-4.2*
622[+]	4 wk b.i.d. ITT	35-38	--	-1.0/-1.7	-7.0*/-5.3*	-13.0*/-4.1*	-9.1*/-6.7*

[source: modification of the tables presented in the separate sections of this review]

Significant differences from placebo are denoted by asterisks ($p \leq 0.05$). The data are based on adjusted mean changes. Trough is defined as approximately 24 hours post-dose, except in study 622 where it is approx.mately 12 hours post-dose. "ITT" denotes an intent to treat analysis; "wk" denotes the treatment week; b.i.d. denotes twice-daily dosing. Measurements were obtained in eithe. the sitting or supine postures. The double cross-hatch symbol (≠) denotes studies which utilized a formulation of uncertain bioequivalence, relative to the formulation used in the other trials.

[8]shown is the difference between means in withdrawn vs not withdrawn patients, corrected for differences manifest at the start of withdrawal.

[9]elderly patients were studied in this trial.

Conclusions: Efficacy

Pivotal evidence of short-term efficacy:

The pivotal studies reported in this application were study 642, and study 638. These were large, randomized, double-blind, placebo-controlled, parallel-group trials involving patients with mild-to-moderate essential hypertension. In each of these studies:

- Moexipril was administered as 3.75, 7.5, 15, or 30 mg once daily.

- BPs were measured approximately 24 hours after dosing (trough).

- The **trough antihypertensive effect of 7.5, 15, and 30 mg/d moexipril monotherapy was significantly greater than that of placebo** after 2-8 weeks of therapy.

Dose-response:

The data show that **the minimum effective dose of once-a-day moexipril monotherapy is 7.5 mg.** The upper end of the dose-response curve is not well characterized. The data from study 642 did not convincingly distinguish the effectiveness of 15 mg/d from that of 7.5 mg/d moexipril, and the data from study 638 did not convincingly distinguish the effect of 30 mg/d moexipril from that of 15 or 7.5. In the latter study, however, there was a tendency for antihypertensive response to increase monotonically over the 7.5-30 mg dose range.

Onset of acute effect:

In clinical efficacy trials (in which patients were not required to fast prior to drug administration) a first moexipril dose (7.5-60 mg) was demonstrated to induce a significant reduction of BP, relative to the effect of placebo, by 2-4 hours post-administration (studies 623, 642, and 640).

Conclusions: Efficacy

Peak-trough difference in effect:

There is reason to exercise caution in extrapolating the clinical trial peak-trough data to the proposed-for-market formulation. The to-be-marketed formulation (which was not used in the efficacy trials) exhibits a food interaction which appreciably reduces the mean AUC and C_{max} for both moexipril and moexiprilat.[10] This interaction is such as to warrant a recommendation to administer moexipril in the fasted state (if approved for marketing). In the worst case scenario (where the food interactino is assumed to be formulation-*in*dependent, and a large majority of patients are assumed to have fed themselves prior to dosing in clinical trials) the mean peak blood pressure data obtained from the trials could plausibly underestimate the mean peak effect of the to-be-marketed formulation (given once-daily under fasting conditions).[11]

Although **one cannot presently rule out the possibility that the mean peak antihypertensive effects observed in clinical trials underestimate the mean peak effect of the to-be-marketed formulation**, in clinical trial 638 the mean trough antihypertensive effect of once-daily moexipril monotherapy (15-30 mg/d) was not obtained at the price of clinically excessive mean diastolic hypotensive effect at peak. Study 623, although utilizing a formulation of undetermined bioequivalence, demonstrated similar findings. The available data from elderly patients (4 week results of study 640) also support the same conclusion (for once-daily moexipril doses of 7.5-15 mg/d). The possibility of extreme peak effects among outliers in these clinical trials is not excluded by these data.

Long-term efficacy:

Uncontrolled studies (630 OL and 640 OL) **suggested that the antihypertensive effects of moexipril (given in effective doses) did not change over 7.5-19 months**. Those subjects remaining in these trials maintained a relatively stable mean diastolic BP with essentially unchanging mean doses of moexipril and stable (or only slightly rising) mean doses of HCTZ. The maximum mean moexipril doses used in these studies was approximately 10-20 mg/d.

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[10]food was associated with a 24 hour mean AUC which was 43% and 46% of that observed in the fasted state for moexipril and moexiprilat, respectively. In the fed state, the mean C_{max} was 40% and 21% of that observed in the fasted state for moexipril and moexiprilat, respectively [study PHAKI 796].

[11]it is not known whether the food interaction is formulation-dependent, nor has it been confirmed that these different formulations are bioequivalent. Patients were not advised to fast prior to drug administration in the clinical trials.

Conclusions: Efficacy

Combination therapy:

The data from study 638 suggested that **the antihypertensive effect of moexipril was approximately additive to the antihypertensive effect of *HCTZ 12.5 mg/d*.** The mean trough effect of combination therapy with moexipril (7.5-15 mg/d) and HCTZ (12.5 mg/d) was not obtained at the price of undue *mean* diastolic hypotensive effect at peak (although once again one must be cautious in extrapolating these peak data to the proposed-for-market formulation).

In study 644, the 3.75 mg once-daily moexipril dose was an effective antihypertensive adjunct in subjects receiving 25 mg/d HCTZ. This contrasts with the ineffectiveness of this moexipril dose when given as monotherapy in study 638. However, **the overall evidence for antihypertensive synergy between moexipril and *HCTZ 25 mg/d* was equivocal**, and population differences could have plausibly accounted for these contrasting responses.

Effect in demographic subgroups:

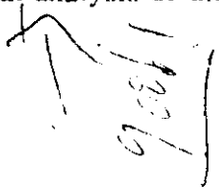
The pooled analysis generally revealed **evidence of a reduced moexipril responsiveness among black patients, relative to that of nonblack patients.** Among blacks, no moexipril dose manifested a mean anti-hypertensive effect which was statistically differentiable from that of placebo (for either systolic or diastolic BP), although directional mean trends towards efficacy were observed in blacks treated with doses ≥15 mg/d.

For each of the moexipril doses studied, female patients tended to have smaller mean reductions in BP than did males, albeit for a minority of the dose levels the differences were clinically trivial.

The antihypertensive response to moexipril was not clearly demonstrated to be a function of age.

Pharmacokinetics of the to-be-marketed formulation:

See Dr. Raj Pradhan's biopharmaceutical review for an evaluation of the bioequivalence of the moexipril formulation used in pivotal studies, relative to that of the to-be-marketed formulation. At the time of this report, his final analysis of this issue is pending.



9 Recommendation regarding Approval

From an efficacy vantage point moexipril is found to be useful monotherapy for patients with essential hypertension. Unless safety or data integrity issues adversely impact the approvability of this NDA, this product is recommended for approval.

Steven M. Rodin, MD 8/3/93

Steven M. Rodin, MD Date
Medical Officer

cc: SRodin/HFD-110; AKarkowsky/HFD-110; SChun/HFD-110
cc: KBongiovanni/HFD-110; HFD-110 division file (NDA 20-312)

Steven M. Rodin, M.D.

Food and Drug Administration — Division of Cardio-Renal Drug Products, HFD-110

Addendum #1 to Medical Review of NDA Efficacy data

1 General information

NDA #:	20-312
Drug:	moexipril (Schwarz Pharma)
Proposed indication:	treatment of essential hypertension
Date of original review:	3 August 1993
Date of latest data submission:	22 September 1993
this addendum last revised:	29 September 1993

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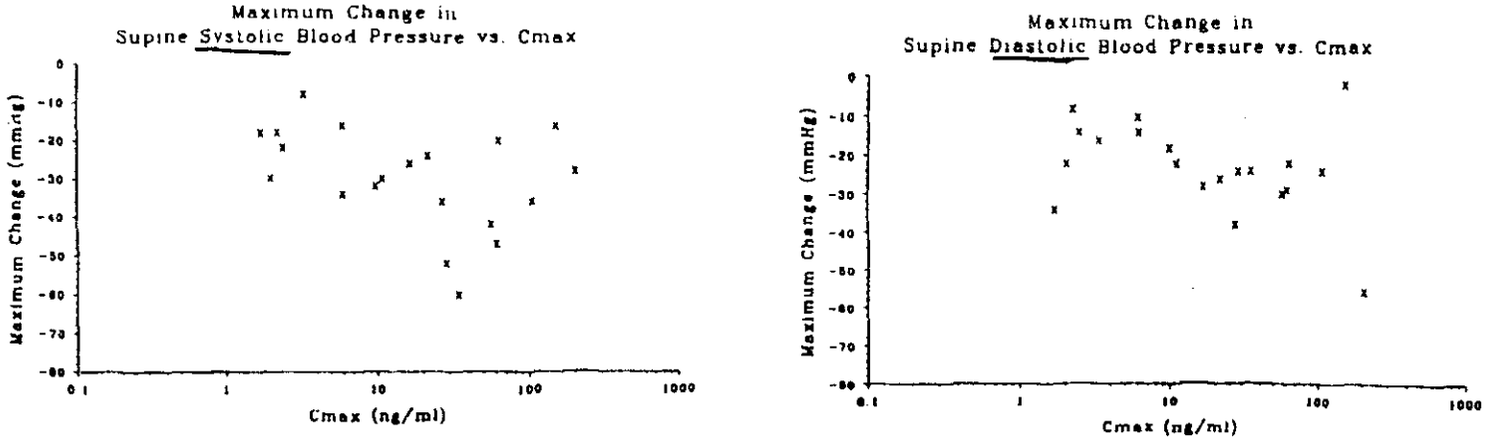
3. Peak-trough difference in antihypertensive effect

It had previously been underscored that the mean peak antihypertensive effects observed in the clinical trials may have underestimated the effect of the proposed-for-market formulation. With none of the steady-state observations in the trials was it known with certainty whether or not patients had fasted prior to dosing. The to-be-marketed formulation (which is very similar to the formulation used in two of the efficacy trials (638, and 640)) exhibited a food interaction whereby the mean C_{max} for moexipril and moexiprilat was reduced by 40 and 21%, respectively. Thus in a worst case scenario where all the trial patients are assumed to have fed themselves just prior to dosing[1], the mean C_{max} for moexiprilat in these trials would have underestimated (by roughly 20%) the levels to be expected during administration of drug under fasting conditions (those being the conditions reasonably proposed for administration of the marketed product).

It remains unclear whether the C_{max}-peak BP response relationship is sufficiently steep (over the range of proposed doses) such that a 20% increase in C_{max} would be of clinical importance. The more recently submitted data do not add substantial insights into this issue. In response to my inquiry about this relationship, the sponsor referred to PK-PD data (study 621) which was widely scattered, and not clearly demonstrative of a relationship between plasma moexiprilat concentration and antihypertensive response to moexipril at doses of 3.75 to 60 mg/d (see below).

Table 1:

Maximal BP change vs C_{max} (study 621)



[source: photocopy of tables in attachment 3 of submission dated 9/22/93]

Fasting, placebo-controlled monotherapy data are available, but these represent *first dose* peak anti-hypertensive effects (studies 621, 638, 640, 642, 649, and 651). In these studies, mean peak (placebo-corrected) diastolic BP changes generally did not exceed -7 mm Hg (except for the highly variable results of study 621 (standard deviations as high as 22.6 mm Hg) where mean diastolic BP changes were as large as -15.9 mm Hg) [for those who are inclined to rely on these study 621 data, it is noted that the large mean response is not accounted for by dissimilar racial demographics, or by explicit selection of ACE inhibitor-responsive subjects]. From all of these fasting data, only limited inferences can be drawn about steady-state because the long terminal half life of moexiprilat makes it plausible that C_{max} may be significantly higher at steady-state than it is following a first dose.

[1]the actual proportion who did so was not characterized.

4. Clinical pharmacology studies

The clinical pharmacology studies were small, and less adequately designed than the previously reviewed clinical trials, hence they provide a less definitive assessment of the anti-hypertensive action of moexipril. Except for *study 621* (which was discussed in the preceding section of this addendum), the mean results of these studies were not discordant with those of the clinical trials.

In study 925-1 there were no clinically significant mean BP effects (as expected) in the normotensive subjects evaluated. In *study 925-3*, moexipril at doses of 4-120 mg/d achieved mean changes in supine diastolic BP of -4.3 to -13.7 mm Hg at 4 hours post-dose, and -0.8 to and -11.0 mm Hg at 24 hours post-dose. *Study 641* also did not demonstrate discordant mean antihypertensive effects. In this open-label study moexipril (at once-daily doses titrated of 7.5-30 mg in addition to hydrochlorothiazide 50 mg/d) was associated with a mean change from pre-treatment sitting diastolic (sitD) BP of -11.6 mm Hg.

Study 646 was a placebo-controlled, double-blind, randomized evaluation of 18 patients with hypertension and impaired renal function (creatinine clearance of 25-65 ml/min). Moexipril, at a once-daily dose titrated as needed from 3.75 to 15 mg, changed pre-treatment mean sitDBP by -7.3 mm Hg at 24 hours post-dose (placebo-corrected), and yet by -only 3.1 mm Hg at 2 hours post-dose. Two of 10 moexipril-treated patients maintained a sitDBP of ≤ 90 mm Hg while on the 3.75 mg/d dose for the duration of the study.

5. Study 624

It is now clear that study 624 was discontinued early for administrative reasons (the previous sponsor decided to discontinue development of moexipril). The sponsor has not submitted sufficient information about the stability of concomitant diuretic doses to draw any unambiguous conclusions about the the longterm persistence of moexipril effect in this trial.

6. Additional trials submitted since the original NDA submission

The mean results of these additional clinical trials were not discordant with those of the previously reviewed clinical trials.

Study 649 was a placebo-controlled, combination drug, double-blind, parallel-group study which randomized 203 hypertensive subjects to receive fixed, once-daily doses of placebo, or moexipril (3.75, 7.5, or 15 mg) as therapy which was sequentially added to controlled-release nifedipine (40 mg/d) for 8 weeks. Moexipril at 3.75, 7.5, and 15 mg/d produced additional changes in mean sitDBP (in addition to those associated with nifedipine monotherapy) of -1.1, -4.1, and -3.8 mm Hg, respectively (placebo-corrected). No definitive conclusions about the additivity of effects can be made because no moexipril monotherapy arm was included. The added effect of moexipril was approximately the same as that observed with moexipril monotherapy in other studies.

Study 645 was a positive-controlled, double-blind, parallel-group study which randomized 178 subjects (patients with mild-to-moderate essential hypertension) to receive sustained release verapamil (180-240 mg/d), or moexipril (7.5-15 mg/d) for 24 weeks. At the end of the study moexipril was associated with a mean change from pre-treatment sitDBP of -9.7 mm Hg, and verapamil was associated with a mean change of -10.6 mm Hg (neither mean result is placebo-corrected).

6. Additional trials submitted since the original NDA submission [continued]

Study 647 was a positive-controlled, double-blind, parallel-group study which randomized 108 subjects (patients who remained hypertensive despite hydrochlorothiazide (HCTZ) 25 mg/d monotherapy) to receive verapamil (180-240 mg/d), or moexipril (7.5-15 mg/d) in addition to the HCTZ background therapy for 12 weeks. After 12 weeks moexipril and verapamil were associated with additional changes in mean sitDBP of -10.7 and -11.2 mm Hg, respectively (relative to those associated with HCTZ monotherapy).

Study 648 was a positive-controlled, double-blind, parallel-group study which randomized 159 hypertensive patients to receive captopril (50-100 mg/d), or moexipril (7.5-15 mg/d) for 12 weeks. At the end of the study moexipril was associated with a mean change from pre-treatment sitDBP of -11.8 mm Hg, and captopril was associated with a mean change of -12.2 mm Hg (24 hours post-dose, not placebo-corrected).

7. Proposed product labelling

a. On page 12 of the proposed product label (sponsor's draft dated 4/28/93) the sponsor makes general assertions regarding the additivity of effects of moexipril and concomitant thiazide diuretics, or calcium channel blockers when in fact only one agent in each of these classes was investigated as a co-therapy (hydrochlorothiazide and nifedipine, respectively). This language is unjustifiably broad.

b. On page 37 of the proposed product label (sponsor's draft dated 4/28/93) the sponsor recommends an initial moexipril dose of 3.75 mg/d and a maximum dose of 15 mg/d in populations with renal insufficiency. However, in study 646, when patients of this type were uptitrated (as needed) to once-daily moexipril doses of 15 mg, neither the mean peak nor trough changes from pre-treatment sitDBP were excessive [see page 3 of this addendum]. Thus there is no support in the *efficacy* data for the sponsor's implied claim that doses higher than 15 mg/d are not more clinically useful in renal insufficiency. My colleague's reviews of the kinetic (study 629) and/or safety data may, however, offer support for this claim.

Steven M. Rodin, MD Date

cc: AKarkowsky/HFD-110; SChun/HFD-110; KBongiovanni/HFD-110; division file/HFD-110
*** no copy to MO**

STATISTICAL REVIEW

K. BONGIOVANNI

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-312 Date:
Applicant: G.H. Besselaar Associates NOV 12 1992
Name of Drug: Moexipril HCL
Indication: Hypertension
Document Reviewed: Volumes 1.1, 1.196, 1.20[illegible], 1.212, 1.215, 1.221, 1.227, 1.233, 1.243, 1.250, received 12/21/92.

1. INTRODUCTION

This application consists of 12 randomized, double-blind, multicenter, parallel studies to evaluate the safety and efficacy of moexipril (MX) doses in hypertensive patients. Seven studies (studies GHBA-622, GHBA-623, GHBA-638, GHBA-640, GHBA-642, GHBA-643, and GHBA-651) were placebo-controlled conducted in patients with mild to moderate essential hypertension; study GHBA-640 included only elderly patients Two placebo-controlled studies (study GHBA-644 and GBHA-649) were conducted in patients with moderate to severe hypertension; study GHBA-644 was to compare moexipril to placebo as add-on therapy to HCTZ and study GHBA-649 was to compare moexipril to placebo as add-on therapy to nifedipine retard 20 mg (BID). Thus, one cannot assess the therapeutic effect of moexipril alone in the last two studies.

Three studies (studies GBHA-645, GBHA-647, and GBHA-648) were active-controlled studies.

This review will only cover studies GHBA-622, GHBA-623, GHBA-638, GHBA-640, GHBA-642, GBHA-643, and GHBA-651.

2. STUDY GHBA-622

This is an 8-week study to evaluate the safety and efficacy of three dose levels of moexipril (BID) in comparison to placebo in the treatment of patients with mild to moderate hypertension.

The 8-week double blind period was divided into three phases: Phase One (one week), Phase Two (five weeks), and Phase Three (two weeks). During Phase One, patients were randomized to receive either placebo, 1.75 mg (which was replaced by placebo), 3.75 mg, 7.5 mg, or 15 mg (BID) of moexipril. During Phase Two, patients not randomized to receive placebo had their dose increased to 3.75 mg, 7.5 mg, or 15 mg of moexipril BID. During Phase Three, patients had their dose reduced to the dose levels of Phase One.

The four moexipril groups were given the notations 0/3.75 mg, 3.75/7.5 mg, 7.5/15 mg, and 15/30 mg, respectively.

Fourteen investigators (in the US) were invclved in the study with the following number of patients randomized to treatment

groups: 39 patients for placebo, 41 patients for each of the two groups of MX 0/3.75 mg and MX 15/30 mg, 44 patients for MX 3.75/7.5 mg group, and 38 patients for the MX 7.5/15 mg group.

The primary measure of efficacy was the change from baseline in supine diastolic blood pressure (SuDBP).

Results

Because of fewer than two patients (as was stated by the sponsor) in some treatment groups at some double-blind time points, the data of 10 investigators were pooled as one center to make up a total of 5 centers in the statistical analysis.

There was no significant treatment x investigator interaction in the analysis at any time point of the double-blind period.

Table 1 shows that after 6 weeks of treatment, none of the moexipril BID doses resulted in a statistically significant reduction in BP over that for placebo.

3. STUDY GHBA-623

This is a 6-week study to evaluate the dose response of four dose levels of moexipril (QD) in comparison to placebo in the treatment of patients with mild to moderate hypertension.

Nineteen investigators (in the US) were involved in the study with the following number of patients randomized to treatment groups: 65 patients for each of the placebo, MX 7.5 mg, MX 15 mg, and MX 30 mg groups and 61 patients for the MX 60 mg group.

The primary measure of efficacy was the change from baseline in supine diastolic blood pressure (SuDBP).

Results

Because of fewer than two patients in some treatment groups at some double-blind time points, the data of 9 investigators were pooled as one center to make up a total of 11 centers in the statistical analysis.

There was no significant treatment x investigator interaction in the analysis at any time point of the double-blind period.

Table 2 shows that at the end of study moexipril 15 mg, 30 mg, and 60 mg (QD) resulted in significant reductions in BP over that of placebo (p-value ranges from 0.001 to 0.016). Moexipril 7.5 mg (QD) shows a marginally significant reduction in BP over that of placebo (p=0.063).

4. STUDY GHBA-638

This is an 8-week study to evaluate the dose response relationship of four dose levels of moexipril (QD) and to evaluate the efficacy, safety and tolerability of these dose levels and specific combinations of moexipril and hydrochlorothiazide (HCTZ) compared to placebo in the treatment of patients with mild to moderate essential hypertension. Patients were randomized to 9 treatment groups in the following manner: 45 patients for placebo, 49 for MX 3.75 mg, 42 for MX 7.5 mg, 47 for MX 15 mg, 45 for MX 30 mg, 48 for HCTZ 12.5 mg, 44 for MX 3.75 mg+HCTZ 12.5 mg, 46 for MX 7.5 mg+HCTZ 12.5 mg, and 47 for MX 15 mg+HCTZ 12.5 mg.

The primary measure of efficacy was the change from baseline in sitting diastolic blood pressure (SDBP).

This study was conducted in the US by 25 investigators.

Results

Tables 3(a,b) show the summary of the sponsor's statistical analysis results for the SDBP for week 8 and endpoint. Table 3a shows that at the end of study moexipril 15 mg and 30 mg (QD) resulted in significant reductions in BP over that of placebo (p-values are 0.036 and 0.020, respectively). However, Moexipril 3.75 mg (QD) did not show a significant reduction in BP over that of placebo (p=0.462) and that moexipril 7.5 mg (QD) resulted in a marginally significant reduction in BP over that of placebo (p=0.052).

5. STUDY GHBA-640

This is an 8-week study to evaluate the safety and efficacy of two dose levels of moexipril (QD) in comparison to hydrochlorothiazide (HCTZ) and placebo in the treatment of elderly patients with mild to moderate hypertension. Fifteen investigators (in 3 European countries) were involved in the study and the treatment groups included 50 patients for each of the MX 7.5 mg and the HCTZ 25 mg groups, 48 for the placebo group, and 53 patients for the MX 15 mg group.

The primary measure of efficacy was the change from baseline in sitting diastolic blood pressure (SDBP).

Results

Six centers out of the 15 centers had fewer than two patients in some treatment groups. Therefore, the data from these centers were pooled to make up a total of 10 centers that were considered in the statistical analysis.

There was no significant treatment x investigator interaction in the analysis at all time points of the double-blind period, except at hour 4 of week 4.

Table 4 shows that at the end of eight weeks of treatment moexipril 7.5 mg and 15 mg (QD) resulted in significant reductions in BP over that of placebo (p-value were ≤0.001).

6. STUDY GHBA-642

This is a 12-week study to evaluate the safety and efficacy of two dose levels of moexipril (QD) in comparison to hydrochlorothiazide (HCTZ) and placebo followed by a one-year open-label treatment period in patients with mild to moderate essential hypertension.

The primary measure of efficacy was the change from baseline in sitting diastolic blood pressure (SDBP).

This study was conducted in the US by 15 investigators. The treatment groups included 51 patients for each of the placebo, MX 7.5 mg, and HCTZ 25 mg groups and 47 patients for the MX 15 mg group.

Results

The sponsor stated that "The data from investigators with fewer than two patients in any treatment group at any double-blind time point for any BP variable were pooled as one center ... ". Consequently, the data from 5 investigators were pooled as one center to make up a total of 11 centers in the statistical analysis.

No treatment x investigator interaction (except at hour 2 of week 0) was observed.

Table 5 shows that at the end of 12-week treatment moexipril 7.5 mg and 15 mg (QD) resulted in significant reductions in BP over that of placebo (p-value are 0.016 and 0.002, respectively).

7. STUDY GHBA-643

This is a 12-week study to evaluate the safety and efficacy of two dose levels of moexipril (QD) followed by a 12-week placebo-controlled withdrawal period in patients with mild to moderate essential hypertension.

This study was conducted in the US by 15 investigators.

Eligible patients were randomized to one of the four treatment groups as shown below.

Treatment Group	N	12-Week Treatment Dosage	12-Week Withdrawal Dosage
I (7.5/7.5)	55	MX 7.5 mg (QD)	MX 7.5 mg (QD)
II (7.5/placebo)	57	MX 7.5 mg (QD)	Placebo
II (15/15)	57	MX 15 mg (QD)	MX 15 mg (QD)
IV (15/placebo)	54	MX 15 mg (QD)	PLacebo

The primary measure of efficacy was the change from baseline in sitting diastolic blood pressure (SDBP).

Results

Eight centers out of the 15 centers had fewer than two patients in some treatment groups. Therefore, the data from these centers were pooled to make up a total of 8 centers that were considered in the statistical analysis.

There was no significant treatment x investigator interaction in the analysis for both the treatment period and the withdrawal period.

The sponsor's results of the statistical analysis for the withdrawal period are summarized in Table 6. This table shows that, during the first 10 weeks of the withdrawal period, the group of patients who were (and had contirued) on moexipril 7.5 mg (QD) shows a significant reduction in BP over the group of patients who were on moexipril 7.5 mg (QD) and had received placebo (p-values range from 0.001 to 0.017) during that period. But the results show a marginally significant reduction (p=0.062) at week 12 of the withdrawal period.

On the other hand, during the first 6 weeks and at the 12th week of the withdrawal period, patients who were (and had continued) on moexipril 15 mg show significant BP reductions (p-values range from 0.001 to 0.033) over those who were on moexipril 15 mg (QD) and had received placebo during that period. But the results show non-significant BP reductions at weeks 8 and 10 (p-values are 0.105 and 0.082, respectively) of the withdrawal period.

8. STUDY GHBA-651

This is a phase II study to evaluate the safety and antihypertensive effect of moexipril (QD) as determined by ambulatory BP monitoring (ABPM) during an 8-week treatment period in patients with mild to moderate essential hypertension. Three investigators (in the US) were involved with a total of 51 patients assigned to 3 groups: 17 patients for placebo, 16 patients for MX 7.5 mg, and 18 patients for MX 15 mg.

Patients were eligible to enter the double-blind period if their

SDBP were between 95-114 mmHg on days -7 and 0 and a difference in SDBP ≤ 10 mmHg between these two days. Additionally, each patient had to have at least 40% of the daytime (06:00 to 22:00 hours) DBP measurement ≥ 90 mmHg during the 24-hour ABPM period commencing on day -7.

The primary measure of effectiveness was the change from baseline in ambulatory DBP with respect to averages determined during a 24-hour period.

Results

There was no significant treatment x investigator interaction in the analysis of the 24-hour interval.

Table 7 summarizes the results of statistical analysis for the average of the ABPM measurements over 24-hour interval. This table shows that at the end of an 8-week treatment moexipril 15 mg (QD) resulted in a significant reduction in BP over that of placebo (p=0.003). Moexipril 7.5 mg (QD) did not show a significant reduction in BP over that of placebo (p=0.386).

9. REVIEWER'S COMMENTS

QD regimen

In all the submitted studies, except study 638, tests for treatment x investigator were performed. In study 638, the sponsor stated that "Since there were fewer than four patients randomized to each treatment group at each study site, a direct test for treatment-by-investigator interaction could not be performed". This is not an accurate statement for the reason of inability to perform the treatment x investigator interaction test. The fact is that some sites had no patients in some treatment groups and that was the actual reason for not being able to test for this interaction.

The sponsor could have (as was done in other studies) made some decision about pooling sites with less than two patients, for instance, to overcome this problem of having empty cells. Then, after such a pooling it would have been possible to test for the treatment x investigator interaction.

All studies, except study 622, were conducted on the basis of moexipril QD regimen. This reviewer has constructed Table 8, based on Tables 2-7, to show a summary of results of 6 studies conducted on the basis of a QD regimen. By examining this table one sees that there is some evidence that moexipril 7.5 mg (QD) resulted in a significant reduction in BP (shown by studies 640 and 642, p-values are ≤0.016) and a marginally significant reduction in BP (shown by studies 623, 638 and 643, p=0.063, 0.052 and 0.062, respectively) over that of placebo. However,

there is a clear evidence that moexipril 15 mg, 30 mg, and 60 mg resulted in significant reductions in BP over that of placebo (the p-values are less than 0.04).

Here, it is to be noted that the results of study 640 (which was conducted on elderly patients) show that, for the same dose of moexipril, an additional drop in BP of about 2 mmHg was observed over those found in other studies.

Ambulatory BP screening and efficacy

In study 651 the screening and the assessment for efficacy were based on the ambulatory blood pressure monitoring (ABPM) data as described earlier. Although the sample sizes for the treatment groups were small (between 14 and 16 patients), yet the results in Table 7 show that moexipril 15 mg resulted in a significant reduction in BP (p=0.003) over that of placebo; but, moexipril 7.5 mg did not result in a significant (p=0.386) reduction in BP over that of placebo.

Dose response

This reviewer has fitted dose response curves using the linear, quadratic, E_{MAX}, and logistic models for the results of studies 623 and 638. The plots of the estimated models are given in Figures 1 through 7.

The choice of the best fitting model, among other models, is based on two items: first, the minimum RMSE and second, how well a model satisfies the clinical expectation of an increase in the dose response with the increase of the dose. It appears from Figures 1 to 3 (for study 623) that the quadratic model is not appropriate for describing the dose response since it decreases as it approaches the maximum dose (MX 60 mg), though its RMSE is 0.295. However, the logistic model shown in Figure 2 provides the best fit to the data, with RMSE=0.669.

Similar comments as above are applied for the models of study 638; the logistic model, shown in Figure 6 with RMSE=0.698, seems more appropriate than other models for fitting the data.

The data of these two studies and their dose response curves seem to suggest that moexipril 7.5 mg (QD) may be considered as the minimum effective dose and that moexipril 60 mg (QD) could be considerd as the maximum tolerable dose.

Withdrawal Study

The results of study 643 (see Table 6) show that, at the end of the withdrawal period, patients who continued on their double-blind regimen show a marginally significant BP reduction (p=0.062) for MX 7.5 mg group and a significant BP reduction

(p=0.033) for MX 15 mg group, compared to their corresponding groups who switched to placebo.

However, this reviewer has calculated, for those patients who completed the withdrawal period using the data provided by the sponsor, the averages of SDBP at baseline, at the begining of the withdrawal period (week 12), and at the end of that period (week 24); the results are shown in Table 6a. This table shows that, at the end of the withdrawal period, patients who remained on their double-blind regimen (MX 7.5 mg or 15 mg) had maintained almost the same BP levels as those when they started this period. But, BP was only increased by about 2 mmHg over that of the begining of the withdrawal period in patients who had switched to placebo. This means that moexipril dose was still effective after it was withdrawn during the 12-week withdrawal period.

Thus, this study did not observe patients in a period long enough to allow for the moexipril effect to wear out after it was withdrawn. This may explain why moexipril 7.5 mg showed only a marginally significant BP reduction (p=0.062) at the end of 12-week withdrawal period. Consequently, the design of this study worked to a disadvantage for moexipril by not showing a significant result for moexipril 7.5 mg dose.

BID regimen

Study 622 is the only study which was conducted on the basis of moexipril BID regimen. It is surprising that the results (see Table 1) indicate that at the end of study (week 6) none of the moexipril doses show a significant reduction in BP over that of placebo and similar results, except for moexipril 30 mg where a significant reduction over that of placebo (p=0.005) was shown at titration endpoint. In fact, the sample sizes were fairly large (between 39 and 41 patients), yet no such a significance was found.

Clearly, one source of this nonsignificant result is due to a relatively high average reduction in BP (-5.7 mmHg) among the placebo patients.

10. SUMMARY AND CONCLUSION (WHICH MAY BE CONVEYED TO THE SPONSOR)

Studies 623, 638, 640, 642, 643 and 651 were conducted on the basis of moexipril QD regimen. Table 8, which was constructed based on their results found in Tables 2-7, shows a clear evidence that moexipril 15 mg, 30 mg, and 60 mg (QD) resulted in significant reductions in BP over that of placebo (the p-values are less than 0.04). However, the results of studies 640 and 642 show some evidence that moexipril 7.5 mg (QD) resulted in a significant reduction in BP over that of placebo (p-values are $\leq$0.016); the results of studies 623, 638 and 643 show that this dose of moexipril resulted in marginally significant reductions

in BP over that of placebo (p=0.063, 0.052 and 0.062, respectively).

In study 643, patients were not observed longer than 12 weeks to allow for moexipril effect to wear out after it was withdrawn. Consequently, the design of this study worked to a disadvantage for moexipril by showing a marginally significant result for moexipril 7.5 mg at the end of the withdrawal period.

This reviewer has fitted linear, quadratic, E_{MAX}, and logistic models to describe the dose response for studies 623 and 638. Logistic model seems to provide the best fit for both studies.

From the results of these studies and by examining the dose response curves, one may conclude that moexipril 7.5 mg (QD) is the minimum effective dose and that moexipril 60 mg (QD) could be the maximum tolerable dose.

The sample sizes in study 622 were fairly large, yet the results (see Table 1), at the end of a 6-week treatment, indicate that none of the moexipril BID doses resulted in a significant reduction in BP over that of placebo (p-values are ≥ 0.059), likely due to a large placebo effect.

Walid A. Nuri, Ph.D.
Mathematical Statistician

This review consists of 9 pages, 8 tables, and 7 figures.

Concur: Dr. Chi 11/3/93

Dr. Dubey 11-3-93

cc: Orig. NDA 20-312
HFD-110/Dr. Rodin
HFD-110/Mrs. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Nuri
Chron:
W A Nuri: x34594 SERB: 10-21-93: DISC6/mxpr14.

Table 1. Adjusted* Mean Change From Baseline in SuDBP Number of subjects, and the p-value for the Multiple Comparisons with Placebo. (Study 622)

		Moexipril BID Regimen			
Week	Placebo	0/3.75 mg	3.75/7.5 mg	7.5/15 mg	15/30 mg
Baseline	99.7 39	100.7 41	100.8 44	100.3 38	102.0 41
6	-5.7 31	-6.3 35 (0.744)	-7.7 34 (0.282)	-6.0 34 (0.854)	-9.2 37 (0.059)
Titration Endpoint	-4.3 38	-5.7 39 (0.445)	-7.2 39 (0.115)	-6.6 38 (0.211)	-9.5 40 (0.005)

* Adjusted by the analysis of covariance

Table 2. Adjusted* Mean Change From Baseline in SuDBP Number of subjects, and the p-value for the Multiple Comparisons with Placebo. (Study 623)

		Moexipril QD Regimen			
Week	Placebo	MX 7.5 mg	MX 15 mg	MX 30 mg	MX 60 mg
Baseline	99.8 65	99.5 65	100.6 65	100.8 65	101.2 61
6	-3.7 57	-6.4 60 (0.063)	-8.1 55 (0.016)	-9.7 59 (<0.001)	-7.9 53 (0.001)
Endpoint	-3.6 62	-6.0 65 (0.051)	-7.7 62 (0.014)	-9.8 62 (<0.001)	-7.3 60 (0.001)

* Adjusted by the analysis of covariance

Table 3a. Adjusted* Mean Change From Baseline in SDBP Number of subjects, and the p-value for the Multiple Comparisons with Placebo. (Study 638)

		Moexipril QD Regimen			
Week	Placebo	MX 3.75 mg	MX 7.5 mg	MX 15 mg	MX 30 mg
Baseline	100.2 45	99.8 49	100.8 42	100.6 47	101.9 45
8	-4.9 43	-5.9 48 (0.462)	-7.6 40 (0.052)	-7.7 47 (0.036)	-8.1 44 (0.020)
Endpoint	-4.6 45	-5.7 49 (0.401)	-7.8 42 (0.025)	-7.7 47 (0.026)	-8.0 45 (0.015)

* Adjusted by the analysis of covariance

Table 3b. Adjusted Mean Change From Baseline in SDBP Number of subjects, and the p-value for the Multiple Comparisons of the Combination Therapies With Their Components. (Study 638)

Week	MX 3.75 mg+ HCTZ 12.5 mg(QD)	MX 7.5 mg+ HCTZ 12.5 mg(QD)	MX 15 mg HCTZ 12.5 mg(D)
Baseline	100.6 44	100.4 46	100.2 47
8	-10.9 43 (<0.001*,0.019+)	-11.3 44 (0.015,0.013)	-9.6 44 (0.118,0.107)
Endpoint	-10.7 44 (<0.001,0.009)	-11.3 46 (0.019,0.003)	-9.6 47 (0.197,0.074)

* p-value versus the Moexipril component
+ p-value versus the HCTZ component

Table 4. Adjusted* Mean Change From Baseline in SDBP Number of subjects, and the p-value for the Multiple Comparisons with Placebo.
(Study 640)

Week	Placebo	HCTZ 25 mg (QD)	MX 7.5 mg (QD)	MX 15 mg (QD)
Baseline	102.5 48	101.6 50	102.1 50	102.3 53
8	-4 1 44	-10.6 46 (<0.001)	-9.1 46 (0.001)	-10.3 49 (<0.001)
Endpoint	-3.9 47	-10.5 49 (<0.001)	-8.7 49 (0.002)	-10.1 51 (<0.001)

* Adjusted by the analysis of covariance

Table 5. Adjusted* Mean Change From Baseline in SDBP Number of subjects, and the p-value for the Multiple Comparisons with Placebo.
(Study 642)

Week	Placebo	HCTZ 25 mg QD	MX 7.5 mg QD	MX 15 mg QD
Baseline	101.2 51	102.1 51	101.8 51	100.9 47
12	-4.1 45	-9.5 44 (<0.001)	-7.5 44 (0.016)	-8.5 43 (0.002)
Endpoint	-3.1 51	-8.8 51 (<0.001)	-7.9 50 (0.001)	-8.3 47 (<0.001)

* Adjusted by the analysis of covariance

Table 6. Adjusted* Mean Change From Baseline in SDBP, Number of subjects, and the p-value for the Multiple Comparisons of the Moexipril Groups versus Those Groups Who Had Placebo During The Withdrawal Period.
(Study 643)

Week	MX 7.5 mg/ Placebo (QD)	MX 7.5 mg/ MX 7.5 mg (QD)	MX 15 mg/ Placebo (QD)	MX 15 mg/ MX 15 mg (QD)
Baseline	100.8 55	101.4 57	100.5 57	101.0 54
12 (Trt.Endpt.)	-8.5 49	-8.5 48 (0.985)	-9.6 47	-10.9 46 (0.334)
14	-5.2 49	-8.8 48 (0.012)	-6.2 47	-11.0 46 (0.001)
16	-6.3 44	-9.9 46 (0.017)	-5.8 46	-10.6 45 (0.002)
18	-4.9 42	-9.2 43 (0.005)	-5.4 43	-9.4 42 (0.009)
20	-6.1 39	-10.7 42 (0.002)	-6.5 38	-8.9 42 (0.105)
22	-4.4 37	-10.3 40 (0.001)	-7.4 37	-10.1 42 (0.082)
24	-6.8 35	-9.6 39 (0.062)	-7.1 37	-10.2 41 (0.033)
Endpoint	-3.7 49	-8.2 48 (0.007)	-4.6 47	-10.6 46 (0.001)

* Adjusted by the analysis of covariance

Table 6a. SDBP results for the group of patients who completed the withdrawal double-blind period. (Study 643)

Week	Hour	MX 7.5 mg/ Placebo (QD)	MX 7.5 mg/ MX 7.5 mg (QD)	MX 15 mg/ Placebo (QD)	MX 15 mg/ MX 15 mg (QD)
Baseline		98.7	99.9	99.4	100.5
	(N)	(35)	(39)	(37)	(41)
12	0	88.8	90.3	89.4	88.7
	(N)	(35)	(39)	(37)	(41)
24	0	91.5	89.5	92.3	89.1
	(N)	(35)	(39)	(37)	(41)

Table 7. Adjusted* Mean Change From Baseline in the Average of a 24-hour Ambulatory DBP, Number of subjects, and the p-value for the Multiple Comparisons with Placebo. (Study 651)

Week	Placebo	MX 7.5 mg QD	MX 15 mg QD
Baseline	88.2	94.9	90.0
	17	16	18
0 (Day 1)	-2.8	-4.3	-8.8
	16	16	17
		(0.435)	(0.002)
8	-1.5	-3.6	-8.9
	14	16	15
		(0.386)	(0.003)

* Adjusted by the analysis of covariance

Table 8. Summary of BP results at the end of 6 studies: change from baseline, N, and p-value versus placebo.

Study	Duration in Weeks	Pla.	MX 3.75 mg	MX 7.5 mg	MX 15 mg	MX 30 mg	MX 60 mg
623	6	-3.7 57	x	-6.4 60 (0.063)	-8.1 55 (0.016)	-9.7 59 (<0.001)	-7.9 53 (0.001)
638	8	-4.9 43	-5.9 48 (0.462)	-7.6 40 (0.052)	-7.7 47 (0.036)	-8.1 44 (0.020)	x
640 (Elderly)	8	-4.1 44	x	-9.1 46 (0.001)	-10.3 49 (<0.001)	x	x
642	12	-4.1 45	x	-7.5 44 (0.016)	-8.5 43 (0.002)	x	x
651 ABPM	8	-1.5 14	x	-3.6 16 (0.386)	-8.9 15 (0.003)	x	x
643	(Withdrawal period)						
	12	-6.8 35	x	-9.6 39 (0.062)	x	x	x
	12	-7.1 37	x	x	-10.2 41 (0.033)	x	x

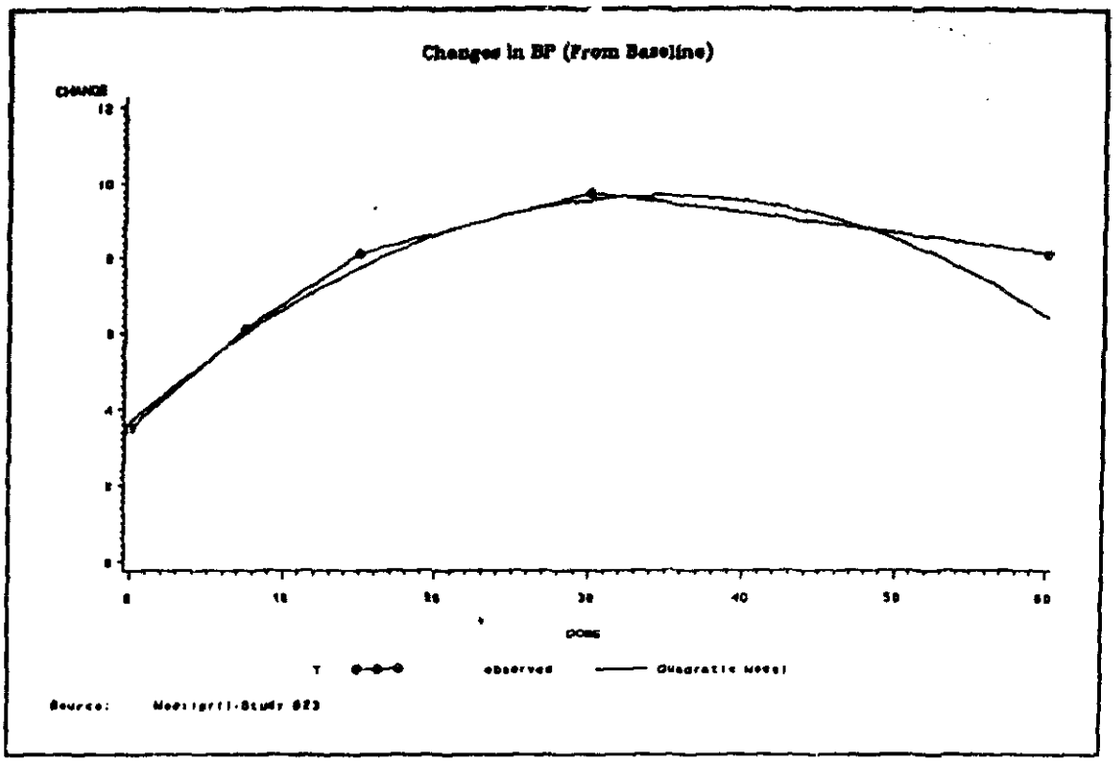
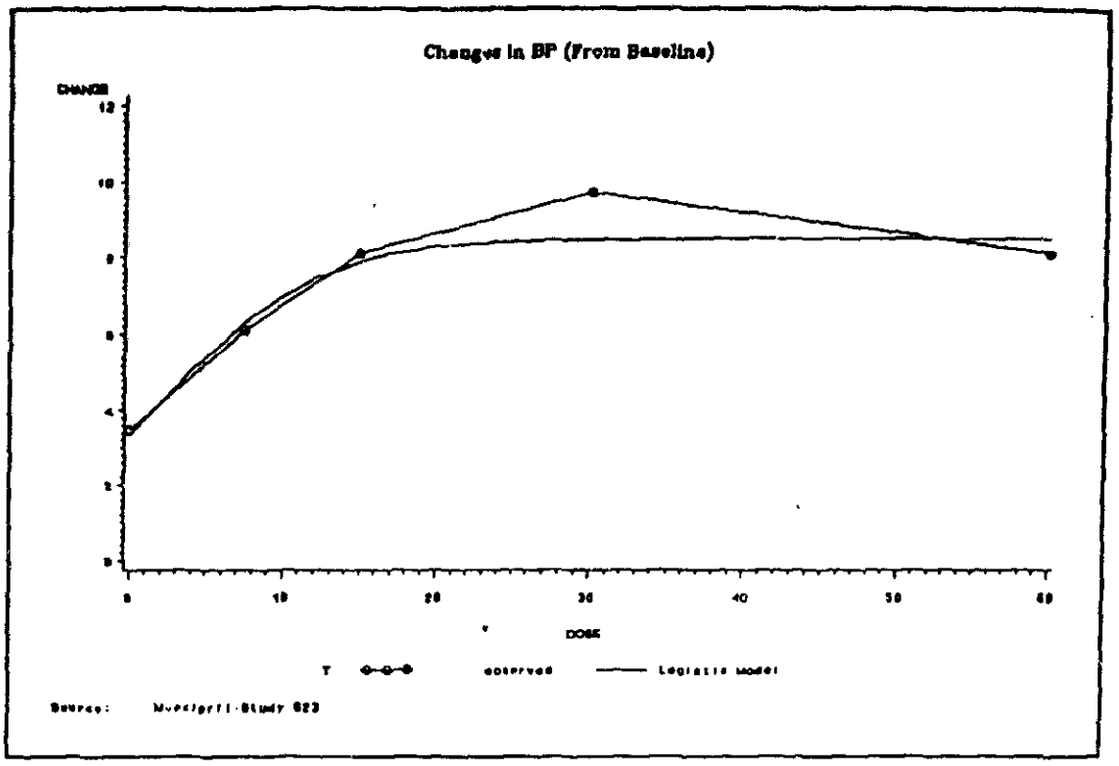


Figure 1. Quadratic model for dose response (Moexipril) for the change from baseline in BP (Study #623)

Estimated Model:

$$\text{Change}=3.67 + 0.35*\text{dose} - 0.004*(\text{dose})^2$$

RMSE=0.295



Fiqure 2. Logistic model for dose response (Moexipril) for the change from baseline in BP (Study #623)

Estimated Model:

Change=8.5/(1 + 1.52*exp(-0.2*dose))

RMSE=0.669

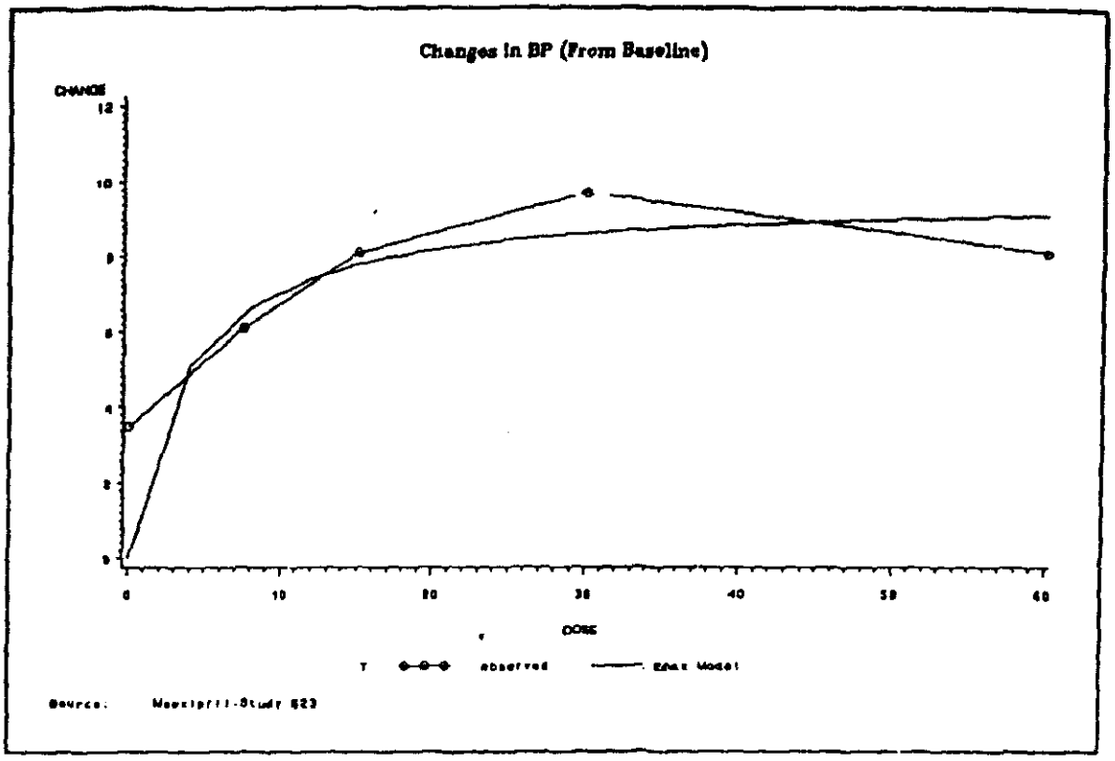


Figure 3. E_{MAX} model for dose response (Moexipril) for the change from baseline in BP (Study 623)

Estimated Model:

Change=9.65*dose/(3.58+dose)

RMSE=2.214

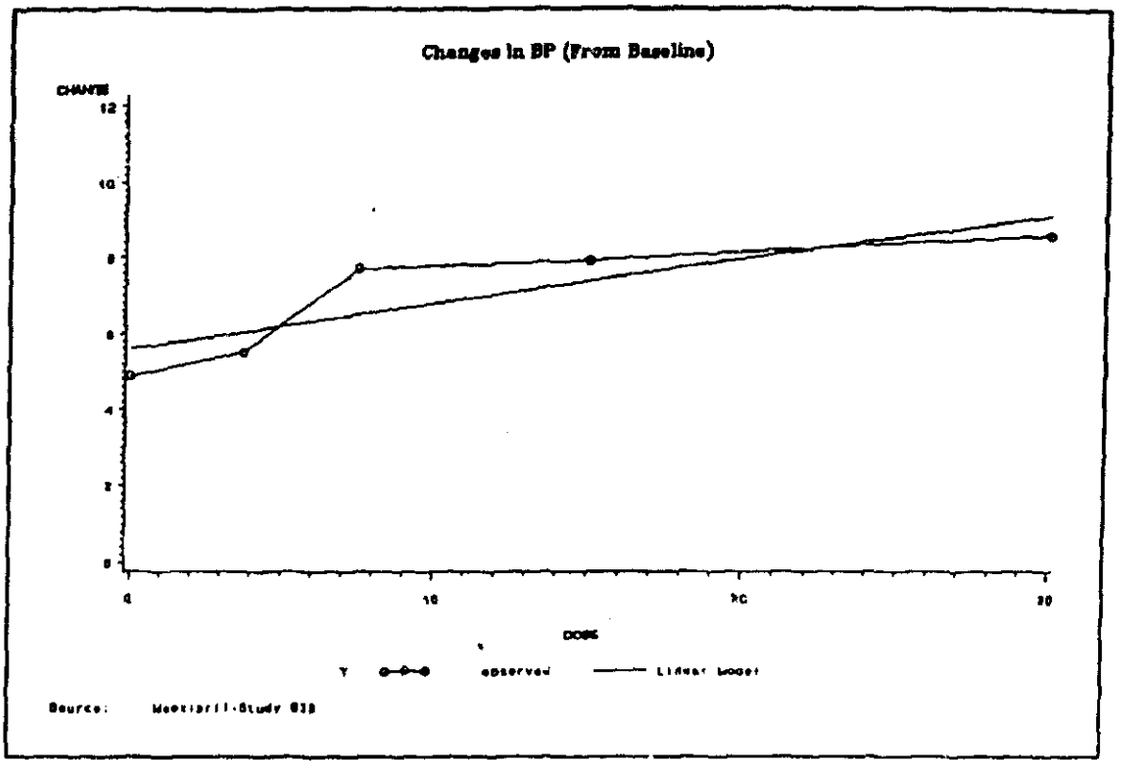
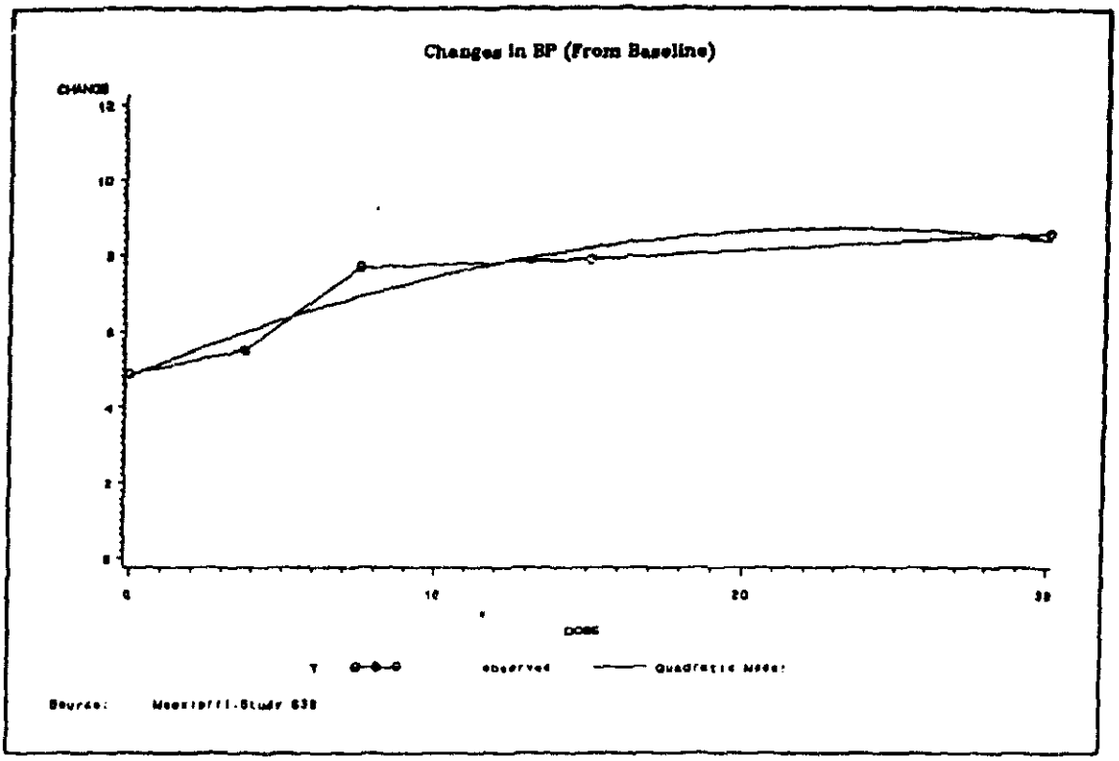


Figure 4. Linear model for dose response (Moexipril) for the change from baseline in BP (Study 638)

Estimated Model: Change=5.61 + 0.12*dose

RMSE=0.972



Fiqure 5. Quadratic model for dose response (Moexipril) for the change from baseline in BP (Study #638)

Estimated Model:

$$\text{Change}=4.68 + 0.33*\text{dose} - 0.006*(\text{dose})^2$$

RMSE=0.689

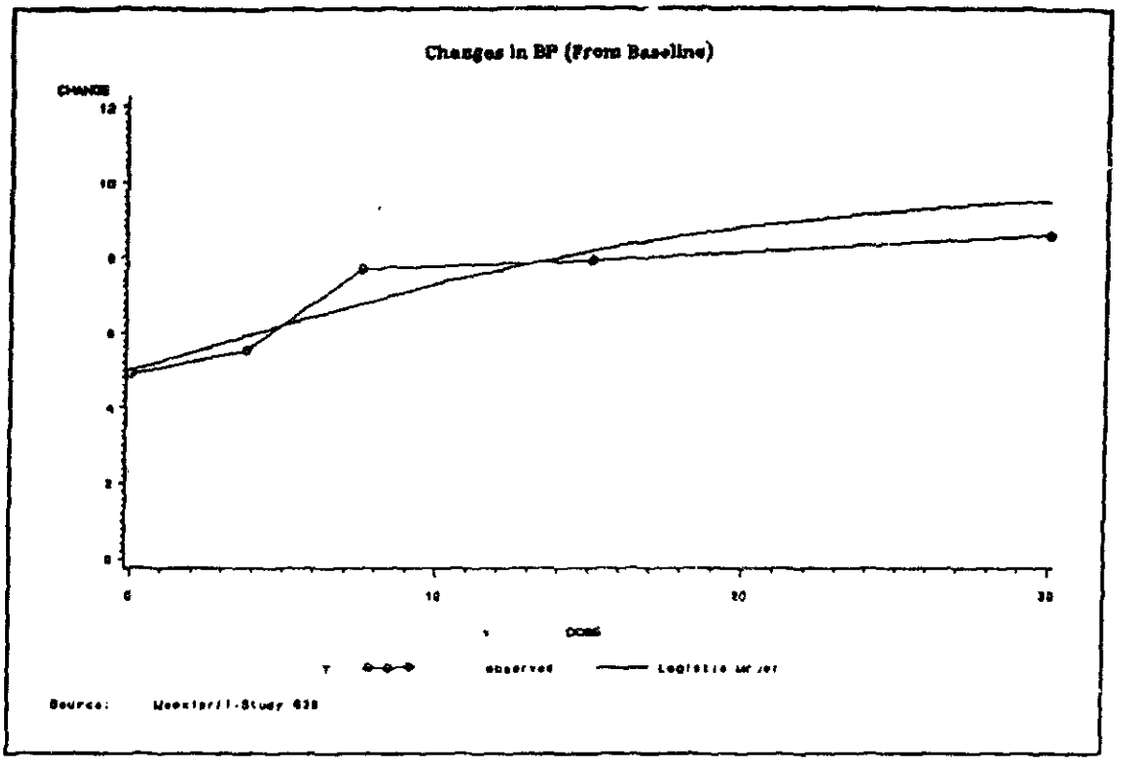


Figure 6. Logistic model for dose response (Moexipril) for the change from baseline in BP (Study #638)

Estimated Model:

Change=10/(1 + 1.007*exp(-0.1*dose))

RMSE=0.698

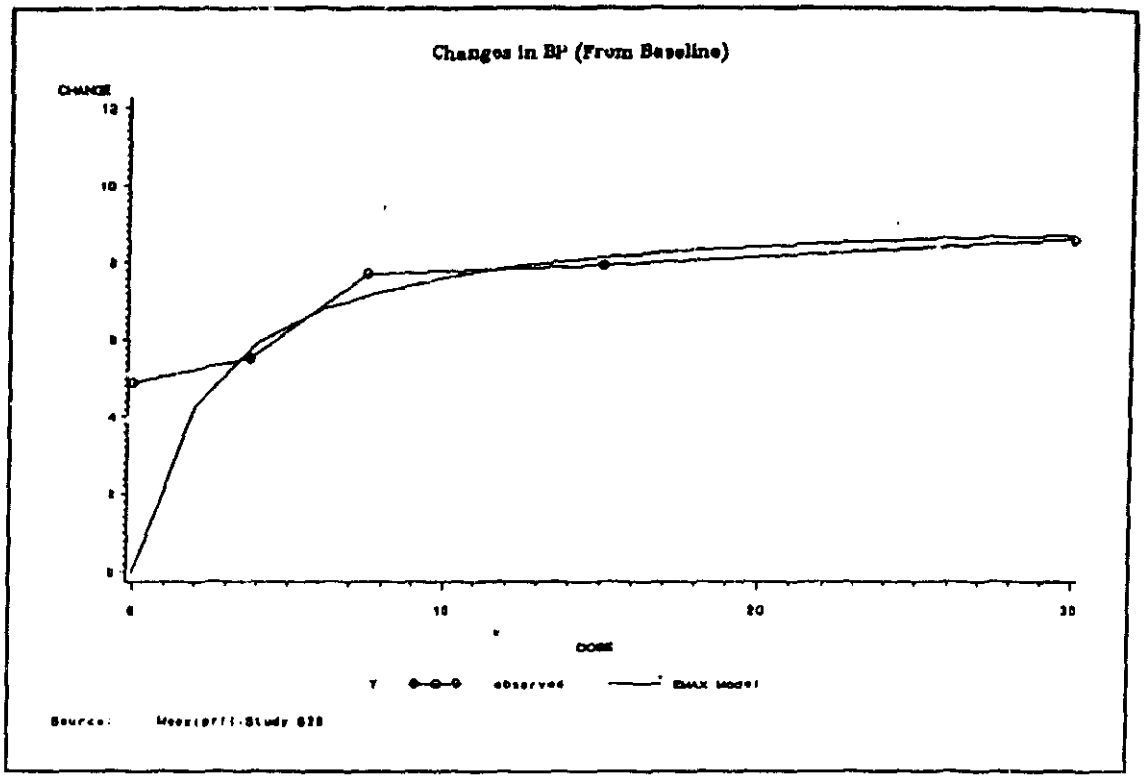


Figure 7. E_{MAX} model for dose response (Moexipril) for the change from baseline in BP (Study 638)

Estimated Model:

Change=9.4*dose/(2.36+dose)

RMSE=2.850

K BONGIOVANNI

Statistical Review and Evaluation

(Addendum)

Sub: Modification of summary

NOV - 8 1993

NDA: 20-312 **Date:**

Applicant: G.H. Besselaar Associates agent for Schwarz Pharma A.G., Monheim, Germany

Name of Drug: Moexipril Hydrochloride

Documents Reviewed: NDA Submission volumes 24 to 45 of 275
Data on floppy diskette supplied by the sponsor.

A report of statistical review and evaluation of the mouse and rat carcinogenicity studies of this NDA was issued by the Division of Biometrics on July 28, 1993. In that review the reviewer's analysis showed a statistically significant positive linear trend in malignant lymphoma in Axillary lymph nodes in male mice. However, a combined analysis of malignant lymphoma with histiocytic sarcoma, leukemoid reaction, and lymphocytic leukemia found in any organ did not show such a significant trend. These results, though mentioned in the main body of the review report, were not mentioned in the summary section. Therefore, the second paragraph of the summary section is modified as follows to include these results:

'The positive linear trend in the incidence of malignant lymphoma in axillary lymph node was found to be statistically significant in male mice. However, an analysis of combined incidences of malignant lymphoma, histiocytic sarcoma, leukemoid reaction, and lymphocytic leukemia in any organ in male mice did not show such a statistically significant positive linear trend.'

Mohammad Atiar Rahman
Mohammad A. Rahman, Ph.D.
Mathematical Statistician

Karl K. Lin · 10/21/93
Concur: Karl K. Lin, Ph.D., Group Leader

cc: Original NDA 20-312
HFD-110/Dr. Lipicky
HFD-110/Dr. Bongiovanni
HFD-110/Dr. Oza
HFD-110/Dr. Patel
HFD-710/Chron
HFD-715/Dr. K. Lin
HFD-715/Dr. Rahman
HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-312 Moexipril Mouse and Rat carcinogenicity studies
HFD-715/Diskette Rahman-1/MOEXIPRL.ADN
HFD-400/Dr. Contrera

K. BONGIOVANNI

Statistical Review and Evaluation

JUL 28 1993

NDA: 20-312 Date:

Applicant: G.H. Besselaar Associates agent for Schwarz Pharma A.G., Monheim, Germany

Name of Drug: Moexipril Hydrochloride

Documents Reviewed: NDA Submission volumes 24 to 45 of 275
Data on floppy diskette supplied by the sponsor.

I. Background: In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. These two studies were intended to assess the carcinogenicity potential of Moexipril in mice and rats when administered orally by gavage once daily at some selected dose levels. The lengths of the mouse study was 83 weeks and that of the rat study was 104 weeks. In the mouse study the animals were given the active drug for 78 weeks. After 78 weeks the surviving animals were held without treatment until there were 20% survival in any group. Ms. Katheleen Bongeovanni, HFD-110, requested the Division of Biometrics to perform the statistical review and evaluation of these studies. The results of the review have been discussed with the reviewing pharmacologists Dr. Narendra B. Oza and Dr. D. G. Patel.

II. The mouse study

IIa. Design: Two separate experiments, one in male and one in female mice, were conducted. In these two experiments there were three treated groups known as low, medium, and high dose groups, and a control group. Three hundred male and three hundred female Swiss-Webster mice were randomly divided into selected sizes of 120, 60, 60,and 60 for control, low, medium, and high dose group, respectively. The dose levels for the treated groups were 3, 15, and 75 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control group received water by gavage once daily.

The animals were checked daily for mortality and morbidity and were examined weekly for the presence of any palpable masses. A complete histopathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment.

IIb. Sponsor's analysis

Survival data analysis: The survival data were analyzed using the National Cancer Institute life-table package which includes the Kaplan-Meier product-limit estimation, Cox's logistic regression and Ghehan-Breslows' generalized Kruskal-Wallis tests.

The tests did not show any statistically significant positive linear trend or increment in mortality in any of the treated groups when compared with the control in either sex.

Tumor data analysis: The tumor data were analyzed using the Cochran -Armitage and the Fishing-Irwin test for positive linear trend and pairwise comparisons, respectively. The tests did not show statistically significant positive linear trend in the incidence of any tumor type in either sex. Pairwise comparison of low dose group with the control showed a statistically significant increment in the incidence of Lung/Alveolar, Bronchiolar adenoma in female mice (P=.0159).

IIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette, except for the body weight data which were taken from the sponsor's hard copy submission.

Survival analysis: The intercurrent mortality data of mouse study are given in table 1. The plots of Kaplan-Meier estimates of the survival distributions of male and female mice are given in Figures 1a and 1b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, High) were tested separately for male and female mice using the Cox test and the Generalized Wilcoxon test. The tests did not show any statistically significant (at .05 level) positive linear trend or difference in the mortality among treatment groups in either sex.

The p-values of the positive linear trend and the pairwise tests are given in Tables 2a and 2b, respectively.

Tumor data analysis: Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method' for testing positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories a combined test was performed. Exact permutation

trend test was used to calculate the p-values of all trend tests, except when the tumors were found in the mixed context (same tumor was found as both cause of death and not cause of death) in which cases the continuity corrected normal test were used. The scores used were 0, 3, 15, and 75 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-52, 53-75, 76-83 weeks, and terminal sacrifice.

The incidence rates of tumor types with p-values less than .05 are listed below.

Male mice	Tumor rate				
Organ/Tumor	C	L	M	H	
	120	60	60	60	Trend test P-value
Lacrimal Gland/Cystadenoma	4	2	2	6	.0233
Lymph node, Axillary/Lymphoma, malignant	0	1	2	3	.0165
Thymus/Lymphoma, malignant	2	4	2	5	.0493

Multiple testing adjustment: The rule proposed by Haseman was used to adjust the effect of multiple testings. Haseman's rule states that in order to keep the false-positive rate at the nominal level of approximately five percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .05 level, otherwise the level should be set at .01 (Haseman, (1983), A re-examination of false-positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339).

On the basis of Haseman's rule the positive linear trend in Axillary lymph node/Malignant lymphoma, in male mice is considered to be statistically significant. None of the tested tumor types in female mice showed statistically significant positive linear trend.

On the request of the supervisory pharmacologist Dr. Albert Defelice the reviewer performed analyses on the incidence of malignant lymphoma in any organ and on the combined incidences of malignant lymphoma, histiocytic sarcoma, leukemoid reaction, and lymphocytic leukemia in any organ. The incidence rates and p-values of these tumor types are as follows:

Male mice

	P-values			
Organ/Tumor	Trend	Pairwise		
		(C,L)	(C,M)	(C,H)
Any organ/Malignant lymphoma 22/120 18/60 14/60 17/60	.1216	.0230	.3158	.0522
Any organ/Malignant lymphoma, histiocytic sarcoma, leukemoid reaction, and lymphocytic leukemia 25/120 20/60 15/60 18/60	.1624	.0220	.3484	.0755

Female mice

Organ/Tumor	P-values Trend	Pairwise (C,L)	(C,M)	(C,H)
Any organ/Malignant lymphoma 36/120 13/60 14/60 16/60	.6672	.3407	.6842	.8375
Any organ/Malignant lymphoma, histiocytic sarcoma, leukemoid reaction, and lymphocytic leukemia 41/120 15/60 14/60 17/60	.7764	.8606	.8734	.9328

Again on the basis of Haseman's rule none of these P-values are considered to be statistically significant.

The incidence rates and p-values of all tumor types tested for positive linear trend are given in Table 3.

III. The rat study

IIIa. Design: Two separate experiments, one in male and one in female rats were conducted. In each of these experiments there were three treated groups, known as low, medium, and high dose groups and a control group. Three hundred male and three hundred female sprague-dawley Crl. CD BR rats were randomly divided into selected sizes of 120, 60, 60,and 60 for control, low, medium, and high dose group, respectively. The dose levels for the treated groups were 3, 15, and 75 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control group received water by gavage once daily.

The animals were checked daily for mortality and morbidity and were examined weekly for the presence of any palpable masses. A complete histopathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment.

IIIb. Sponsor's analysis

Survival data analysis: The survival data were analyzed using the National Cancer Institute life-table package which includes the Kaplan-Meier product-limit estimation, Cox's logistic regression and Ghehan-Breslow generalized Kruskal-Wallis tests.

The tests did not show any statistically significant positive linear trend or increment in mortality in any of the treated groups when compared with the control in either sex.

Tumor data analysis: The tumor data were analyzed using the Cochran -Armitage and Fishing-Irwin test for positive linear trend and pairwise comparisons, respectively. The tests did not show statistically significant positive linear trend in the incidence of any tumor types in either sex. Pairwise comparison of medium dose group with the control showed a statistically significant increment in the incidence of Skin/Keratoacanthoma in male rats (P=.0019).

IIIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (1972) and of Gehan (1965) were used. The tumor data analyses were performed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette, except for the body weight data which were taken from the sponsor's hard copy submission.

Survival analysis: The intercurrent mortality data of the rat study are given in table 4. The plots of Kaplan-Meier estimates of the survival distributions for male and female rats are given in Figures 2a and 2b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, and High) were tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The test did not show any statistically significant (at .05 level) positive linear trend or difference in the mortality among treatment groups in either sex.

The p-values of the trend and the pairwise tests are given in Tables 5a and 5b.

Tumor data analysis: Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al.(1980), the reviewer applied the 'death rate method' and the 'prevalence method' for testing the positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories a combined test was performed. Exact permutation trend test was used to calculate the p-values of all trend tests. The scores used were 0, 3, 15, and 75 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-52, 53-78, 79-95, 96-104 weeks, and terminal sacrifice for both male and female rats. None of the tested tumor types showed any statistically significant positive linear trend in either sex.

The incidence rates and p-values of all tumor types tested for positive linear trend are given in Table 6.

IV. Evaluation of validity of the design

The reviewer's analysis showed that except for malignant lymphoma in axillary lymph node in male mice, no other tested tumor types had statistically significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic, it is important to look into the following two issues as having been pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Statistical Application and Research Branch, Division of Biometrics, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure.

In addition Chu, Cueto and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum

tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy.

i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Moexipril mouse and rat carcinogenicity study, in the light of the above guidelines.

IVa. Mouse study

The following are summary survival data of mice in the high dose group.

	End of 52 weeks	End of 75 weeks	End of 83 weeks (End of the study)
Male	86.67%	46.67	28.33%
Female	75.00%	35.00	23.33%

From this summary data, and the survival criteria mentioned above, it can be concluded that there were not enough number of mice exposed for sufficient amount of time to the drug in either sex.

The following are summary body weight gains data of the mouse study.

		Mean body weight(gms) Beginning of study	End of study	Weight gain	Percentage of Control
Male	Control	23.21	39.84	16.63	
	Low	23.12	39.05	15.93	95.79
	Medium	23.22	39.14	15.92	95.73
	High	23.03	37.00	13.97	84.00
Female	Control	21.20	33.97	12.77	
	Low	21.37	33.56	12.19	95.45
	Medium	20.95	34.53	13.58	106.34
	High	21.02	29.00	7.98	62.49

Therefore, relative to the control, male and female mice had decrement of weight gain in the high dose group equal to 16% and 37.51%, respectively.

The mortality rate at the end of the experiment are as follows:

	Control	High
Male	78.33%	71.67%
Female	71.67%	76.67%

The morality rate in the high dose group is slightly lower in male mice and higher in female mice than that of the controls.

Thus, from the weight gain criterion it can be concluded that the high dose used is over MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

IVb. Rat study

The following are summary survival data of rats in the high dose group.

	End of 52 weeks	End of 85 weeks	End of 104 weeks (End of the study)
Male	88.33%	60.00%	45.00%
Female	91.67%	63.33%	33.33%

From this summary data, and the survival criteria mentioned above, it can be concluded that in both sexes there were enough number of rats exposed for sufficient amount of time to the drug.

The following are summary body weight gains data of the rat study.

		Mean body weight(gms) Beginning of study	End of study	Weight gain	Percentage of Control
Male	Control	155	678	523	
	Low	155	663	508	97.13
	Medium	159	648	489	93.49
	High	153	622	469	89.67
Female	Control	144	502	358	
	Low	137	463	326	91.06
	Medium	138	470	332	92.73
	High	139	448	309	68.97

Therefore, relative to the control, male and female rats had decrement of weight gain in the high dose group equal to 10.33% and 31.03%, respectively.

The mortality rate at the end of the experiment are as follows:

	Control	High
Male	59.71%	55.00%
Female	63.67%	66.67%

The morality rate of the high dose group is slightly lower in male mice and higher in female mice than that of the controls.

Thus, from the weight gain criterion it can be concluded that the high dose used is close to MTD for male rats but over MTD for female rats. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

V. Summary

Mouse study: No statistically significant (at .05 level) positive linear trend or differences in the mortality among treatment groups was found in either sex.

The positive linear trend in the incidence of malignant lymphoma in axillary lymph node was found to be statistically significant in male mice.

Using the survival criteria it can be concluded that there were not enough number of mice exposed for sufficient amount of time to the drug in either sex.

From the weight gain criterion it can be concluded that the high dose used is over MTD. To draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

The rat study: No statistically significant (at .05 level) positive linear trend or difference in the mortality among treatment groups was found in either sex.

None of the tested tumor types showed any statistically significant positive linear trend or increment when compared with the control.

Using the survival criteria it can be concluded that in both sexes there were enough animals exposed for sufficient amount of time to the drug.

From the weight gain criterion it can be concluded that the high dose used is close to MTD for male rats but over MTD for female rats. To draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

Mohammad Ataur Rahman.
Mohammad A. Rahman, Ph.D.
Mathematical Statistician

Karl K. Lin 7/28/93
Concur: Karl K. Lin, Ph.D., Group Leader

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HFD-110/Dr. Lipicky
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HFD-110/Dr. Oza
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HFD-710/Chron
HFD-715/Dr. K. Lin
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HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-312 Moexipril Mouse and Rat carcinogenicity studies
HFD-715/Diskette Rahman-1/MOEXIPRL.CAR
HFD-400/Dr. Contrera

Table 1

Intercurrent mortality rates in the mouse study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	27/120 (22.50)	10/ 60 (16.67)	17/ 60 (28.33)	8/ 60 (13.33)
	53- 75	39/ 93 (55.00)	16/ 50 (43.33)	15/ 43 (53.33)	24/ 52 (53.33)
	76- 83	28/ 54 (78.33)	16/ 34 (70.00)	12/ 28 (73.33)	11/ 28 (71.67)
	TERM. SACR	26/120 (21.67)	18/ 60 (30.00)	16/ 60 (26.67)	17/ 60 (28.33)
FEMALE					
	0 - 52	39/120 (32.50)	11/ 60 (18.33)	9/ 60 (15.00)	15/ 60 (25.00)
	53- 75	23/ 81 (51.67)	22/ 49 (55.00)	21/ 51 (50.00)	24/ 45 (65.00)
	76- 83	24/ 58 (71.67)	10/ 27 (71.67)	13/ 30 (71.67)	7/ 21 (76.67)
	TERM. SACR	34/120 (28.33)	17/ 60 (28.33)	17/ 60 (28.33)	14/ 60 (23.33)

Note: Except the TERM. SACR. row, an entry of this table =number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 2a

P-values of tests for positive linear trend in mortality in the mouse study

Test of homogeneity

Sex	Test	P-value (One tail Chi-Sqr.)
Male	Cox	.4780
	Wilcoxon	.3842
Female	Cox	.6706
	Wilcoxon	.4629

Test of Positive linear trend

Sex	Test	P-value (One tail Normal)
Male	Cox	.2625
	Wilcoxon	.2031
Female	Cox	.1604
	Wilcoxon	.1831

Table 2b

P-values of pairwise tests for the differences in mortality between treatment groups in the mouse study

Male mice

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: b:lta.mma

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		1.0866	NEG	1.8729	1.8655		1.9650		1.9603
	PROB	.1487	.2972		.1711	.1720		.1610		.1615
0 VS. 2	CHISQ		.3144	NEG	.0941	.0939		.0045		.0045
	PROB	.2850	.5750		.7590	.7593		.9468		.9468
0 VS. 3	CHISQ		.6455	NEG	.8912	.8904		1.3963		1.3951
	PROB	.2078	.4217		.3452	.3454		.2373		.2375
1 VS. 2	CHISQ		.0410	POS	.5120	.5105		1.2246		1.2220
	PROB	.4198	.8395		.4743	.4749		.2685		.2690
1 VS. 3	CHISQ		.0000	POS	.0946	.0941		.0976		.0973
	PROB	.5000	1.0000		.7584	.7590		.7547		.7551
2 VS. 3	CHISQ		.0000	NEG	.2523	.2514		1.2422		1.2392
	PROB	.5000	1.0000		.6154	.6161		.2651		.2656

Female mice

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: b:lta.fma

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.0000	POS	.0526	.0525		.5243		.5236
	PROB	.5728	1.0000		.8186	.8187		.4690		.4693
0 VS. 2	CHISQ		.0000	POS	.1674	.1672		1.0038		1.0022
	PROB	.5728	1.0000		.6824	.6826		.3164		.3168
0 VS. 3	CHISQ		.2876	POS	.3507	.3492		.1605		.1601
	PROB	.2984	.5917		.5537	.5545		.6887		.6890
1 VS. 2	CHISQ		.0000	POS	.0021	.0021		.0576		.0576
	PROB	.5802	1.0000		.9631	.9632		.8103		.8104
1 VS. 3	CHISQ		.1740	POS	.8831	.8806		1.6295		1.6243
	PROB	.3385	.6766		.3474	.3480		.2019		.2025
2 VS. 3	CHISQ		.1740	POS	1.1667	1.1626		2.2419		2.2346
	PROB	.3385	.6766		.2801	.2809		.1343		.1350

Table 3

Tumor rates and p-values of the tested tumor types for positive linear trend in mouse study

Male mice	Tumor rate				
Organ/Tumor	C	L	M	H	P-value
	120		60	60	60
Adrenals/Lymphoma, Malignant	4	2	0	4	.0971
Brain/Lymphoma, Malignant	2	3	0	2	.3006
Gallbladder/Lymphoma, Malignant	5	4	5	3	.4808
Intestine-Small/Lymphoma, Malignant	6	7	2	4	.4696
Kidney/Lymphoma, Malignant	15	17	10	14	.0918
Lacrimal gland/Cystadenoma	4	2	2	6	.0233
Lacrimal gland/Lymphoma, Malignant	4	4	1	3	.4525
Liver/Lymphoma, Malignant	12	15	11	12	.2261
Lung/Alveolar, Bronchiolar adenoma	13	7	8	9	.2226
Lung/Lymphoma, Malignant	13	12	8	12	.0643
Lymph node/Lymphoma, Malignant	7	4	3	4	.3470
Lymph node, Axillary/Lymphoma, Malignant	0	1	2	3	.0165
Lymph node, Mandibular/Lymphoma, Malignant	17	14	10	11	.3289
Lymph node, Mesenteric/Lymphoma, Malignant	20	18	13	16	.1845
Lymph node, Renal/Lymphoma, Malignant	6	3	5	5	.1668
Lymph node, Sublumbar/Lymphoma, Malignant	3	2	5	4	.1155
Lymph node, Tracheobronchial/Lymphoma, Malignant	4	4	4	4	.2332
Nasal cavity, Turbinate/Lymphoma, Malignant	5	6	2	4	.3777
Pancreas/Lymphoma, Malignant	11	9	6	10	.0687
Pituitary/Lymphoma, Malignant	2	0	1	2	.1861
Salivary gland/Lymphoma, Malignant	9	9	3	7	.2748
Spleen/Lymphoma, Malignant	19	17	12	16	.0889
Stomach/Lymphoma, Malignant	3	5	2	6	.0664
Subcutaneous tissue/Schwannoma, Malignant	0	0	0	1	.2208
Thymus/Lymphoma, Malignant	2	4	2	5	.0493
Thyroid/Lymphoma, Malignant	2	2	1	3	.1137
Trachea/Lymphoma, Malignant	0	1	0	1	.2028

Table 3 continued to the next page

Table 3 continued from the previous page

Female mice

Bone, Other sites/Osteoma, Benign	0	1	0	1	.2101
Intestine-large, Cecum/Lymphoma, Malignant	9	5	3	6	.2506
Intestine-large, Colon/Lymphoma, Malignant	9	5	4	5	.4262
Intestine-small, Ileum/Lymphoma, Malignant	12	4	1	8	.1557
Intestine-small, Jejunum/Lymphoma, Malignant	7	4	1	5	.2808
Lacrimal gland/Lymphoma, Malignant	7	3	1	4	.3736
Lung/Alveolar, Bronchiolar adenoma	9	12	3	9	.1777
Thyroid/Lymphoma, Malignant	7	2	4	3	.5382
Urinary bladder/Lymphoma, Malignant	14	8	6	8	.4867

Table 4

Intercurrent mortality rates in the rat study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	8/120 (6.67)	2/ 60 (3.33)	2/ 60 (3.33)	7/ 60 (11.67)
	53- 78	11/112 (15.83)	5/ 58 (11.67)	10/ 58 (20.00)	14/ 53 (35.00)
	79- 95	30/101 (40.83)	15/ 53 (36.67)	14/ 48 (43.33)	7/ 39 (46.67)
	96-104	22/ 71 (59.17)	10/ 38 (53.33)	7/ 34 (55.00)	5/ 32 (55.00)
	TERM. SACR	49/120 (40.83)	28/ 60 (46.67)	27/ 60 (45.00)	27/ 60 (45.00)
FEMALE					
	0 - 52	4/120 (3.33)	1/ 60 (1.67)	2/ 60 (3.33)	5/ 60 (8.33)
	53- 78	26/116 (25.00)	11/ 59 (20.00)	16/ 58 (30.00)	13/ 55 (30.00)
	79- 95	26/ 90 (46.67)	17/ 48 (48.33)	14/ 42 (53.33)	15/ 42 (55.00)
	96-104	20/ 64 (63.33)	12/ 31 (68.33)	8/ 28 (66.67)	7/ 27 (66.67)
	TERM. SACR	44/120 (36.67)	19/ 60 (31.67)	20/ 60 (33.33)	20/ 60 (33.33)

Note: Except the TERM. SACR. row, an entry of this table =number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 5a

P-values of tests for positive linear trend in mortality in the rat study

Test of homogeneity

Sex	Test	P-value (One tail Chi-Sqr.)
Male	Cox	.8402
	Wilcoxon	.5624
Female	Cox	.8297
	Wilcoxon	.6398

Test of Positive linear trend

Sex	Test	P-value (One tail Normal)
Male	Cox	.3892
	Wilcoxon	.1574
Female	Cox	.2198
	Wilcoxon	.1329

Table 5b

P-values of pairwise tests for the differences in mortality between treatment groups in the rat study

Male rats

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: b:ltb.mrt

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.3433	NEG	.4923	.4919		.6677		.6674
	PROB	.2785	.5579		.4829	.4831		.4138		.4140
0 VS. 2	CHISQ		.1395	NEG	.0426	.0426		.0135		.0135
	PROB	.3536	.7088		.8365	.8365		.9076		.9076
0 VS. 3	CHISQ		.1395	NEG	.0002	.0002		.6085		.6075
	PROB	.3536	.7088		.9884	.9884		.4354		.4357
1 VS. 2	CHISQ		.0000	POS	.0929	.0929		.3977		.3975
	PROB	.5000	1.0000		.7605	.7[illegible]		.5283		.5284
1 VS. 3	CHISQ		.0000	POS	.4561			1.8757		1.8715
	PROB	.5000	1.0000		.4995	.4[illegible]		.1708		.1713
2 VS. 3	CHISQ		.0000	POS	.1017	.1015		.8047		.8036
	PROB	.5727	1.0000		.7498	.7500		.3697		.3700

Female rats

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: b:ltb.frt

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.2475	POS	.1603	.1599		.0543		.0543
	PROB	.3111	.6190		.6889	.6893		.8157		.8158
0 VS. 2	CHISQ		.0758	POS	.4559	.4556		1.1248		1.1239
	PROB	.3936	.7831		.4996	.4997		.2889		.2891
0 VS. 3	CHISQ		.0758	POS	.4145	.4142		.9166		.9162
	PROB	.3936	.7831		.5197	.5198		.3384		.3385
1 VS. 2	CHISQ		.0000	NEG	.0282	.0281		.5695		.5690
	PROB	.5000	1.0000		.8667	.8668		.4504		.4507
1 VS. 3	CHISQ		.0000	NEG	.0280	.0280		.5065		.5061
	PROB	.5000	1.0000		.8671	.8672		.4767		.4768
2 VS. 3	CHISQ		.0000	POS	.0001	.0001		.0015		.0015
	PROB	.5767	1.0000		.9931	.9931		.9691		.9691

Figure 1b

Kaplan-Meier Estimates of the survival distributions (Female mice)

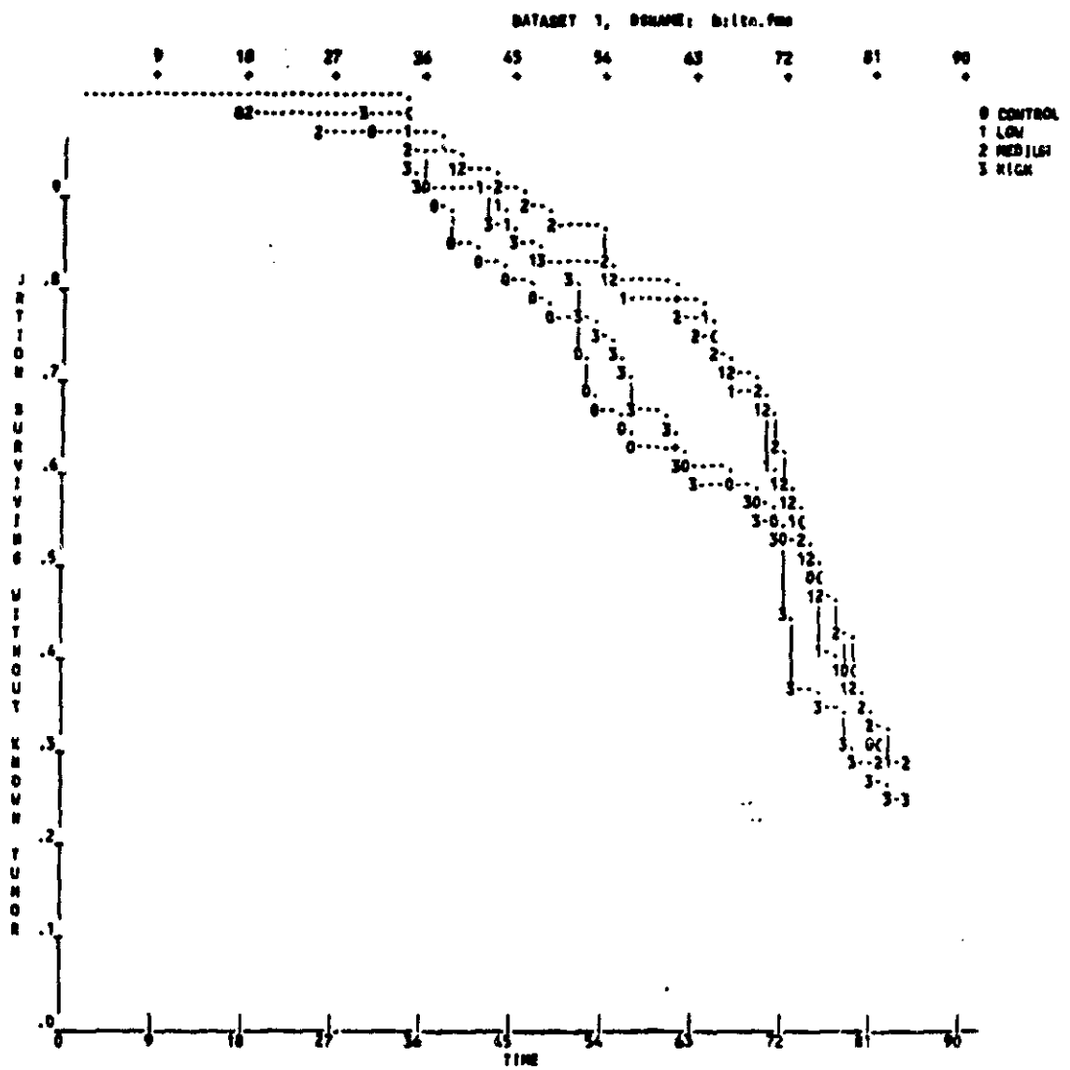


Figure 2a

Kaplan-Meier Estimates of the survival distributions (Male rats)

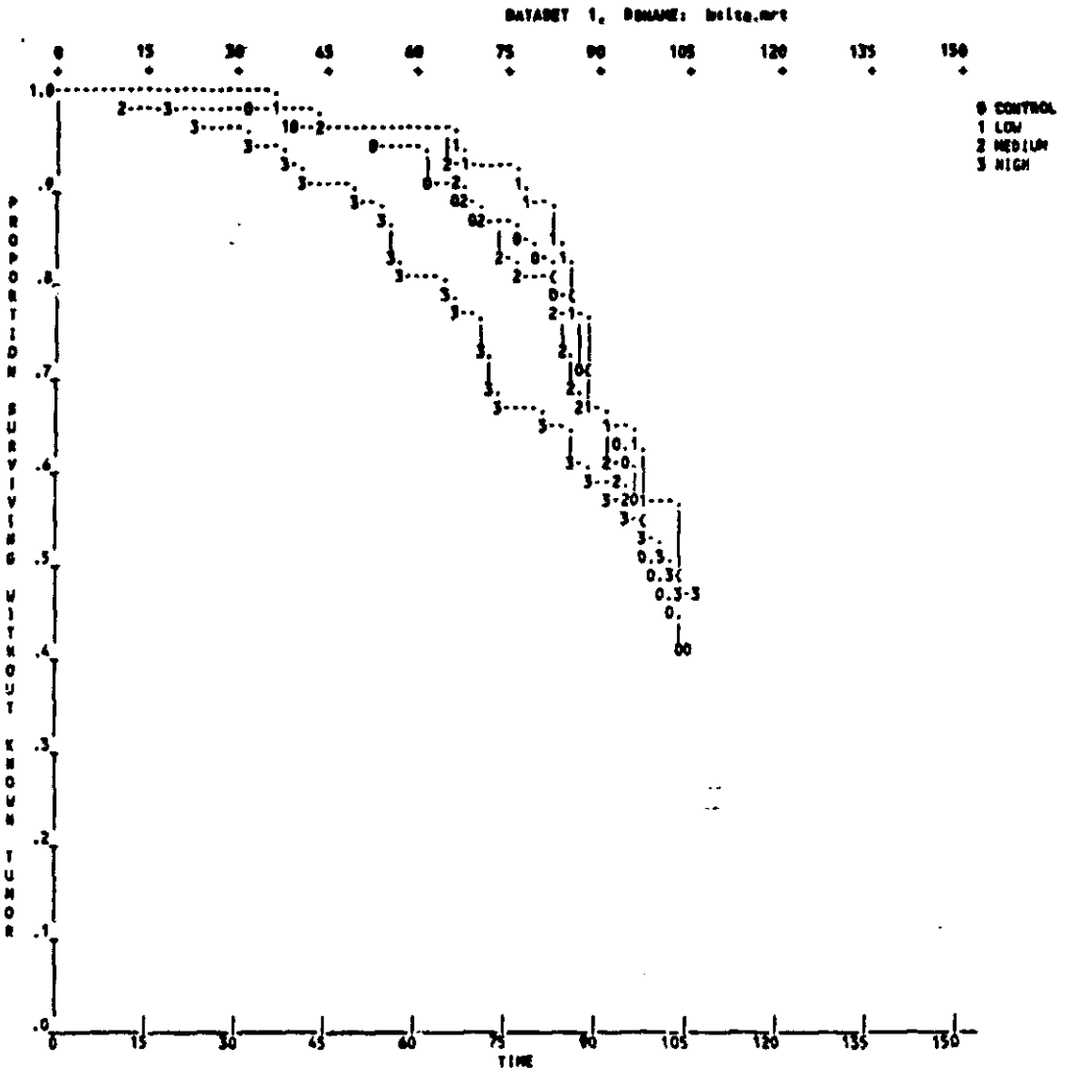
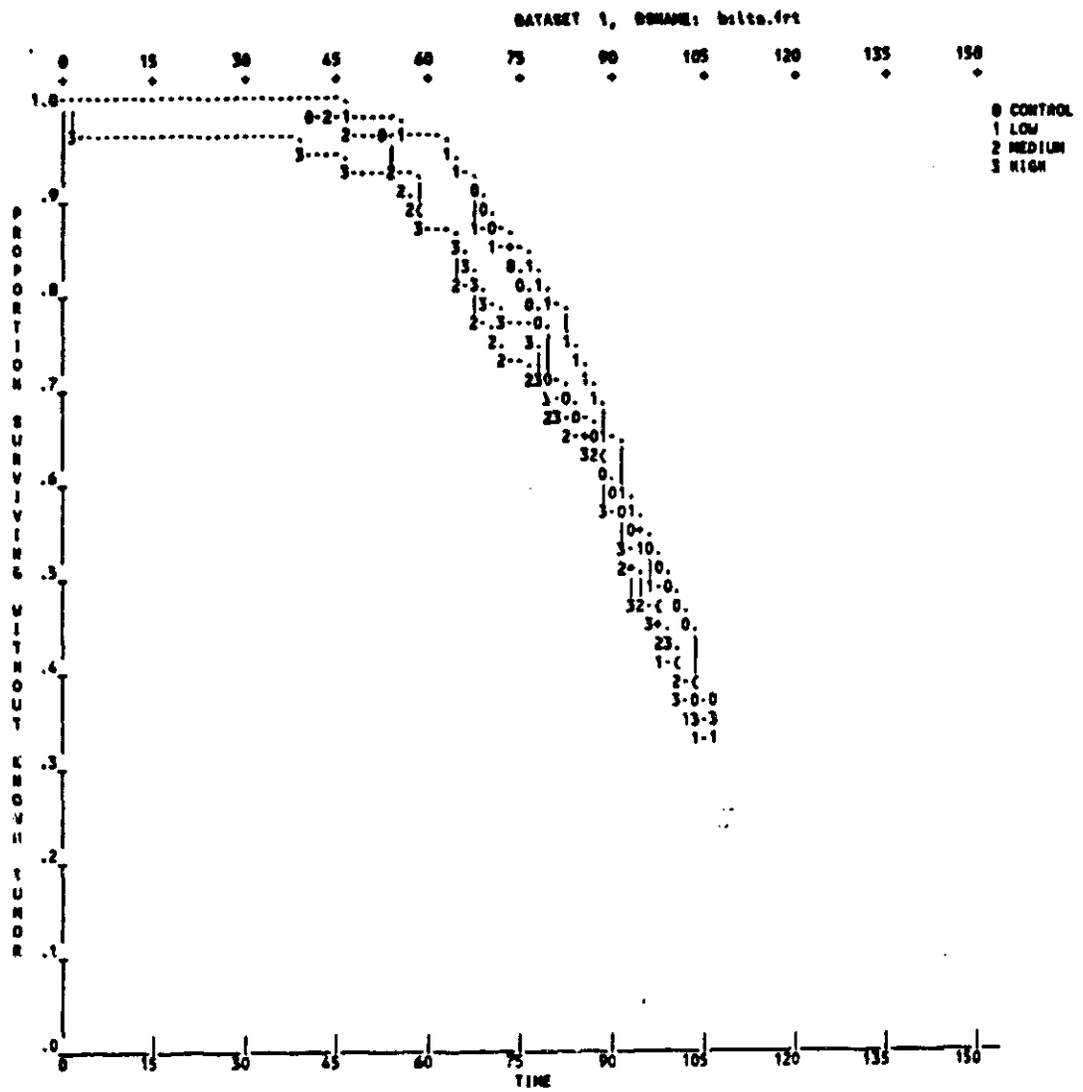


Figure 2b

Kaplan-Meier Estimates of the survival distributions (Female rats)



PHARMACOLOGY REVIEW

K. BONGIOVANNI

PHARMACOLOGIST'S REVIEW COVERSHEET ~~OCT 26 1993~~

OCT 14 1993

NDA No.:	20-312
SPONSOR:	G.H. Besselaar Associations Princeton Forrestal Center 103 College Road Princeton, NJ 08540-6681
DRUG:	Moexipril
CATEGORY:	Nonpeptidyl, nonsulfahydryl ACE inhibitor
EVALUATION:	Pre-Clinical Pharmacology and Toxicology

- The submission generally consistent with Agency's Format Guidelines: Yes (X) No ( )

- Appropriate studies submitted: Yes (X) No ( )

- Primary adverse pharmacological effect:

  Hyperplasia of JG apparatus; elevated BUN and creatinine in rats and dogs.

- Target organs in toxicity studies:

  Kidney

- Reproductive or developmental toxicity: Yes (X) No ( )

  If yes, explain briefly: Insignificant isolated dose-independent instances of cytoskeletal abnormatlities in rats and rabbits of Segment II (teratogenicity) study.

- Carcinogenicity studies:

  Number of studies: Rat: 1 Mouse: 1 Other:
  Results: +, -, ± (-) (-) ( )

- Sub-chronic/Chronic blood level studies:

  Rat: X Dog: X Other: Mice

- GLP Problems: Yes ( ) No (X)

- OTHER COMMENTS

cc: Orig. NDA 20-312
HFD-345/GJames
HFD-110
HFD-110/CSO
HFD-110/DPatel
HFD-110/NOza

K.F. N... JANN...

OCT 14 1993

NDA 20-312

REVIEW AND EVALUATION OF PRE-CLINICAL PHARMACOLOGY AND TOXICOLOGY DATA

Narendra B. Oza and D.G. Patel

NDA 20-312

TABLE OF CONTENTS

REVIEW AND EVALUATION OF PRE-CLINICAL PHARMACOLOGY AND TOXICOLOGY DATA

Narendra Oza, Ph.D. & D.G. Patel, Ph.D.

ORIGINAL NDA:	20-312
DATED:	December 18, 1992
CENTER RECEIPT DATE:	December 18, 1992
REVIEWER RECEIPT DATE:	February 23, 1993
SPONSOR:	G.H. Besselaar Associates Princeton Forrestal Center 103 College Road Princeton, NJ 08540-6681
DRUG:	
PROPRIETARY NAME:	MOEXIPRIL
GENERIC NAME:	Not given
CODE NAME/NUMBER:	CI-925; RS10085-197
STRUCTURE:	
CHEMICAL NAME:	2-[2-[[(1-Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-6,7-dimethoxy -1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, hydrochloride
MOLECULAR WEIGHT:	535.04
FORMULATION:	Tablets containing 7.5 and 15 mg Moexipril Hydrochloride and Lactose (NF), Crospovidine (NF), Magnesium Oxide (USP), Gelatin (NF) and Magnesium Stearate (NF).
RELEVANT IND'S:	
PHARMACOLOGIC CLASS:	Nonpeptidyl, nonsulfahydryl ACE inhibitor.

INDICATION: Hypertension

PROPOSED DOSING: 7.5, 15 or 30 mg daily

I. PHARMACODYNAMICS:

A. Actions Related to Primary Therapeutic Use:

(1) In Vitro Studies:

(a): In Vitro Angiotensin Converting Enzyme (ACE) Inhibitory Activity:

Unpurified Enzyme in Rat Plasma and Guinea Pig Serum: The following compounds were evaluated for their ability to inhibit ACE in unpurified rat plasma and guinea pig serum (Table I). In cases where the compound is a prodrug, the IC_{50} value (concentration that inhibits 50% of the enzyme activity) for the active metabolite is shown in parenthesis.

TABLE I

Compound	IC_{50}(M)
Moexipril[a]	1.65×10^{-7} ($1.75 \times 10_{,9}$ = diacid, Moexiprilat)
Moexipril[b]	4.10×10^{-8} (2.60×10^{-9} = diacid, Moexiprilat)
Enalapril[a]	2.00×10^{-7} (6.00×10^{9} = diacid, Enalaprilat)
Enalapril[b]	1.42×10^{-7} (3.07×10^{-9} = diacid, Enalaprilat)
Ramipril[a]	8.00×10^{-9} (4.00×10^{-10} = diacid, Ramiprilat)
Perindopril[a]	2.50×10^{-9} (8.00×10^{-10} = diacid, Perindoprilat)
Lisinopril[a]	2.90×1^{-9}
Captopril[a]	4.00×10^{-7}
Captopril[b]	1.32×10^{-8}

[a] rat plasma
[b] guinea pig serum

The diacid, "biologically-active" forms of Moexipril and Enalapril (Moexiprilat and Enalaprilat) were nearly equipotent in vitro, while their respective monoesters (prodrugs) had potency ratio of 3 to 1, in guinea pig serum. The diacid, Moexiprilat, was approximately five times as potent as Captopril.

The relative potency of Moexiprilat as compared to Captopril was dependent on enzyme source; Moexiprilat was 23 and 5 fold more potent than Captopril in rat plasma and guinea pig serum, respectively.

Enzyme Purified from Rabbit Lung: The following compounds were evaluated for their ability to inhibit ACE purified from rabbit lung (Table II).

TABLE II

Activities of ACE Inhibitors in Purified ACE from Rabbit Lung:

Compound	IC_{50}(M)
Moexipril	2.7×10^{-6} (2.1×10^{-9} = diacid, Moexiprilat)
Enalapril	7.7×10^{-6} (5.4×10^{-9} = diacid, Enalaprilat)
Ramipril	5.5×10^{-6} (1.5×10^{-9} = diacid, Ramiprilat)
Perindopril	4.0×10^{-6} (3.2×10^{-9} = diacid, Perindoprilat)
Lisinopril	2.9×10^{-9}
Captopril	6.7×10^{-9}

Due to the absence of hydrolases in the purified ACE preparation the prodrug inhibitors were not converted to the active diacids in vitro. Therefore, the prodrug ACE inhibitors Moexipril, Ramipril, Enalapril and Perindopril were weak inhibitors of purified ACE from rabbit lung (Table II). The diketopiperazine derivative of Meoxipril was biologically inactive at concentrations up to 10^{-5}M. Moexiprilat and Ramiprilat were more potent inhibitors of ACE than Perindoprilat, Enalaprilat, Captopril or Lisinopril. The ratios between IC_{50} values for prodrugs and respective diacids reveal that the active diacids were a thousand times more active against purified ACE than the respective prodrugs.

(b). Specific Spasmolytic Activity (Rabbit Aorta):

Moexipril, its active metabolite Moexiprilat, were compared to reference agents

(Enalapril and Enalaprilat), for the ability to affect vascular contractions induced in isolated rabbit aortae. Cumulative concentration-response curves to the agonists, KCl, phenylephrine, angiotensin I and angiotensin II, were obtained with and without the ACE inhibitors. Contractions induced by KCl, phenylephrine and angiotensin II were not altered by high concentrations (10^{-5}M) of ACE inhibitors. However, angiotensin I-induced contractions of isolated rabbit aortic rings were selectively attenuated by ACE inhibitors with a significant right-ward shift in the dose response curve. Angiotensin I ED_{50} values at 10^{-7} M of Moexipril and Moexiprilat were two- and six-fold greater than control values, respectively. These data indicate that ACE exists in vascular tissue and that Moexiprilat is a potent selective ACE inhibitor in vascular tissue.

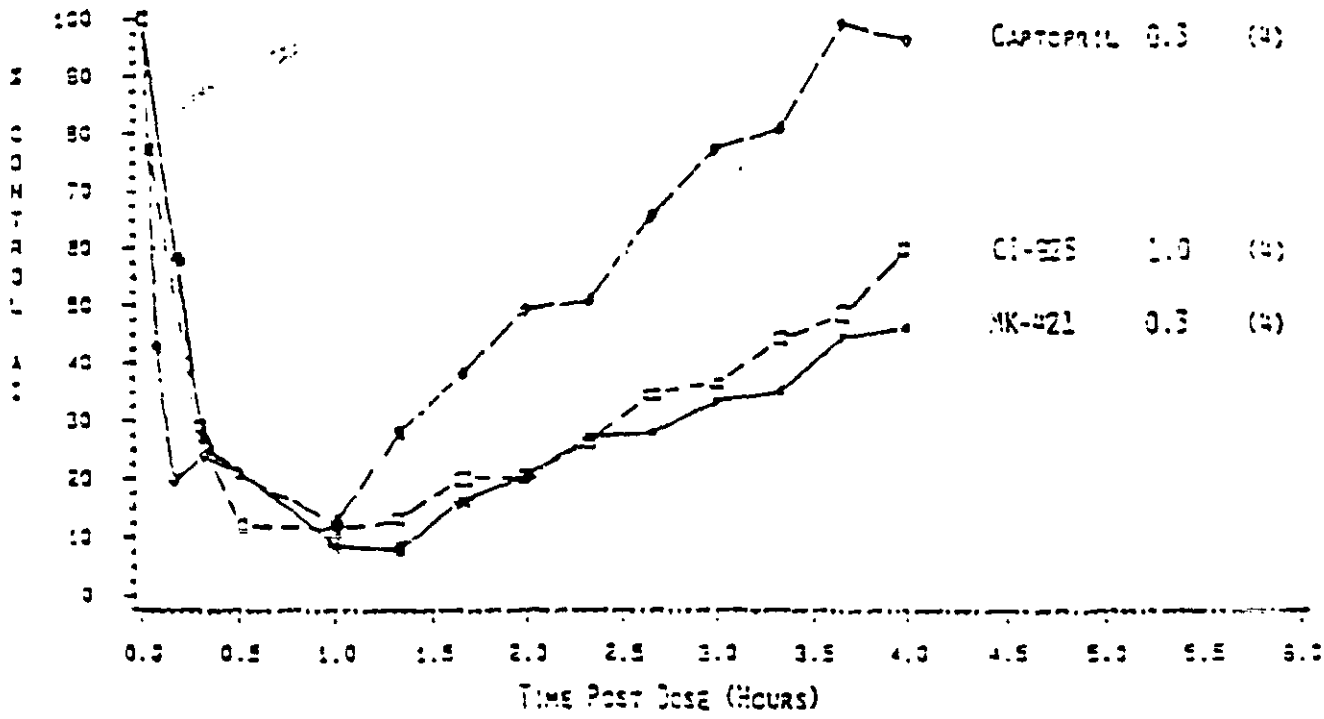
(2): In Vivo Studies:

(a): Antihypertensive Effect (Peripheral):

Rats: Blood pressure and heart rate responses to intravenous angiotensin I (0.32 µg/kg), angiotensin II (0.32 µg/kg), norepinephrine (1 µg/kg), or bradykinin (10 µg/kg) were determined in conscious male normotensive rats before and after a single oral dose of Moexipril (0.3, 1, and 3 mg/kg), Enalapril (0.1, 0.3, 1, and 3 mg/kg) or Captopril (0.03, 0.1, 0.3 and 3 mg/kg).

Moexipril, Enalapril and Captopril had no significant direct effect on blood pressure or heart rate. Similarly, these ACE inhibitors did not change blood pressure or heart rate responses to angiotensin II or norepinephrine. The ACE inhibitors did, however, block the vasopressor response to angiotensin I and potentiated the vasodepressor response to bradykinin. Onset of action was rapid (within five minutes), with maximum inhibition of the angiotensin I response occurring within one hour of dosing. Figure 1 shows the time-response curves expressed as percent of control angiotensin I-induced blood pressure response to a single oral dose of 0.3 mg/kg of the ACE inhibitors Captopril and Enalapril and 1.0 mg/kg of Moexipril. At equieffective doses, Moexipril exhibited a longer duration of action than Captopril and was somewhat less potent (1/2 log unit) than Enalapril and Captopril (Table III).

The dose-dependent antihypertensive effects of chronic Moexipril (0.1 to 30 mg/kg, orally) was examined in SHR. Oral treatment of SHR with Moexipril produced dose-dependent decreases in blood pressure (Figure 2). At a dose of 0.1 mg/kg/day the blood pressure decrease was significant after 4 weeks of treatment when compared to the vehicle-treated control group (177 mmHg vs 194 mmHg). A consistent blood pressure reduction was seen at 1 mg/kg/day. The highest dose of 30 mg/kg/day Moexipril normalized blood pressure after 4 weeks of treatment (121 mmHg vs 194 mmHg).



Values are expressed as mean of percent of control vasopressor response to angiotensin I.

FIGURE 1 ACE Inhibition in Conscious Rats

Systolic blood pressure during chronic oral treatment with the ACE inhibitor moexipril

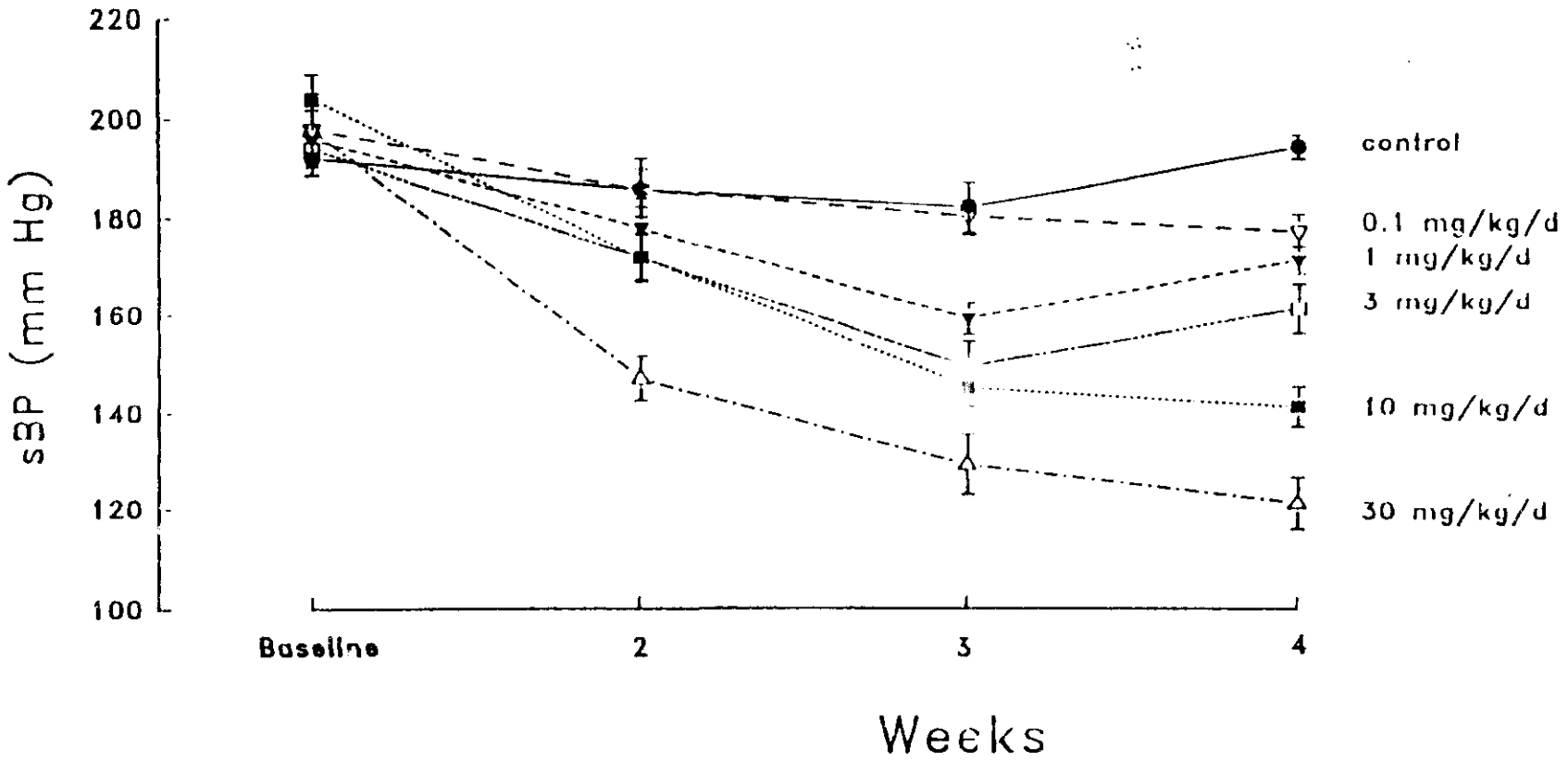


TABLE III

Inhibition of Vasopressor Response to Angiotensin I (AI) in Conscious Normotensive Rats

Treatment mg/kg PO	Minutes from Dose to Max AI Inhibition	Max % AI Inhibition	Time (Minutes) to 50% Recovery from Max AI Inhibition
Moexipril			
0.3	57 ± 30	42 ± 17	154 ± 24
1.0	50 ± 12	92 ± 3	214 ± 15
3.0	40 ± 14	96 ± 2	233 ± 8
Enalapril			
0.1	75 ± 15	59 ± 7	115 ± 6
0.3	53 ± 8	78 ± 3	180 ± 12
1.0	37 ± 14	87 ± 5	>240
3.0	95 ± 37	88 ± 1	218 ± 23
Captopril			
0.03	29 ± 13	31 ± 11	39 ± 15
0.1	46 ± 9	60 ± 6	100 ± 9
0.3	36 ± 10	84 ± 6	128 ± 8
3.0	44 ± 19	100 ± 0	217 ± 12

All drugs were administered by gavage
Angiotensin I dose = 0.3 µg/kg IV
Control blood pressure changes in response to AI were 45-55 mm/Hg

Spontaneously hypertensive rats (SHR) were given Moexipril (10 mg/kg/day), Enalapril (10 mg/kg/day) or vehicle for 4 weeks. Blood pressure was measured in conscious unrestrained SHR challenged with intravenous injections of angiotensin I (100 ng), angiotensin II (100 ng) or bradykinin (10, 100, 300 and 1000 ng).

Following four weeks of treatment averages for mean arterial blood pressure were 140 ± 6.5, 139 ± 3.5 and 174 ± 6.1 mmHg, in the Moexipril, Enalapril and control groups, respectively. Both Moexipril and Enalapril selectively inhibited (by 85% and 88%, respectively; figure 3) the vasopressor response to intravenous angiotensin I and potentiated the depressor response to intravenous bradykinin (Figure 4). Moexipril and Enalapril proved to be equipotent at lowering blood pressure with similar inhibition of ACE activity occurring in vivo after chronic oral treatment.

Figure 3

Blood pressure response to i.v. Angiotensin I and Angiotensin II

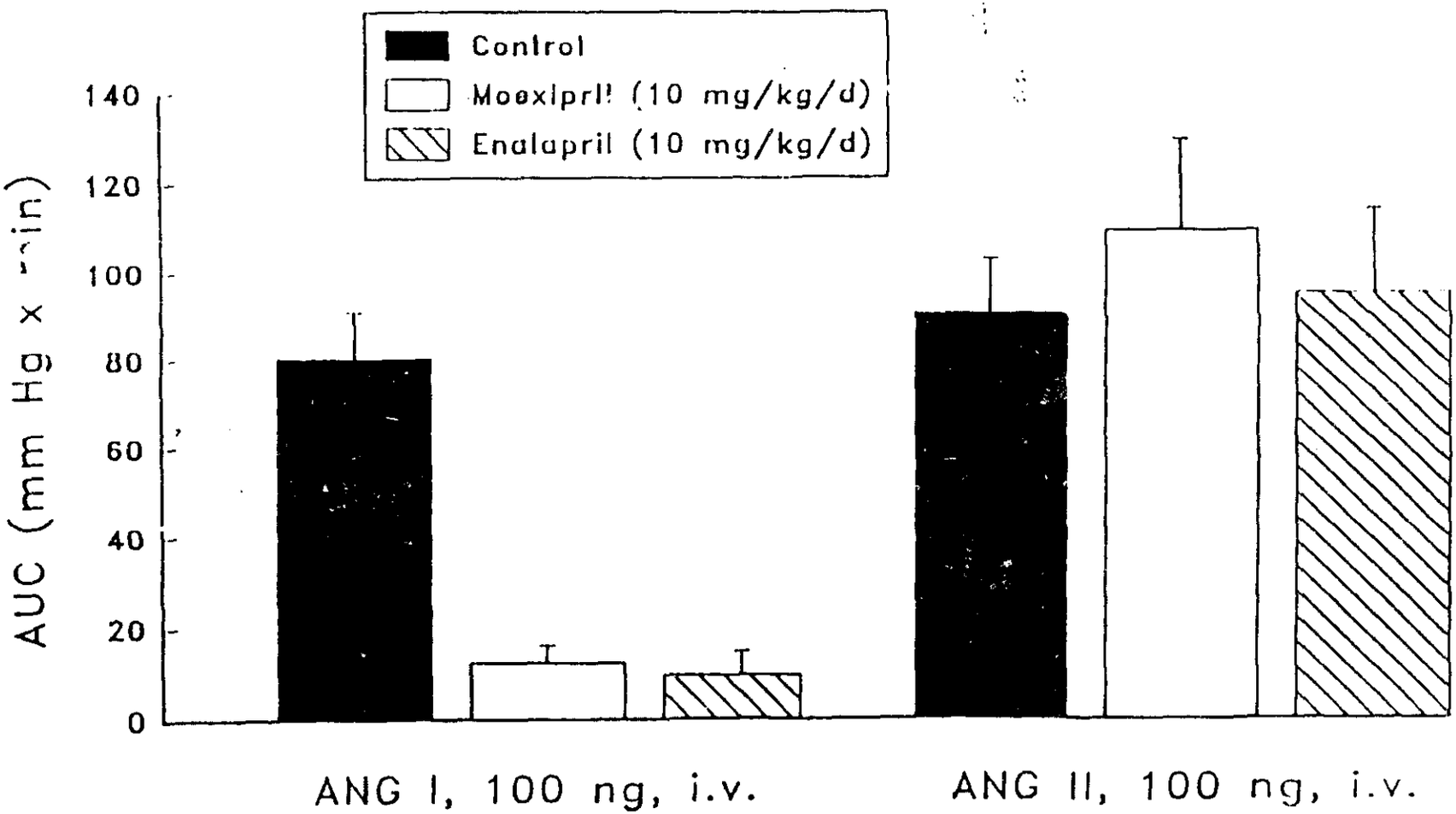
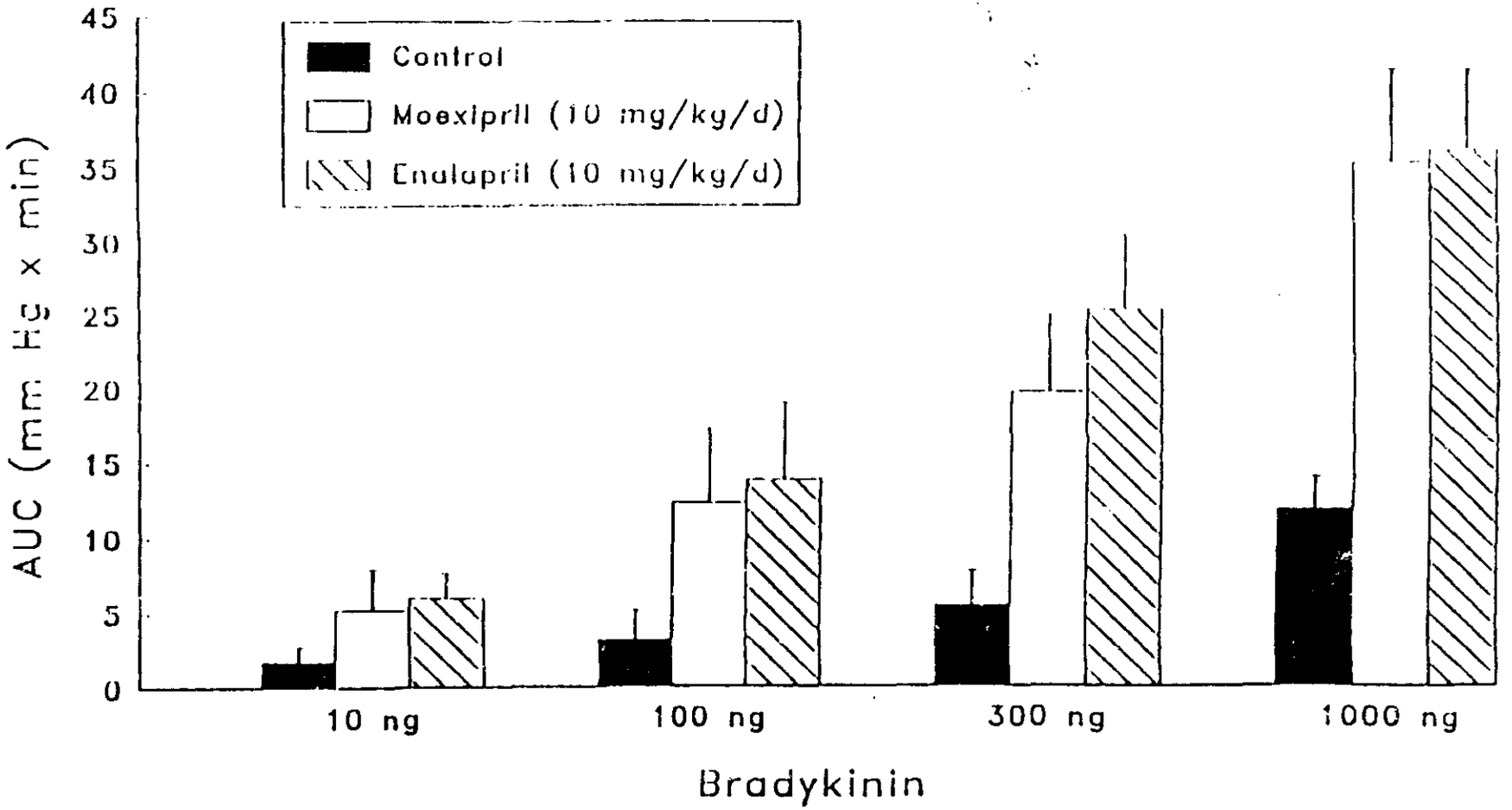


Figure 4

Decreases in blood pressure after various doses of i.v. bradykinin



Renin-dependent hypertensive rats (the left renal artery clipped) were used to assess antihypertensive effects of ACE inhibitors. Orally administered Moexipril (0.03 to 10 mg/kg), Enalapril (0.03 to 10 mg/kg) and Captopril (0.03 to 100 mg/kg) induced dose-related decreases in aortic blood pressure with only minimal effects on heart rate (Figures 5-7).

In SHR rats, the combination of Moexipril 10 mg/kg and Hydrochlorothiazide 5 mg/kg produced a synergistic reduction in blood pressure. Additionally, the combination of orally administered Moexipril (10 mg/kg) plus Nicardipine (10 mg/kg) potentiated the decrease in blood pressure seen after administration of the agents individually.

Dogs: Aortic blood pressure and heart rate were determined in conscious normotensive Mongrel dogs. Effects of orally administered Moexipril (CI-925; 0.3, 1, 3, and 10 mg/kg), Enalapril (0.1, 0.3, 1, and 3 mg/kg) and Captopril (0.1, 0.3, 1, and 3 mg/kg) were evaluated in terms of reduction of the blood pressure response to angiotensin I. Captopril had a more rapid onset (Figure 8) than either Moexipril or Enalapril, and the ACE inhibitory potency (Table IV) of Moexipril (0.3 mg/kg, 11.0 ± 4.0 % AI inhibiton)) was less than that of either Captopril (0.3 mg/kg, 74.7 ± 5.2 % AI inhibition) or Enalapril (0.3 mg/kg, 84.6 ± 5.7 % AI inhibition).

In anesthetized and vagotomized dogs, Moexiprilat (0.3 and 3.0 mg/kg IV) selectively inhibited the pressor responses to angiotensin I (100% inhibition at either dose) without any significant effect on the pressor responses to epinephrine, norepinephrine, tyramine, DMPP, angiotensin II or carotid occlusion. At 3.0 mg/kg Moexiprilat selectively potentiated the depressor response to bradykinin without any significant effect on the vasodepressor responses to acetylcholine or isoproterenol. The amplitude of the bradykinin vasodepressor response was potentiated by about 33%. The time for 50% recovery of blood pressure was potentiated from a control of 28 ± 8 seconds to 1790 ± 460 seconds after 3.0 mg/kg of Moexiprilat.

The antihypertensive effects of orally administered Moexipril and Enalapril at doses of 3 and 10 mg/kg were examined in perinephritic (two-kidney) hypertensive dogs. Moexipril and Enalapril had equipotent antihypertensives effect at both doses. #/group?

Monkeys: Blood pressure and heart rate responses to intravenous angiotensin I and bradykinin were examined in conscious, chair-restrained female rhesus monkeys before and after a single oral dose of Moexiprilat (3 mg/kg) or Enalaprilic acid (10 mg/kg). Moexiprilat moderately decreased mean arterial blood pressure (-19 mmHg) and heart rate (-17 beats/min). Angiotensin I-induced pressor responses were modestly inhibited (-26%) and bradykinin depressor responses were moderately potentiated (33%). Enalaprilic acid decreased mean arterial pressure (-14 mmHg) with no apparent effect on heart rate. The pressure responses to angiotensin I were inhibited (-35-59%).

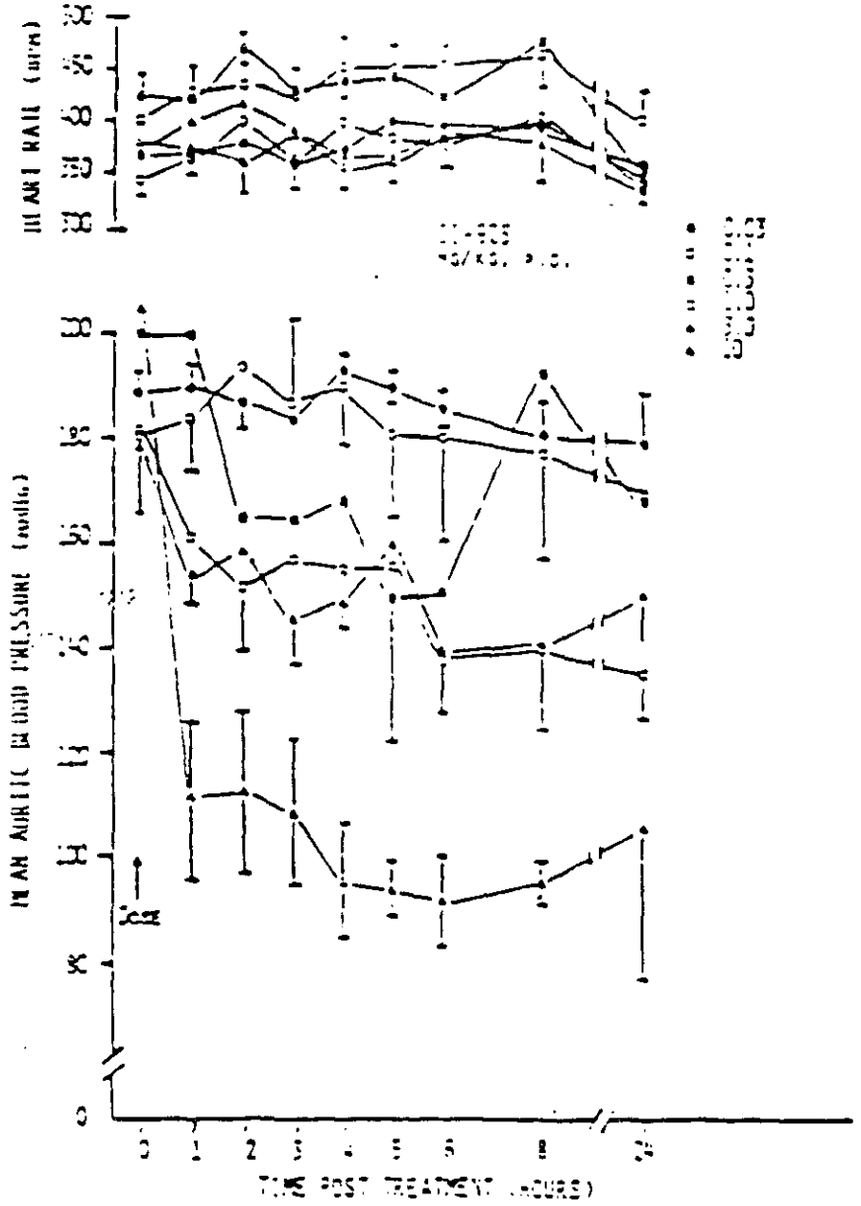


FIGURE 5 Effect of CI-925 on Blood Pressure in Conscious Renal Hypertensive Rats

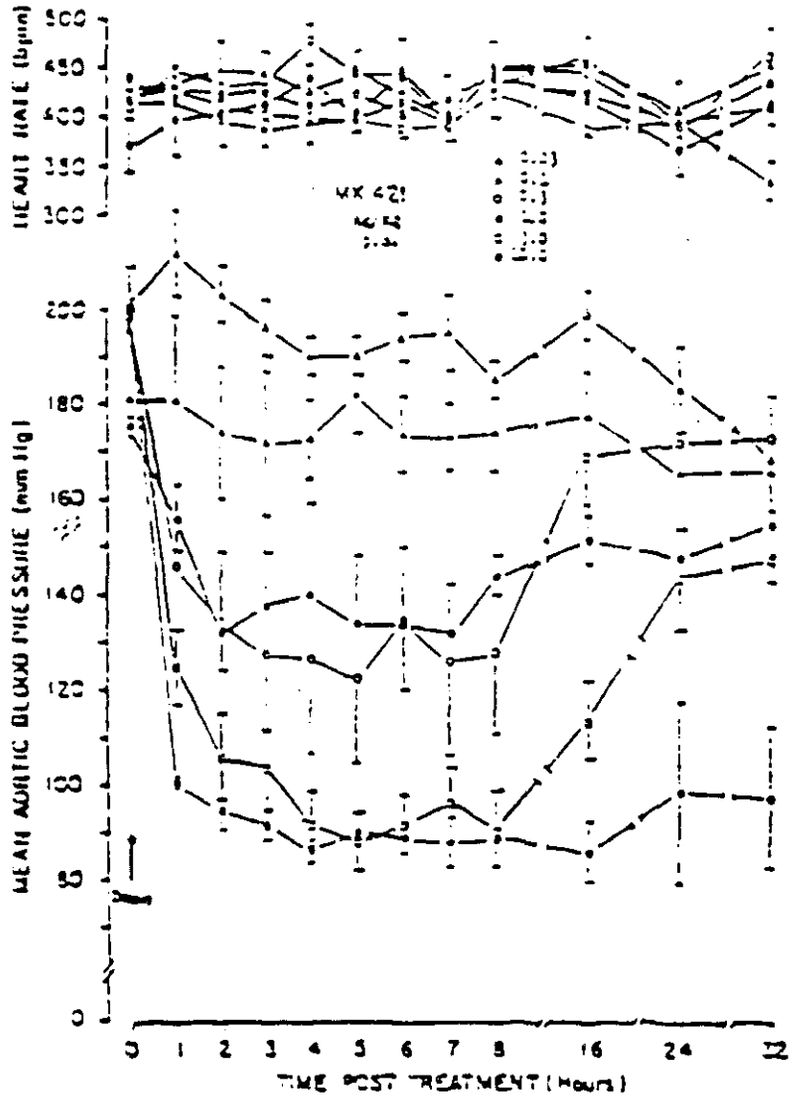


FIGURE 6 Effect of Enalapril on Blood Pressure in Conscious Renal Hypertensive Rats

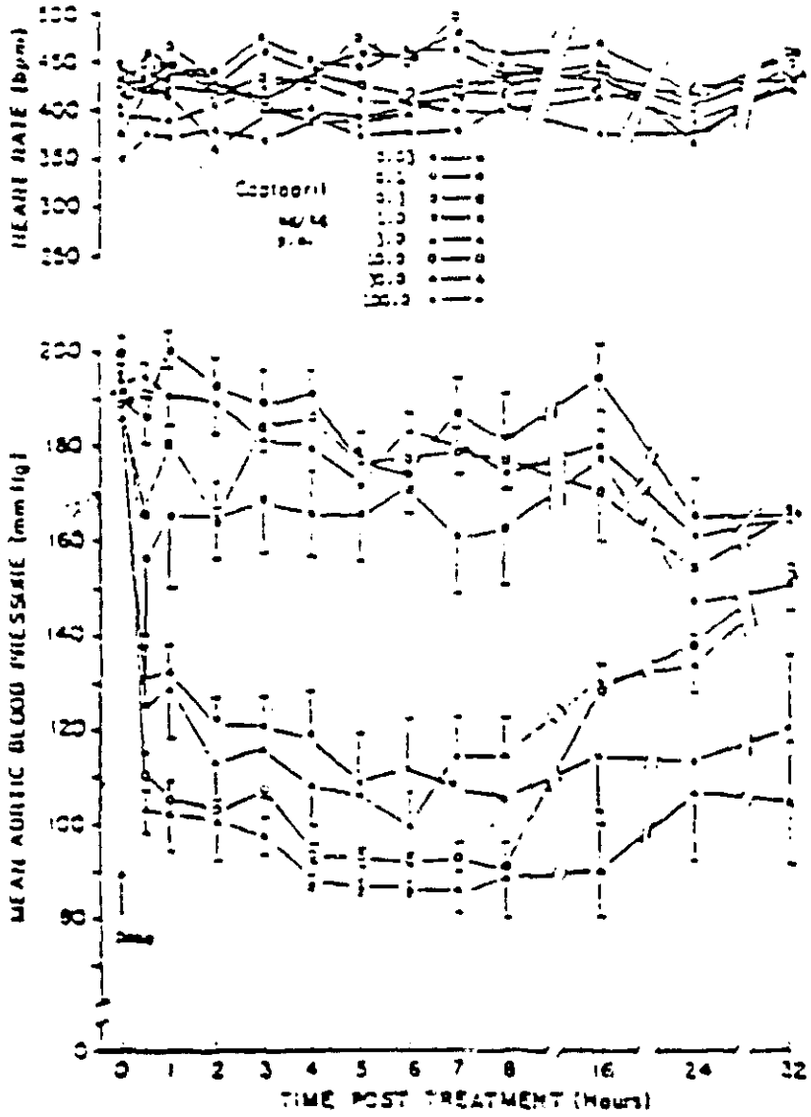


FIGURE 7 Effect of Captopril on Blood Pressure in Conscious Renal Hypertensive Rats

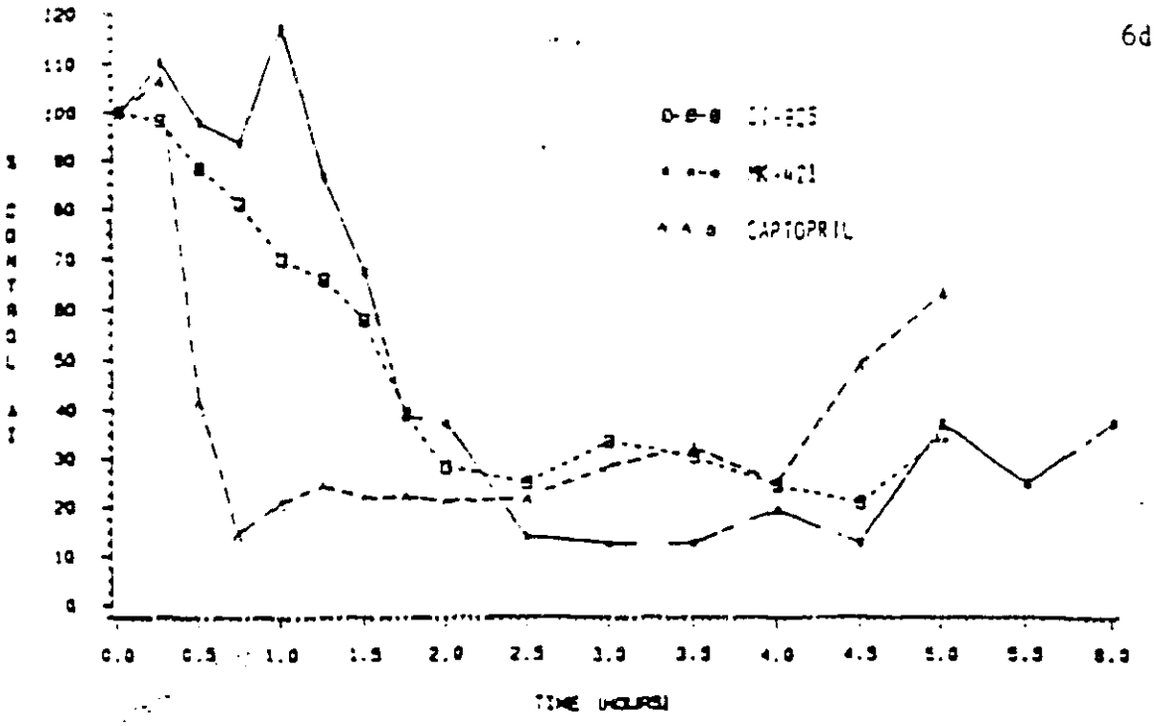


FIGURE 8 ACE Inhibition in Conscious Dogs Following Oral Administration of Converting Enzyme Inhibitors .3 mg/kg)

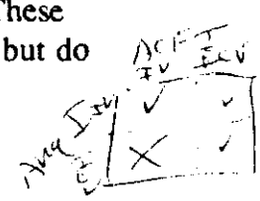
TABLE IV Inhibition of Angiotensin Responses in Conscious Normotensive Dogs

Treatment mg/kg PO		Minutes from Dose to Max AI Inhibition	Max % AI Inhibition	Time (Minutes) To 50% Recovery from Max AI Inhibition
CI-925	0.3	100 ± 13	11.0 ± 4.0	118 ± 2
(N=2)	1.0	250 ± 25	49.0 ± 6.0	>300
	3.0	196 ± 46	89.0 ± 6.0	>300
	10	135 ± 38	97.0 ± 1.0	248 ± 52
Enalapril	0.1	45 ± 15	19.6 ± 5.3	86 ± 14
(N=2)	0.3	165 ± 15	84.6 ± 5.7	296 ± 1
	1.0	180 ± 0	91.0 ± 0.1	>300
	3.0	165 ± 15	93.2 ± 6.8	>300
Captopril	0.1	60 ± 6	45.8 ± 12.6	119 ± 11
(N=4)	0.3	62 ± 4	74.7 ± 5.2	179 ± 34
	1.0	68 ± 13	86.4 ± 3.3	215 ± 38
	3.0	35 ± 5	89.4 ± 0.5	250 ± 9

Standard dose of AI=0.3 ug/kg, IV.
Control blood pressure changes in response to AI were 40-50 mmHg.

(b): Antihypertensive Effect (Central)

Moexipril, Moexiprilat, Enalapril or Captopril were given to normotensive rats either orally (PO), intravenously (IV) or intracerebral ventricularly (ICV). Angiotensin I was administered either IV or ICV before oral and after IV or ICV dosing of ACE inhibitors. After PO or IV administration, all of the ACE inhibitors attenuated the pressor response to IV angiotensin I, but had no effect on the pressor response to ICV angiotensin I. When ACE inhibitors were administered ICV, however, the pressor response to Angiotensin I was attenuated after its IV or ICV administration. These studies show that ACE inhibitors have an effect when administered centrally, but do not easily cross the blood brain barrier.



(c): Effects on Cardiovascular Function:

Several cardiovascular parameters were evaluated in the fully instrumented conscious normotensive dogs after oral administration of Moexipril, Enalapril or Captopril at 10 mg/kg. Heart rate increased 26 ± 7% above control value at 30-45 minutes post Moexipril dosing and remained elevated until approximately two hours following dose (Tables V & VI). Slight reductions in mean blood pressure of 10-13% were observed following Moexipril dosing. Cardiac output, dp/dt and dQ/dt were essentially unchanged for the first two hours following Moexipril dosing. Subsequently, cardiac output, dp/dt and dQ/dt were 6-14%, 16-18% and 13-17% below control values, respectively (Tables V & VI). Stroke volume decreased 12 ± 4% from a control value at 15 minutes following Moexipril dosing and remained approximately 20% below control for the remainder of the four-hour observation period. The sponsor has reported that essentially identical results were observed with Captopril and Enalapril. Furthermore, the sponsor also has reported that slight changes detected in most of the examined cardiovascular parameters were consistent with vehicle control studies previously observed in this model and with similar studies with the other ACE inhibitors. However, no data to support these observations was submitted. The sponsor concluded that oral administration of Moexipril to the conscious chronically-instrumented dogs at 10 mg/kg did not cause remarkable alterations in cardiovascular function. However, it is apparent from the data that Moexipril (10 mg/kg, po) induced moderate tachycardia on depression of cardiovascular indices relative to control behavior.

Intraduodenal administration of Moexipril (0.1 mg/kg to 10 mg/kg) to chronically instrumented anesthetized beagle dogs induced dose-dependent reductions in systolic and diastolic blood pressures measured via the femoral artery, with the maximal effect at 3 mg/kg (Table VII). Cardiac output, stroke volume, left ventricular pressures, dp/dt, respiratory rate, respiratory volume and pulmonary arterial or central venous pressures were altered but not dose-dependently (Table VII). Moexipril did not influence the norepinephrine - or isoproterenol - induced responses.

Table V

DRUG: PD 109,735-2K (P,Q)

DOSE: 10.0 mg/kg

ROUTE: PO

Effects of CI-925 on Cardiovascular Function in the Conscious Dog

n = 6

	CONTROL AVERAGE	Minutes Posttreatment							
		0 - 15	15 - 30	30 - 45	45 - 60	60 - 75	75 - 90	90 - 105	105 - 120
HR beats/min	82±8	4±7	12±8	26±7*	23±6*	23±6*	23±6*	18±4*	14±4*
MBP † mm Hg	84±7	0±8	-4±8	-9±7	-8±7	-12±5	-11±4	-12±4*	-9±4
SBP † mm Hg	114±8	0±5	-2±5	-6±5	-8±4	-12±2*	-9±4	-11±3*	-9±4
DBP † mm Hg	60±5	1±11	-2±15	-10±12	-11±10	-13±9	-14±8	-12±7	-11±8
TPR †† mm Hg/L/min	22.8±0.3	2±12	-6±15	-17±13	-16±11	-15±11	-10±10	-7±8	0±9
LV dP/dt mm Hg/sec	3524±495	0±2	2±4	0±5	4±4	-2±2	-7±3	-10±3*	-9±4
CO † L/min	2.48±0.37	-4±4	0±6	0±6	6±5	2±5	-3±5	-6±4	-9±4
SV † ml/beat	29.5±5.2	-8±5	-12±4*	-15±3*	-17±2*	-20±2*	-23±4*	-22±4*	-22±4*
d0/dt † ml/sec^2	10012±1145	1±2	2±4	0±5	1±3	-3±3	-7±3	-6±3	-10±2*

† n = 5
†† n = 4
*Significant at $p < .05$

(Values are % change from Control Average ± SEM)

Table VI

DRUG: PD 109,735-2K (P,Q)

DOSE: 10.0 mg/kg

ROUTE: PO

Effects of CI-925 on Cardiovascular Function in the Conscious Dog

n = 6

	CONTROL AVERAGE	Minutes Posttreatment							
		120-135	135-150	150-165	165-180	180-195	195-210	210-225	225-240
HR beats/min	82±8	13±6	16±7	14±6	17±7	14±8	14±6	12±7	11±6
MBP † mm Hg	84±7	-7±3	-4±3	-9±4	-2±4	-6±3	-10±1 *	-13±3 *	-10±4
SBP † mm Hg	114±8	-7±3	-5±3	-9±4	-4±3	-7±3	-9±1 *	-14±3 *	-11±1 *
DBP † mm Hg	60±5	-10±4	-4±6	-8±6	-3±6	-7±6	-12±5	-16±6	-9±7
TPR †† mm Hg/L/min	22.8±0.3	11±10	10±7	9±8	8±5	2±4	-2±6	-5±7	-3±7
LV/dP/dt mm Hg/sec	3524±495	-12±5	-12±5	-17±3 *	-16±2 *	-16±4 *	-16±3 *	-18±5 *	-14±6
CO † L/min	2.48±0.37	-14±4 *	-13±3 *	-13±4 *	-10±1 *	-10±1 *	-7±5	-9±2 *	-6±2 *
SV † ml/beat	29.5±5.2	-21±4 *	-25±6 *	-29±4 *	-22±5 *	-22±5 *	-21±5 *	-18±5 *	-19±3 *
dQ/dt † ml/sec^2	10012±1145	-13±2 *	-13±2 *	-15±2 *	-15±1 *	-16±2 *	-16±2 *	-17±2 *	-16±2 *

(Values are % change from Control Average ± SEM)

† n = 5
†† n = 4
*significant at $p < .05$

TABLE VII

Effects of Moexipril on Cardiovascular Function in Anesthetized Dogs:

Parameters	% Maximum Change ≤120 Min Post Moexipril (mg/kg)				
	0.1	0.3	1.0	3.0	10.0
Femoral					
Systolic BP	-0.78	-11.5	-22.0	-23.5	-19.0
Diastolic BP	-10.8	-25.0	-29.4	-34.8	-28.0
Pulmonary					
Systolic BP	-4.0	0	0	-2.8	-5.7
Diastolic BP	0	0	-10.0	-6.3	-11.0
Systolic BP (Left Ventricular)	-3.6	-9.5	-19.0	-16.0	-24.3
Central Venous Pressure	0	0	0	-6.3	-22.0
Heart rate	-5.0	-3.5	-19.0	-1.8	-30.0
Cardiac Output	-11.0	-30.0	-25.8	-10.5	-12.3
Stroke Volume	-3.0	-27.5	-4.4	-9.0	+37.3
dp/dt	-4.2	-12.0	-11.4	-20.0	-22.0
Pulmonary Capillary Pressure	0	0	-4.0	-5.0	-11.0
Respiratory Rate	+17.2	+25.0	+20.4	+23.8	+34.0
Respiratory Volume	+15.0	0	+18.6	+12.5	+2.67

(d): Effects on Renal Function and Electrolyte Excretion:

In normotensive rats during the first collecting period (0-5 hr), Moexipril (1000 mg/kg) caused a significant decrease in urine volume (control 21.5 ± 4.18 ml/kg vs Moexipril 11.6 ± 5.56 ml/kg, $p < 0.01$) with significant increase in potassium (control 27.5 ± 7.61 mmol/l urine vs Moexipril 39.4 ± 6.56 mmol/l urine, $p < 0.01$) and chloride (control 29.5 ± 9.12 mmol/l urine vs 49.9 ± 16.42 mmol/l urine, $p < 0.01$) excretion and no significant change in sodium excretion (control 14.4 ± 7.83 mmol/l/urine vs Moexipril 9.6 ± 4.49 mmol/l urine). During the second collecting period (5-24 hr), no substance related effect on urine volume was observed at 1000 mg/kg dose (control 28.6 ± 6.08 ml/kg vs Moexipril 24.8 ± 3 ± 58 ml/kg); while significant decrease in sodium (control 107 ± 14.14 vs Moexipril 71.2 ± 17.07. $p < 0.01$) and significant increase in chloride (control 107.0 ± 10.94 vs Moexipril 140.6 ± 11.76, $p < 0.01$) excretion was observed.

In SHR, Moexipril (30 mg/kg, orally) produced significant increases in sodium excretion and sodium/potassium excretion ratio at 3 hr and 3 and 6 hr post drug, respectively as compared to vehicle control (Table VIII). No significant changes in urine volume or potassium excretion were observed woth Moexipril alone. Hydrochlorothiazide (10 mg/kg, orally) resulted in significant increases in urine volume at 3 and 6 hr as well as increases in sodium and potassium excretion at 1, 3 and 6 hr after drug, but no significant change in sodium/potassium ratio, as compared with control vehicle (Table VIII). However, coadministration of Moexipril (30 mg/kg, orally) and Hydrochlorothiazide (10 mg/kg, orally) resulted in significant increases in urine volume, sodium and potassium excretion as well as the sodium/potassium ratio at 1, 3, and 6 hr as compared with control vehicle (Table VIII). This suggests that administration of Moexipril with Hydrochlorothiazide produced synergistic increases in urine volume and sodium excretion with a more favorable sodium/potassium ratio, indicating that the combination of the ACE inhibitor, Moexipril, and Hydrochlorothiazide is interactive.

In normotensive male rats, a combination of Moexipril 10 µg/kg/min, IP and Fenoldopam (DA_1 agonist) 10 µg/kg/min, IP produced significantly greater increases in renal blood flow and renal vascular resistance than the individual agents. Cumulative decreases in mean blood pressure and increases in heart rate induced by the combination were significantly greater than Moexipril but not different from Fenoldopam. Furthermore, 15 mg/kg Moexipril or 15 mg/kg Fenoldopam given orally had no significant effect on urine volume and sodium and potassium excretion in SHR rats. However, a combination of Moexipril (15 mg/kg, PO) and Fenoldopam (15 mg/kg, PO) induced significantly higher urine volume and sodium and potassium excretion, as compared with control vehicle and each drug given individually.

RESULTS:

Table 1 : Summary of Mean Pharmacokinetic Parameters of Moexipril (n=12)
Treatment A: Test Product
Moexipril-Formula 4A, 1 coated tablet of 15 mg
Treatment B: Reference Product
Moexipril-Formula 4A, i.v.-inf. of 5.35 mg
Treatment C: Reference Product
Moexiprilat-Formula 4A, i.v.-inf. of 5.05 mg

Pharm. Parameter	Treatment A mean	sdev	Treatment B mean	sdev	Treatment C mean	sdev
AUC(0-24) (h*ng/ml)	86.45	37.26	216.70	72.00	1.35	0.54
AUC-1 (h*ng/ml)	85.73	37.18	215.98	71.95	1.28	0.50
AUC-3 (h*ng/ml)	86.41	37.15	216.74	71.90	1.42	0.09(n=4)
C_{max} (ng/ml)	60.86	27.16	554.60	147.67	2.74	0.73
T_{max} (h)	0.92	0.44	0.24	0.02	0.24	0.02
$t_{½}$ (h)	1.07	0.29	1.33	0.32	0.73	0.32(n=9)
k (1/h)	0.6905	0.1693	0.5562	0.1737	1.0979	0.3960(n=9)
after dose-normalization of data						
$AUC(0-24)_{norm}$ (h*ng/ml)*	6.140	2.646	42.332	13.511	0.267	0.099
$AUC-3_{norm}$ (h*ng/ml)*	6.137	2.639	42.341	13.491	0.299	0.013(n=4)
$AUC(0-24)_{sum}$** (h*ng/ml)*	11.08	4.09	79.94	26.29	77.08	18.36
$AUC-3_{sum}$** (h*ng/ml)*	13.24	1.92(n=5)	85.93	26.23(n=10)	80.37	4.39(n=4)
CL (ml/min)	-	-	441.35	177.89	-	-
F(A|B)(%)	13.9		—		—	
F(A|B)(%)	12.8		—		—	

* : normalized to 1 mg applied dose
** : sum of Moexipril and Moexiprilat, normalized for Moexipril

mean = arithmetic mean value, sdev = standard deviation

000045

Table 2 : Summary of Mean Pharmacokinetic Parameters of Moexiprilat (n=12)
Treatment A: Test Product
Moexipril-Formula 4A, 1 coated tablet of 15 mg
Treatment B: Reference Product
Moexipril-Formula 4A, i.v.-inf. of 5.35 mg
Treatment C: Reference Product
Moexiprilat-Formula 4A, i.v.-inf. of 5.05 mg

Pharm. Parameter	Treatment A mean	sdev	Treatment B mean	sdev	Treatment C mean	sdev
AUC(0-24) (h*ng/ml)	61.90	26.39	170.64	66.27	346.08	96.12
AUC-3 (h*ng/ml)	86.30	25.69(n=5)	196.35	60.51(n=10)	361.05	94.72
C_{max} (ng/ml)	15.58	8.04	93.88	39.07	458.80	113.36
T_{max} (h)	1.60	0.56	0.77	0.17	0.26	0.03
$t_{½}$ (h)	12.27	3.19(n=11)	10.47	5.10	9.81	3.22
k (1/h)	0.0605	0.0177(n=11)	0.0763	0.0250	0.0765	0.0202
after dose-normalization of data						
$AUC(0-24)_{norm}$ (h*ng/ml)*	4.659	1.986	35.494	13.870	72.486	17.252
$AUC-3_{norm}$ (h*ng/ml)*	6.495	1.934(n=5)	40.711	12.867(n=10)	75.660	16.912
$AUC(0-24)_{sum}$** (h*ng/ml)*	10.453	3.862	75.443	24.811	72.738	17.324
$AUC-3_{sum}$** (h*ng/ml)*	12.491	1.811(n=5)	81.092	24.752(n=10)	75.846	4.147(n=4)
CL (ml/min)	-	-	-	-	232.45	61.98
F (A|C) (%)	6.0					

* : normalized to 1 mg applied dose
** : sum of Moexipril and Moexiprilat, normalized for Moexiprilat

mean = arithmetic mean value, sdev = standard deviation

Bioavailability Data - Plasma

Table 3: Summary of Mean Plasma Concentrations (ng/ml) and Pharmacokinetic Parameters of DKP of Moexipril (n=12)
Treatment A: Test Product
Moexipril-Formula 4A, 1 coated tablet of 15 mg
Treatment B: Reference Product
Moexipril-Formula 4A, i.v.-inf. of 5.35 mg
Treatment C: Reference Product
Moexiprilat-Formula 4A, i.v.-inf. of 5.05 mg

Pharm. Parameter	Treatment A mean	Treatment A sdev	Treatment B mean	Treatment B sdev	Treatment C mean	Treatment C sdev
AUC(0-24) (h*ng/ml)	112.65	62.34	-	-	-	-
AUC-1 (h*ng/ml)	94.61	53.99	-	-	-	-
C_{max} (ng/ml)	85.72	40.84	-	-	-	-
T_{max} (h)	0.98	0.40	-	-	-	-
after dose-normalization of data						
$AUC(0-24)_{norm}$ (h*ng/ml)*	8.300	4.593	-	-	-	-
$AUC-1_{norm}$ (h*ng/ml)*	6.971	3.978	-	-	-	-

* : normalized to 1 mg applied dose

mean = arithmetic mean value, sdev = standard deviation

Bioavailability Data - Plasma

Table 4: Summary of Mean Plasma Concentrations (ng/ml) and Pharmacokinetic Parameters of DKP of Moexiprilat (n=12)
Treatment A: Test Product
Moexipril-Formula 4A, 1 coated tablet of 15 mg
Treatment B: Reference Product
Moexipril-Formula 4A, i.v.-inf. of 5.35 mg
Treatment C: Reference Product
Moexiprilat-Formula 4A, i.v.-inf. of 5.05 mg

Pharm. Parameter	Treatment A mean	sdev	Treatment B mean	sdev	Treatment C mean	sdev
AUC(0-24) (h*ng/ml)	50.20	12.68(n=5)	-	-	-	-
AUC-1 (h*ng/ml)	33.85	11.51(n=5)	-	-	-	-
C_{max} (ng/ml)	35.55	5.52(n=5)	-	-	-	-
T_{max} (h)	1.71	0.28(n=5)	-	-	-	-
after dose-normalization of data						
$AUC(0-24)_{norm}$ (h*ng/ml)*	3.929	0.992(n=5)	-	-	-	-
$AUC-1_{norm}$ (h*ng/ml)*	2.649	0.900(n=5)	-	-	-	-

Note: Pharmacokinetic parameters of treatment A could only be calculated for 5 subjects with concentrations exceeding the lower limit of quantification
* : normalized to 1 mg applied dose

mean = arithmetic mean value, sdev = standard deviation

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Table 5

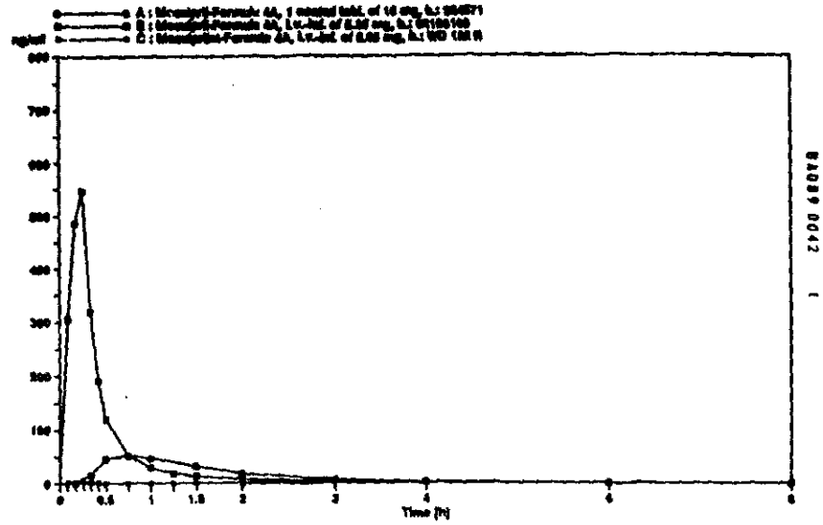
SUMMARY OF URINARY EXCRETION AND PK PARAMETERS

	Treatment A[a]	Treatment B[a]	Treatment C[a]
Moexipril			
Ae (μg)	142.44 (29.1)	831.10 (174.5)	47.84 (53.7)
E_{max} (μg/ml)	53.2 (25.0)	411.07 (141.8)	19.44 (260.9)
%Ae (%)	1.01 (0.43)	16.66 (4.4)	0.954 (1.1)
F (A/B) (%)	5.5	-	
F (A/C) (%)	10.2	-	
Moexiprilat			
Ae (μg)	417.24 (237.4)	1254.10 (491.8)	3059.27 (956.8)
E_{max} (μg/ml)	102.61 (77.1)	460.81 (218.0)	1261.29 (416.87)
%Ae (%)	3.14 (1.8)	26.60 (11.0)	64.42 (20.1)
DPK-Moexipril			
Ae (μg)	14.93 (18.0)	5.65 (7.3)	-
E_{max} (μg/ml)	9.14 (11.5)	2.38 (3.5)	-
%Ae (%)	0.11 (0.1)	0.12 (0.2)	-
DPK-Moexiprilat			
Ae (μg)	259.32 (128.0)	74.47 (43.8)	3.98 (10.6)
E_{max} (μg/ml)	73.91 (31.2)	28.40 915.7)	1.71 (4.3)
%Ae (%)	2.03 (1.0)	1.63 (0.98)	0.08 (0.2)

[a] Mean (Standard Deviation).

Figure 1

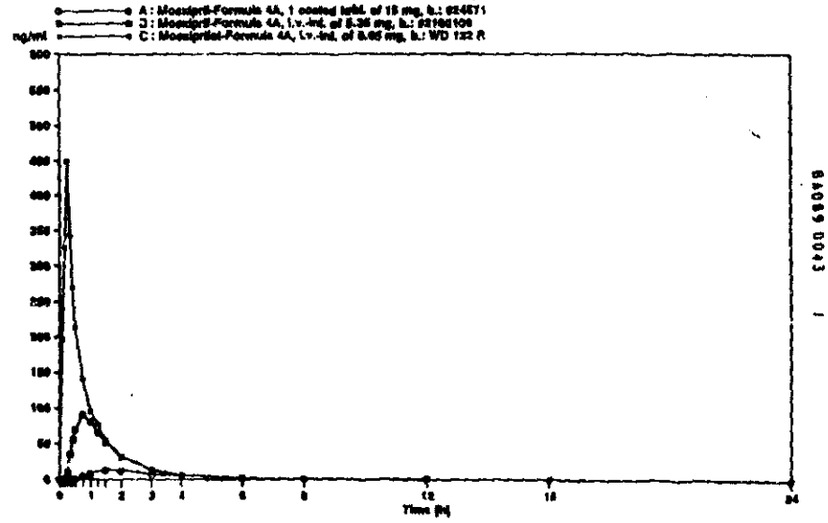
Plasma Concentrations of Moexipril
Mean over 12 Subjects



8 8 0 8 9 0 0 1 2

Figure 2

Plasma Concentrations of Moexiprilat
Mean over 12 Subjects



8 8 0 8 9 0 0 1 3

Figure 3

Plasma Concentrations of Di-keto-piperazine of Moexipril
Mean over 12 Subjects

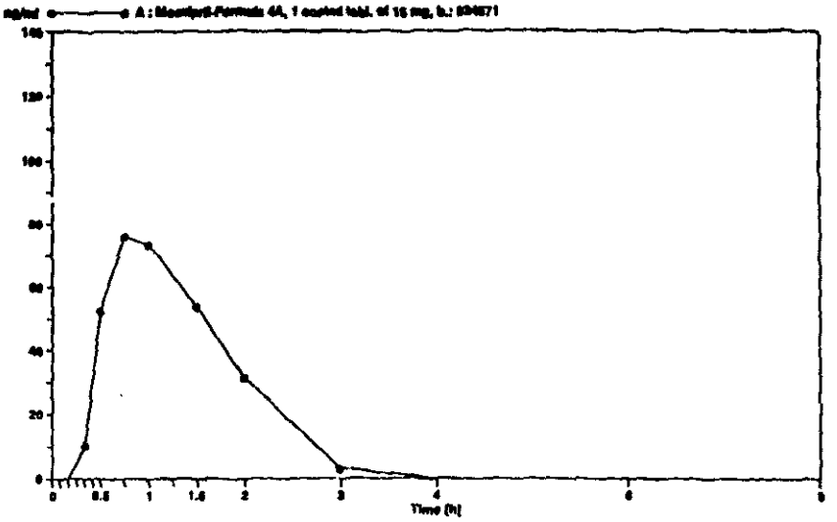


Figure 4

Plasma Concentrations of Di-keto-piperazine of Moexiprilat
Mean over 12 Subjects

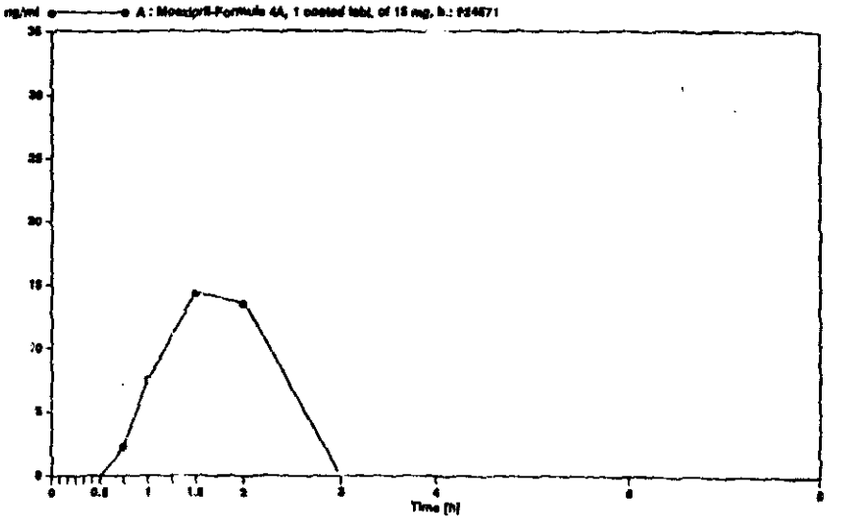


Figure 5

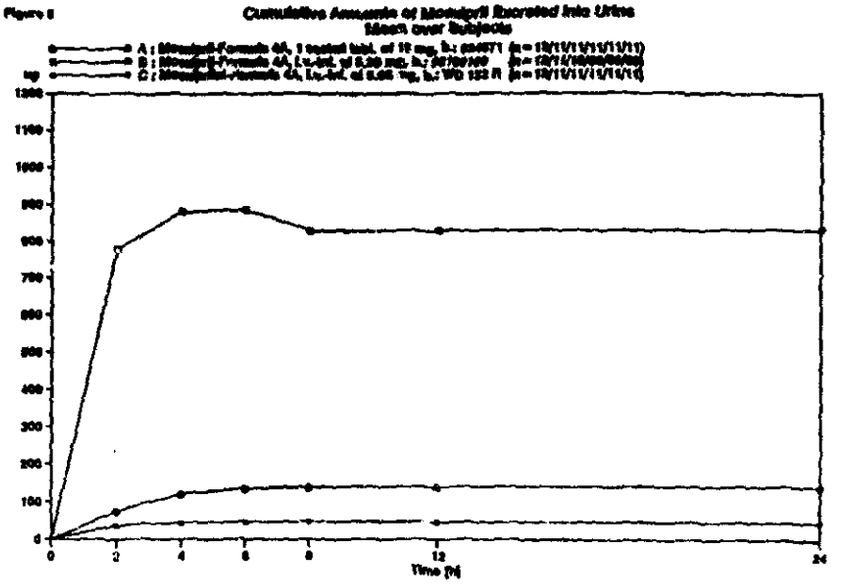


Figure 6

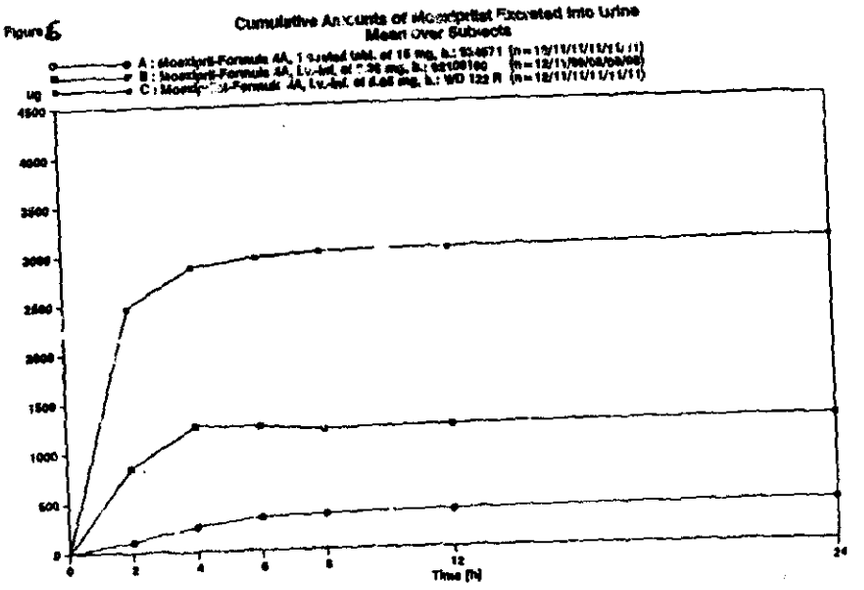
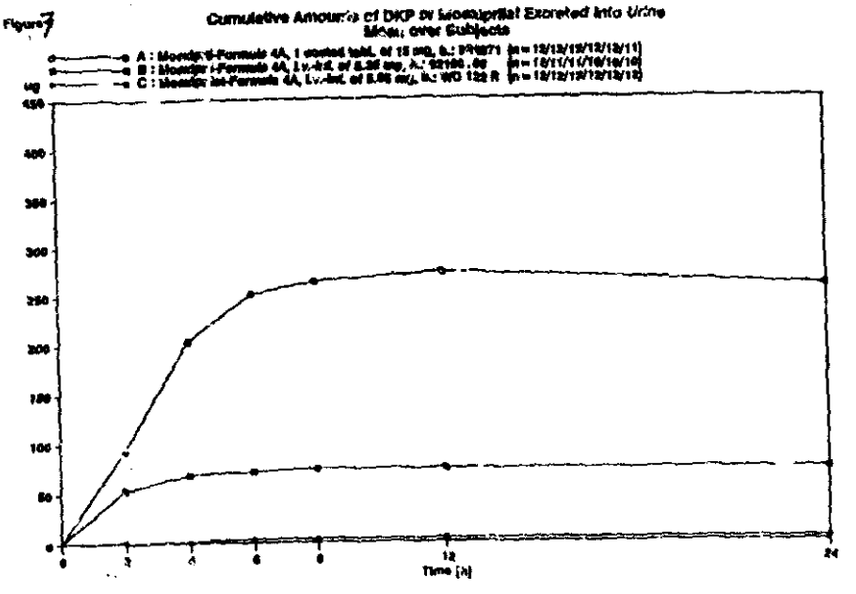


Figure 7



CONCLUSION: The absolute bioavailability of is about 14% as moexipril and 13% as moexiprilat based on plasma -AUCs with corresponding values in urine of 6% and 10%, respectively.

FOOD EFFECT STUDY

STUDY NUMBER: CA649 **VOLUMES:** 6 - 7

INVESTIGATOR AND LOCATION:

STUDY PERIOD: FEBRUARY 11, 1994 MARCH 15,1994.

OBJECTIVES: (i) to determine bioavailability and pharmacokinetic parameters of moexipril hydrochloride tablet following oral administration under fasting conditions as well as after food intake (ii) to measure angiotensin-converting enzyme (ACE) inhibitory effect under both conditions.

FORMULATION:
15 mg Moexipril hydrochloride coated Tablet, Batch No 930543; Expiration Date - August 30, 1994.

STUDY DESIGN: Randomized, open, two-period crossover study with 24 subjects and a wash period of 2 weeks . Subjects received a single 15 mg oral dose of moexipril hydrochloride coated tableton two occasions (once under fasting conditions (Treatment A) and once under fed conditions (Treatment B). Subjects fasted 10 hours prior to dosing, the fed were given a standardized light breakfast 30 minutes prior to dosing and then fasted for 4 hours while the fasting group remained fasting for 4 four hours post dose. Blood samples (7 ml) were collected (predose), 5, 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post dose for the evaluation of the plasma concentrations of moexipril and moexiprilat. Blood samples (3 ml) were collected 0 (predose), 5, 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72 hours post dose for the determination of the ACE inhibitory effect of moexipril.Sample for evaluation of the plasma concentrations were stored st -70°C until analyzed while samples for the measurement of ACE inhibition were stored at -20°C until analyzed.
The standard meal consisted of :
240 g of low fat milk (1.5%)
30 g of toast
10 g medium fat margarine
2 eggs
180 g orange juice
Caloric content = 485 Kcal (25.3 g of protein, 46.6 g of carbohydrate, 21.8 g of fat).

ASSAYS:

PLASMA SAMPLES - MOEXIPRIL AND MOEXIPRILAT - GC/MS

Linearity: Satisfactory. Standard curves from 0.25 to 300 ng/ml.

Accuracy: Satisfactory. 100.0% at 0.5 ng/ml, 100.7% at 250 ng/ml for moexipril; and 98.0% at 0.5 ng/ml, 102.9% at 250ng/ml for moexiprilat.

Precision: Satisfactory. %CV - 7.7% at 0.5 ng/ml, 4.6% at 250 ng/ml for moexipril; and 8.0% at 0.5 ng/ml, 5.2% at 250 ng/ml for moexiprilat.

Sensitivity: LOQ - 0.25 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

PLASMA SAMPLES - ACE INHIBITORY EFFECT OF MOEXIPRIL

Linearity: Satisfactory. Standard curves from 5.92 to 94.7 U/l.

Accuracy: Satisfactory. 107.8% at 7.54 U/l, 100.8% at 43.4 U/l and 101.3% at 75.4 U/l.

Precision: Satisfactory. %CV - 13.7% at 7.54 U/l, 4.5% at 43.4 U/l and 2.0% at 75.4 U/l.

Sensitivity: LOQ - 5.92 U/l.

Specificity: Satisfactory.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC_{24}, $AUC_{0-\infty}$,C_{max}, T_{max}, k and $t_{1/2}$ were calculated.

RESULTS:

	FASTING (Treatment A)*	POSTPRANDIAL (Treatment B)*	Ratio of Geometric means (Fed/Fasted)	90% CI
Moexipril				
AUC_{24} (h*ng/ml)	127.2 (60.7)	72.1 (36.8)	56.61	49 - 65
$AUC_{0-\infty}$ (h*ng/ml)	128.4 (61.8) n=23	87.0 (36.5) n=16	54.02	45 - 65
C_{max} (ng/ml)	78.2 (35.3)	40.2 (21.7)	49.03	41 - 58
T_{max} (h)	0.96 (0.34)	1.18 (0.54)	-	-
k (h^{-1})	0.43 (1.03)	0.56 (0.09)	-	-
$t_{1/2}$ (h)	1.80 (0.68)	1.27 (0.20)	-	-
Moexiprilat				
AUC_{24} (h*ng/ml)	72.2 (26.1)	40.8 (10.7)	57.99	52 - 65
$AUC_{0-\infty}$ (h*ng/ml)	83.3 (28.3) n=5	67.5 n=1	-	-
C_{max} (ng/ml)	18.4 (9.9)	5.4 (2.9)	30.69	25 - 37
T_{max} (h)	1.67 (0.24)	2.23 (0.91)	-	-
k (h^{-1})	0.03 (0.01)	0.02 (0.01)	-	-
$t_{1/2}$ (h)	27.31 (14.64)	35.48 (21.09)	-	-
Serum Concentrations of ACE				
I_{max} (%)	100.0 (0.00)	99.4 (3.17)	-	-
I_{ave} (%)	68.7 (13.82)	70.02 (14.96)	101.61	93 - 111
I_{24h} (%)	80.41 (17.72)	78.54 (18.32)	96.82	86 - 108

* Mean (Standard Deviation).

I_{ave} - Average inhibition during the interval of observation, calculated as predose - $AUC_{(0-\tau)}/72_h$, expressed as percent of predose (%).

I_{24h} - Inhibition at 24 h, expressed as percent of predose.

Figure 1:

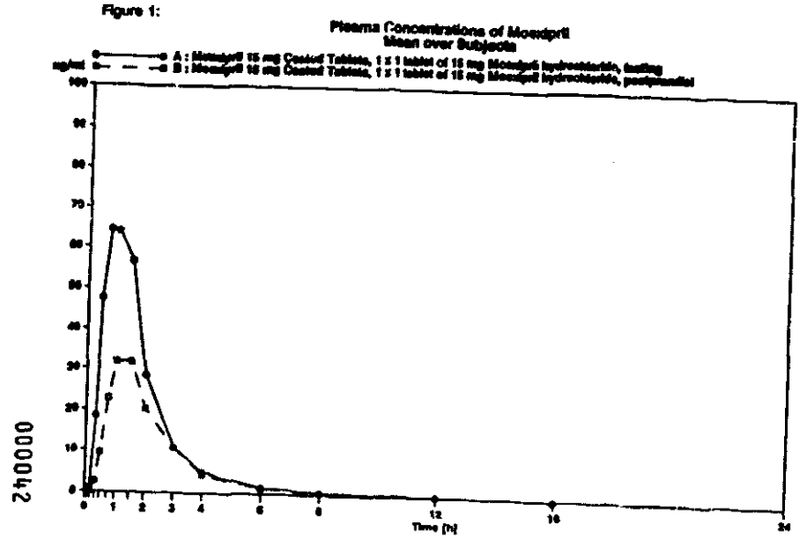


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Figure 2:

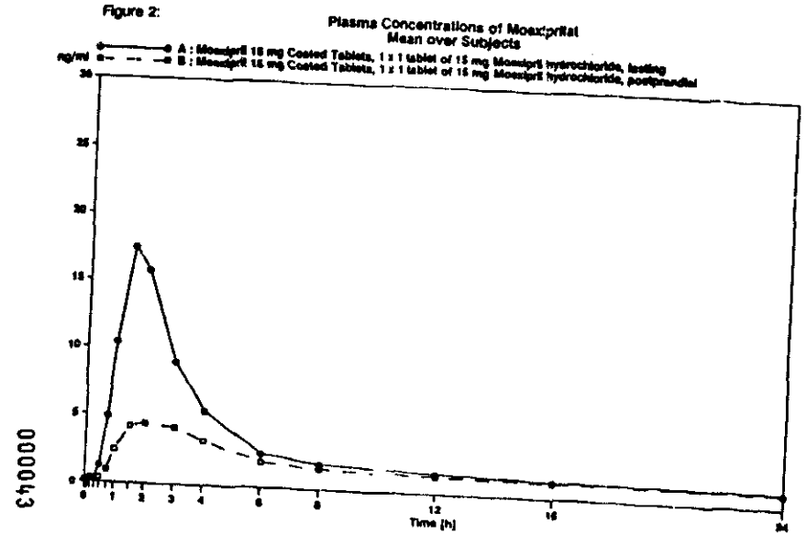

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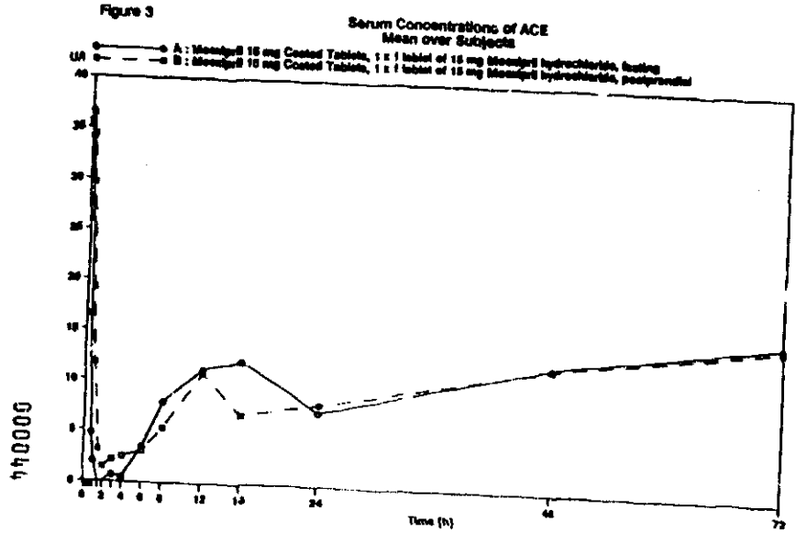
Figure 3



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CONCLUSIONS: Administration of moexipril with food results in (i) decrease in Cmax and $AUC_{0-\infty}$ (32% and 49% respectively) of moexipril (ii) a decrease in Cmax and AUC_{24} (71% and 43% respectively) and a delay of 0.5 hour in Tmax of moexiprilat (iii) no effect on the ACE inhibition by moexipril.

PROPOSED LABELING

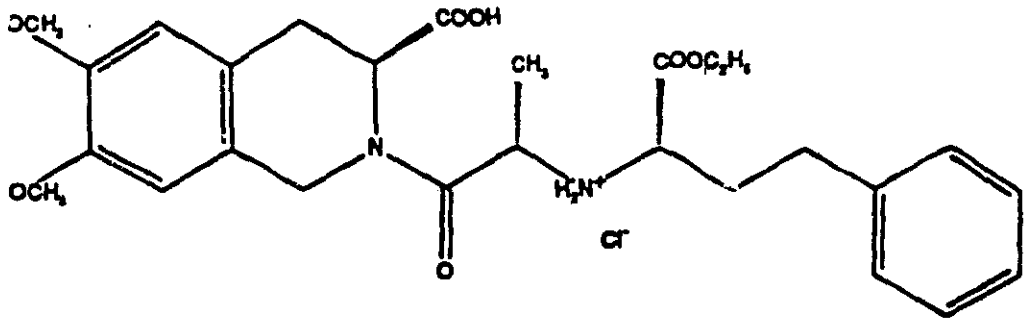
UNIVASC™ R
(moexipril hydrochloride)
Tablets

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, UNIVASC should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

UNIVASC (moexipril hydrochloride), the hydrochloride salt of moexipril, has the empirical formula $C_{27}H_{35}N_2O_7Cl$ and a molecular weight of 535.04. It is chemically described as (3*S*)-2-[(2*S*)-2-{[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino}-1-oxopropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, hydrochloride. It is a non-sulfhydryl containing precursor of the active angiotensin-converting enzyme (ACE) inhibitor moexiprilat and its structural formula is:



Moexipril hydrochloride is a fine white to off-white powder. It is soluble (about 10% weight-to-volume) in distilled water at room temperature.

UNIVASC is supplied as scored, coated tablets containing 7.5 mg and 15 mg of moexipril hydrochloride for oral administration. In addition to the active ingredient, moexipril hydrochloride, the tablet core contains the following inactive ingredients: lactose, magnesium oxide, crospovidone, magnesium stearate and gelatin. The film coating contains hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol 6000, magnesium stearate, titanium dioxide, and ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Moexipril hydrochloride is a prodrug for moexiprilat, which inhibits angiotensin-converting enzyme in humans and animals. The mechanism through which moexiprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes the conversion of the inactive decapeptide angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor that also stimulates aldosterone secretion by the adrenal cortex and provides negative feedback on renin secretion. ACE is identical to kininase II, an enzyme that degrades bradykinin, an endothelium-dependent vasodilator. Moexiprilat is about 1000 times as potent as moexipril in inhibiting ACE and kininase II. Inhibition of ACE results in decreased angiotensin II formation, leading to decreased vasoconstriction, increased plasma renin activity, and decreased aldosterone secretion. The latter results in diuresis and natriuresis and a small increase in serum potassium concentration (mean increases of about 0.25 mEq/L were seen when moexipril was used alone, see PRECAUTIONS).

Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of moexipril remains to be elucidated. Although the principal mechanism of moexipril in blood pressure reduction is believed to be through the renin-angiotensin-aldosterone system, ACE inhibitors have some effect on blood pressure even in apparent low renin hypertension. As is the case with other ACE inhibitors, however, the antihypertensive effect of moexipril is considerably smaller in black patients, a predominantly low-renin population, than in non-black hypertensive patients.

Pharmacokinetics and Metabolism

Pharmacokinetics: Moexipril's antihypertensive activity is almost entirely due to its deesterified metabolite, moexiprilat. Bioavailability of oral moexipril as moexiprilat is low, about 20%, and is markedly affected by food, which reduces peak plasma level (C_{max}) and AUC by about 50%. Moexipril should therefore be taken in a fasting state. The time of peak plasma concentration

(T_{max}) of moexiprilat is about 1½ hours and elimination half-life ($t_{½}$) is estimated at 2 to 9 hours in various studies, the variability reflecting a complex elimination pattern that is not simply exponential. Like all ACE inhibitors, moexiprilat has a prolonged terminal elimination phase, presumably reflecting slow release of drug bound to the ACE. Accumulation of moexiprilat with repeated dosing is minimal, about 30%, compatible with a functional elimination half-life of about 12 hours. Over the dose range of 7.5 to 30 mg, pharmacokinetics are approximately dose proportional.

Absorption: Moexipril is incompletely absorbed, with bioavailability of about 20%. Bioavailability varies with formulation and food intake, falling by up to 50% with the marketed formulation after ingestion of a relatively high-fat breakfast. New study

Distribution: The clearance (CL) for moexipril is 441 mL/min and for moexiprilat 232 mL/min with a $t_{½}$ of 1.3 and 9.8 hours, respectively. Moexiprilat is about 50% protein bound.

Metabolism and Excretion: Moexipril is relatively rapidly converted to its active metabolite moexiprilat, but persists longer than some other ACE inhibitor prodrugs, such that its half-life is over one hour and it has a significant AUC. Both moexipril and moexiprilat are converted to diketopiperazine derivatives and unidentified metabolites. After IV administration of moexipril, about 40% of the dose appears in urine as moexiprilat, about 26% as moexipril, with small amounts of the metabolites; about 20% of the IV dose appears in feces, principally as moexiprilat. After oral administration, only about 7% of the dose appears in urine as moexiprilat, about 1% as moexipril, with about 5% as other metabolites. Fifty-two percent of the dose is recovered in feces as moexiprilat and 1% as moexipril.

Special Populations:
Decreased Renal Function: The effective elimination half-lives and AUC of both moexipril and moexiprilat are increased with decreasing renal function. There is insufficient information available to characterize this relationship fully, but at creatinine clearances in the range of 10 to 40 mL/min, the half-life of moexiprilat is increased by a factor of 3 to 4.

Decreased Hepatic Function: In patients with mild to moderate cirrhosis given single 15 mg doses of moexipril, the C_{max} of moexipril was increased by about 50% and the AUC increased by about 120%, while the C_{max} for moexiprilat was decreased by about 50% and the AUC increased by almost 300%.

Elderly Patients: In elderly male subjects (65-80 years old) with clinically normal renal and hepatic function, the AUC and C_{max} of moexiprilat is about 30% greater than those of younger subjects (19-42 years old).

Pharmacokinetic Interactions With Other Drugs: No clinically important pharmacokinetic interactions occurred when UNIVASC was administered concomitantly with hydrochlorothiazide, digoxin, or cimetidine.

Pharmacodynamics and Clinical Effect

Single and multiple doses of 15 mg or more of UNIVASC caused a sustained inhibition of plasma ACE activity of 80 to 90% for at least 24 hours after dosing. After administration of a 15 mg dose of UNIVASC in healthy volunteers, ACE activity was completely inhibited within 2 hours. After 24 hours the enzyme inhibition was still 80%. The mean inhibition over 72 hours was 70% after a single dose. The time course of the inhibition was not significantly affected by a low fat breakfast.

In controlled trials, the peak effects of orally administered moexipril increased with the dose administered over a dose range of 7.5 to 60 mg, given once a day. Antihypertensive effects were first detectable about 1 hour after dosing, with a peak effect between 3 and 6 hours after dosing. Just before dosing (i.e., at trough), the antihypertensive effects were less prominently related to dose and the antihypertensive effect tended to diminish during the 24-hour dosing interval when the drug was administered once a day.

In multiple dose studies in the dose range of 7.5 to 30 mg once daily, UNIVASC lowered sitting diastolic and systolic blood pressure effects at trough by 3 to 6 mmHg and 4 to 11 mmHg, more than placebo, respectively. There was a tendency toward increased response with higher doses over this range. These effects are typical of ACE inhibitors but, to date, there are no trials of adequate size comparing moexipril with other antihypertensive agents.

The trough diastolic blood pressure effects of moexipril were approximately 3 to 6 mmHg in various studies. Generally, higher doses of moexipril leave a greater fraction of the peak blood pressure effect still present at trough. During dose titration, any decision as to the adequacy of a dosing regimen should be based on trough blood pressure measurements. If diastolic blood pressure control is not adequate at the end of the dosing interval, the dose can be increased or given as a divided (BID) regimen.

During chronic therapy, the antihypertensive effect of any dose of UNIVASC is generally evident within 2 weeks of treatment, with maximal reduction after 4 weeks. The antihypertensive effects of UNIVASC have been proven to continue during therapy for up to 24 months.

UNIVASC, like other ACE inhibitors, is less effective in decreasing trough blood pressures in blacks than in non-blacks. Placebo-corrected trough group mean diastolic blood pressure effects in blacks in the proposed dose range varied between +1 to -3 mmHg compared with responses in non-blacks of -4 to -6 mmHg.

The effectiveness of UNIVASC was not significantly influenced by patient age, gender, or weight. UNIVASC has been shown to have antihypertensive activity in both pre and postmenopausal women who have participated in placebo-controlled clinical trials.

Formal interaction studies with moexipril have not been carried out with antihypertensive agents other than thiazide diuretics. In these studies, the added effect of moexipril was similar to its effect as monotherapy. In general, ACE inhibitors have less than additive effects with beta-adrenergic blockers, presumably because both work by inhibiting the renin-angiotensin system.

INDICATIONS AND USAGE

UNIVASC is indicated for treatment of patients with hypertension. It may be used alone or in combination with thiazide diuretics.

In using UNIVASC, consideration should be given to the fact that another ACE inhibitor (captopril) has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that UNIVASC does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

UNIVASC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including UNIVASC) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema involving the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including UNIVASC. Symptoms suggestive of angioedema or facial edema occurred in <0.5% of moexipril-treated patients in placebo-controlled trials. None of the cases were considered life-threatening and all resolved either without treatment or with medication (antihistamines or glucocorticoids). One patient treated with

hydrochlorothiazide alone experienced laryngeal edema. No instances of angioedema were reported in placebo-treated patients.

In cases of angioedema, treatment should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with involvement of the tongue, glottis, or larynx, may be fatal due to airway obstruction. Appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) and/or measures to ensure a patent airway, should be promptly provided (see ADVERSE REACTIONS).

Anaphylactoid Reactions During Desensitization
Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

Hypotension
UNIVASC can cause symptomatic hypotension, although, as with other ACE inhibitors, this is unusual in uncomplicated hypertensive patients treated with UNIVASC alone. Symptomatic hypotension was seen in 0.5% of patients given moexipril and led to discontinuation of therapy in about 0.25%. Symptomatic hypotension is most likely to occur in patients who have been salt- and volume-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and salt-depletion should be corrected and, in general, diuretics stopped, before initiating therapy with UNIVASC (see PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS).

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or progressive azotemia, and rarely, with acute renal failure and death. In these patients, UNIVASC therapy should be started under close medical supervision, and patients should be followed closely for the first two weeks of treatment and whenever the dose of moexipril or an accompanying diuretic is increased. Care in avoiding hypotension should also be taken in patients with ischemic

heart disease, aortic stenosis, or cerebrovascular disease, in whom an excessive decrease in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with an intravenous infusion of normal saline. UNIVASC treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in patients with uncomplicated hypertension, but more frequently in hypertensive patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Although there were no instances of severe neutropenia (absolute neutrophil count <500/mm^3) among patients given UNIVASC, as with other ACE inhibitors, monitoring of white blood cell counts should be considered for patients who have collagen-vascular disease, especially if the disease is associated with impaired renal function. Available data from clinical trials of UNIVASC are insufficient to show that UNIVASC does not cause agranulocytosis at rates similar to captopril.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosis have also been reported, although it is not clear whether these were caused by the ACE-inhibitor exposure.

Fetal and neonatal morbidity do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester. Mothers who have used ACE inhibitors only during the first trimester should be informed of this. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of moexipril as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, moexipril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be detected until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Theoretically, the ACE inhibitor could be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

No embryotoxic, fetotoxic, or teratogenic effects were seen in rats treated with moexipril up to 250 mg/kg/day or in rabbits treated with up to 1.0 mg/kg/day. On a mg/kg basis, these multiples are 500 times and 2 times, respectively, the maximum recommended human dose (or 90.9 times and 0.7 times on a mg/m^2 basis).

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. There is no clinical experience of UNIVASC in the treatment of hypertension in patients with renal failure.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when UNIVASC has been given concomitantly with a thiazide diuretic. This is more likely to occur in patients with preexisting renal impairment. There may be a need for dose adjustment of UNIVASC and/or the discontinuation of the thiazide diuretic.

Evaluation of hypertensive patients should always include assessment of renal function. (see DOSAGE AND ADMINISTRATION)

Hypertensive Patients With Congestive Heart Failure: In hypertensive patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including UNIVASC, may be associated with oliguria and/or progressive azotemia and, rarely, acute renal failure and/or death.

Hypertensive Patients With Renal Artery Stenosis: In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Hyperkalemia: In clinical trials, persistent hyperkalemia (serum potassium above 5.4 mEq/L) occurred in approximately 1.3% of hypertensive patients receiving UNIVASC. Risk factors for the development of hyperkalemia with ACE inhibitors include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with UNIVASC (see PRECAUTIONS, Drug Interactions).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, moexipril may block the effects of compensatory renin release. If hypotension occurs in this setting and is considered to be due to this mechanism, it can be corrected by volume expansion.

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials with moexipril, cough was present in 6.1% of moexipril patients and 2.2% of patients given placebo.

Information for Patients

Food: Patients should be advised to take moexipril one hour before meals (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Angioedema: Angioedema, including laryngeal edema, may occur with treatment with ACE inhibitors, usually occurring early in therapy (within the first month). Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of the face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more UNIVASC until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur with UNIVASC, especially during the first few days of therapy. If fainting occurs, the patient should stop taking UNIVASC and consult the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult their physician if they develop these conditions.

Hyperkalemia: Patients should be told not to use potassium suppiements or salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) that could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors and should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Diuretics: Excessive reductions in blood pressure may occur in patients on diuretic therapy when ACE inhibitors are started. The possibility of hypotensive effects with UNIVASC can be minimized by discontinuing diuretic therapy for several days or cautiously increasing salt intake before initiation of treatment with UNIVASC. If this is not possible, the starting dose of moexipril should be reduced. (See WARNINGS and DOSAGE AND ADMINISTRATION).

Potassium Supplements and Potassium-Sparing Diuretics: UNIVASC can increase serum potassium because it decreases aldosterone secretion. Use of potassium-sparing diuretics (spironolactone, triamterene, amiloride) or potassium supplements concomitantly with ACE inhibitors can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored.

Oral Anticoagulants: Interaction studies with warfarin failed to identify any clinically important effect on the serum concentrations of the anticoagulant or on its anticoagulant effect.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be

coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other Agents: No clinically important pharmacokinetic interactions occurred when UNIVASC was administered concomitantly with hydrochlorothiazide, digoxin, or cimetidine.

UNIVASC has been used in clinical trials concomitantly with calcium-channel-blocking agents, diuretics, H_2 blockers, digoxin, oral hypoglycemic agents, and cholesterol-lowering agents. There was no evidence of clinically important adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was detected in long-term studies in mice and rats at doses up to 75 mg/kg/day (150-times the Maximum Recommended Human Dose (MRHD) on a mg/kg basis and 14 or 27.3 times MRHD on a mg/m^2 basis).

No mutagenicity was detected in the Ames test and microbial reverse mutation assay, with and without metabolic activation, or in an *in vivo* nucleus anomaly test. However, increased chromosomal aberration frequency in Chinese Hamster Ovary cells was detected under metabolic activation conditions and at the highest tested concentration (5100 μg/mL) at a 20 hour harvest time.

Reproduction studies have been performed in rabbits at oral doses up to 1 mg/kg (2 times the MRHD on a mg/kg basis and 0.7 times the MRHD on a mg/m^2 basis) and in rats up to 250 mg/kg (500 times the MRHD on a mg/kg basis and 90.9 times the MRHD on a mg/m^2 basis). No indication of impaired fertility, reproductive toxicity, or teratogenicity was observed.

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters).
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers
It is not known whether UNIVASC is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when UNIVASC is given to a nursing mother.

Geriatric Use
Of the patients who received UNIVASC in controlled clinical studies, 33% were 65 years of age or older. No overall differences in effectiveness or safety were observed between these patients and younger patients. In elderly patients receiving UNIVASC, plasma levels of drug are slightly higher and renal clearance is reduced when compared to younger patients, but this did not have detectable consequences.

Pediatric Use
Safety and effectiveness of UNIVASC in children have not been established.

ADVERSE REACTIONS

UNIVASC has been evaluated for safety in more than 2500 patients with hypertension; more than 250 of these patients were treated for approximately one year. The overall incidence of reported adverse events was only slightly greater in patients treated with UNIVASC than patients treated with placebo.

Reported adverse experiences were usually mild and transient, and there were no differences in adverse reaction rates related to gender, race, age, duration of therapy, or total daily dosage within the range of 3.75 mg to 60 mg. Discontinuation of therapy because of adverse experiences was required in 3.4% of patients treated with UNIVASC and in 1.8% of patients treated with placebo. The most common reasons for discontinuation in patients treated with UNIVASC were cough (0.7%) and dizziness (0.4%).

All adverse experiences considered at least possibly related to treatment that occurred at any dose in placebo-controlled trials of once daily dosing in more than 1% of patients treated with UNIVASC alone and that were at least as frequent in the UNIVASC group as in the placebo group are shown in the following table:

ADVERSE EVENTS IN PLACEBO-CONTROLLED STUDIES

ADVERSE EVENT	UNIVASC (N=674)	PLACEBO (N=226)
	N (%)	N (%)
Cough Increased	41 (6.1)	5 (2.2)
Dizziness	29 (4.3)	5 (2.2)
Diarrhea	21 (3.1)	5 (2.2)
Flu Syndrome	21 (3.1)	0 (0)
Fatigue	16 (2.4)	4 (1.8)
Pharyngitis	12 (1.8)	2 (0.9)
Flushing	11 (1.6)	0 (0)
Rash	11 (1.6)	2 (0.9)
Myalgia	9 (1.3)	0 (0)

Other adverse events occurring in more than 1% of patients on moexipril that were at least as frequent on placebo include: headache, upper respiratory infection, pain, rhinitis, dyspepsia, nausea, peripheral edema, sinusitis, chest pain, and urinary frequency. See WARNINGS and PRECAUTIONS for discussion of anaphylactoid reactions, angioedema, hypotension, neutropenia/agranulocytosis, second and third trimester fetal/neonatal mortality and morbidity, hyperkalemia, and cough.

Other potentially important adverse experiences reported in controlled or uncontrolled clinical trials in less than 1% of moexipril patients or that have been attributed to other ACE inhibitors include the following:

Cardiovascular: Symptomatic hypotension, postural hypotension, or syncope were seen in 9/1750 (0.51%) of patients; these reactions led to discontinuation of therapy in controlled trials in 3/1254 (0.24%) patients who had received UNIVASC monotherapy and in 1/344 (0.3%) patients who had received UNIVASC with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other adverse events included angina/myocardial infarction, palpitations, rhythm disturbances, and cerebrovascular accident.

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DEC 15 1993

NDA: 20-312 **Submission Date:** 12-07-93
Moexipril HCl Tablet, 7.5 and 15 mg
Brand Name: Moex™
Sponsor: [illegible]
Reviewer: Rajendra S. Pradhan
Type of Submission: Amendment
Priority: 1S

Background: The sponsor has requested the approval of Moex™ tablet (7.5 and 15 mg). In the original submission the sponsor had submitted an in vitro protein binding study (using equilibrium dialysis method), which showed the protein binding in young healthy subjects (under 45 yr), for moexipril to be 88.2% (SD 1.8) and for moexiprilat (an active metabolite of moexipril) to be 60.3 (SD 6.2). In elderly healthy subjects (over 65 yr), moexipril and moexiprilat showed a decreased protein binding. The recovery of moexipril and moexiprilat from the equilibrium dialysis method was considered to be 100%.

The sponsor in this submission is amending the findings of in vitro protein binding study (BA 601) in the light of new findings from a latest protein binding study (BA018).

Comments: The recovery of moexipril from the equilibrium dialysis method is approximately 68.7% at concentrations of 165 ng/ml (~ Cmax), whereas the recovery of moexiprilat is approximately 64.4% at 45 ng/ml (~ Cmax). Therefore, taking this level of recovery in to account, moexipril and moexiprilat protein binding (in study BA 601) was re-interpreted. In BA 601 study the binding was determined only at one concentration for moexipril (330 ng/ml) and moexiprilat (90 ng/ml).

Conclusions: In young healthy subjects (under 45 yr), serum protein binding for moexipril is 84.4% (SD 2.4) and moexiprilat is 48.2% (SD 8.0). In elderly subjects (over 65), serum protein binding for moexipril is 79.6% (SD 3.4) and moexiprilat is 32.3% (SD 6.9).

Recommendations: The above conclusions were based on all the information provided by the firm. The information on the protein binding of moexipril and moexiprilat should be updated and incorporated in the labelling.

12/14/93

Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics

RD Initialed by Ameeta Parekh, Ph.D. For Ameeta Parekh 12/15/93

cc NDA 20-312, HFD 110, HFD 426 (Fleischer/Pradhan), Reviewer, Chron, Drug, FOI (HFD-19), HFD-340 (Viswanathan)

NOV 9 1993

NDA 20-312 Submission Date: 10-4-93
Moexipril HCl Tablet, 7.5 and 15 mg.
Brand Name:Moex™
Sponsor:Besselaar **Reviewer:Rajendra S. Pradhan**
Type of Submission: Amendment **Priority: 1S**

Background: The sponsor has requested for an approval of Moex tablets, 7.5 and 15 mg, which are scored. Since the tablets have score on them and they are compositionally proportional, they could be administered as half or full tablets. The Division of Biopharmaceutics had requested the firm to provide a comparative in vitro dissolution data on full and broken tablets (7.5 and 15 mg), to asses the similarity in dissolution between them. The sponsor is amending their pending application NDA 20-312, Moexipril HCl tablet (7.5 and 15 mg) by providing in vitro dissolution on Moex™ tablets (full and half).

Comments: The firm used the following dissolution method (proposed and accepted method in the original review by the Division of Biopharmaceutics)
Dissolution apparatus: II (paddle).
Medium: Deionized water, 900 ml, 37°.
Rpm: 50
Analysis: UV, 280 nm.
Recommended specifications: Q of NLT in 15 minutes.
The mean data is attached in the appendix I.

It can be concluded that the in vitro dissolution profiles of Moex™ tablet full versus half (broken at the score and used half of a broken tablet), are similar. The firm has not used the bio-batch #920512 for this in vitro dissolution comparison. The in vitro dissolution of the 15 mg tablet (batch # 924571) is faster than 15 mg tablet (batch #920512-the bio-batch), at 5 min time point. However, this batch to batch difference in dissolution is considered to be not significant in terms of bio-performance, as it was noted that moexipril pharmacokinetic parameters (Cmax, Tmax and AUC) were ~~not significantly different~~ between 15 mg tablet (batch #920512/Study PHAKI-794) and solution (Study PHAKI-795R).

Recommendation: The firm has appropriately addressed the concerns raised by the Division of Biopharmaceutics.

11/8/93

Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics

RD Initialed by Ameeta Parekh, Ph.D. Ameeta Parekh 11/9/93

cc NDA 20-312, HFD-110, HFD-426 (Fleischer/Pradhan) Reviewer, Chron, Drug, FOI (HFD-19), HFD-340 (Viswanathan)

APPENDIX I

Dissolution Of Divided And Undivided
Moexipril Hydrochloride
Film - Coated Tablets

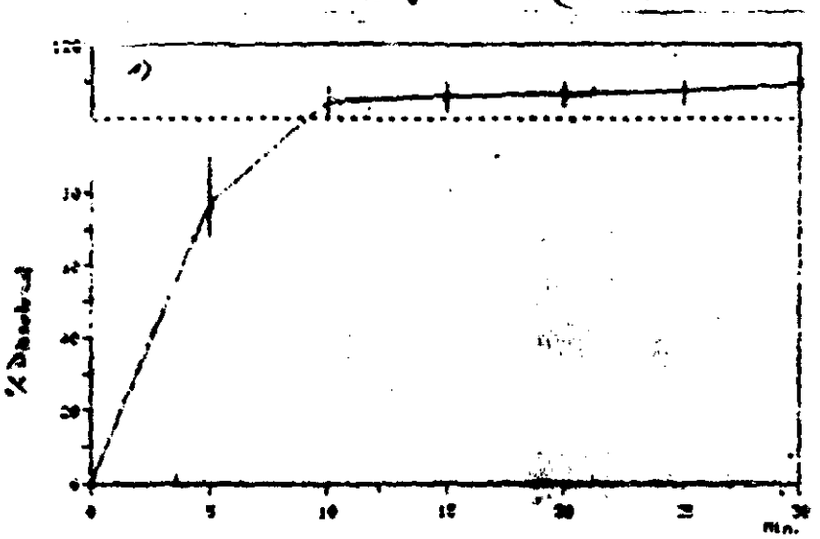
MOT_PERF/00 [redacted]

COMPARISON TABLES DIVIDED VERSUS UNDIVIDED TABLETS

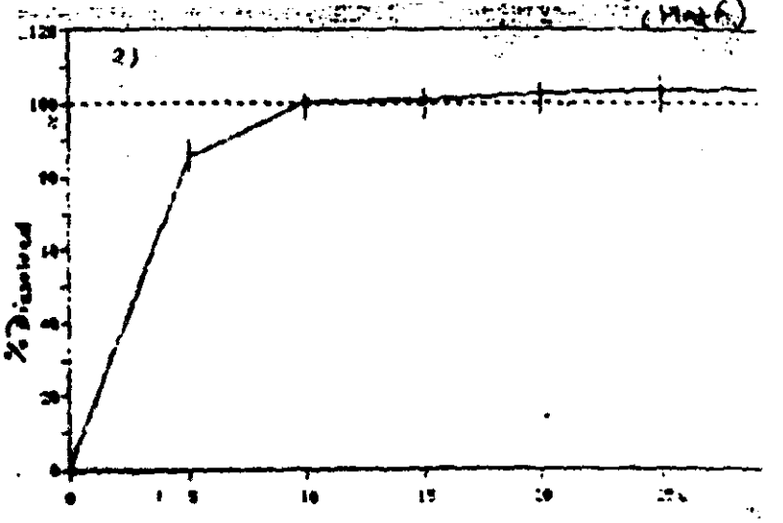
15 mg batch no. 924571 half tablets (n = 12)				*entire tablets (n = 6)*		
sampling time (min)	mean (%)	range (%)	CV (%)	mean (%)	range (%)	CV (%)
5'	81.3		8.7	60.6		11.4
10'	102.3		3.3	101.2		2.0
15'	103.3		3.6	103.5		1.4
20'	104.6		3.5	106.9		1.3
25'	105.3		3.5	106.5		1.3
30'	106.5		3.9	106.5		1.3

7.5 mg batch no. 925001 half tablets (n = 12)				*entire tablets (n = 6)*		
sampling time (min)	mean (%)	range (%)	CV (%)	mean (%)	range (%)	CV (%)
5'	83.1		6.9	70.9		11.5
10'	102.1		5.6	102.1		4.2
15'	109.5		4.7	107.2		3.5
20'	109.0		6.3	108.3		2.6
25'	108.7		6.9	112.5		2.5
30'	109.5		4.9	111.8		2.1

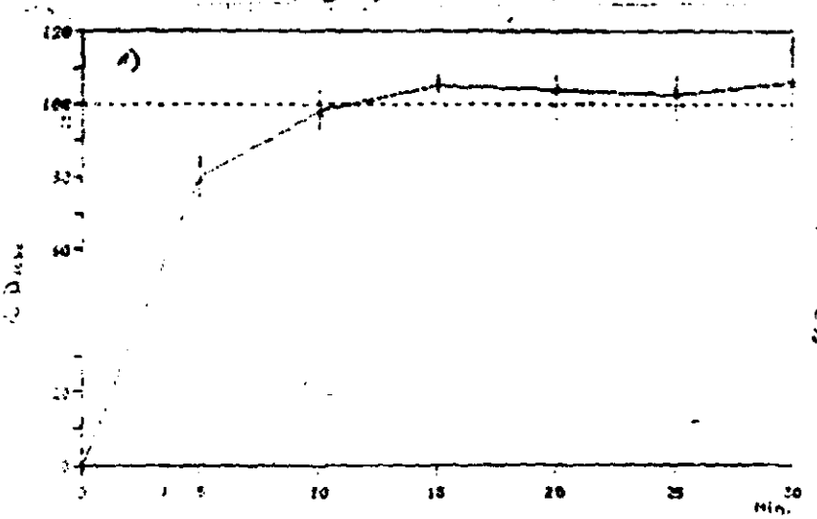
1) Dissolution profile of tablet halves 1-6
Batch no. 904071 15mg Tablet (Half)



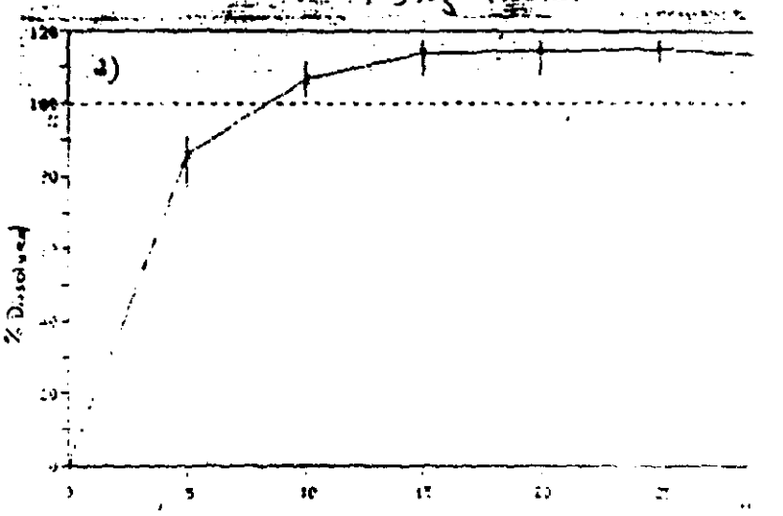
2) Dissolution profile of tablet halves 7-12
batch no. 904071 15mg Tablet (Half)



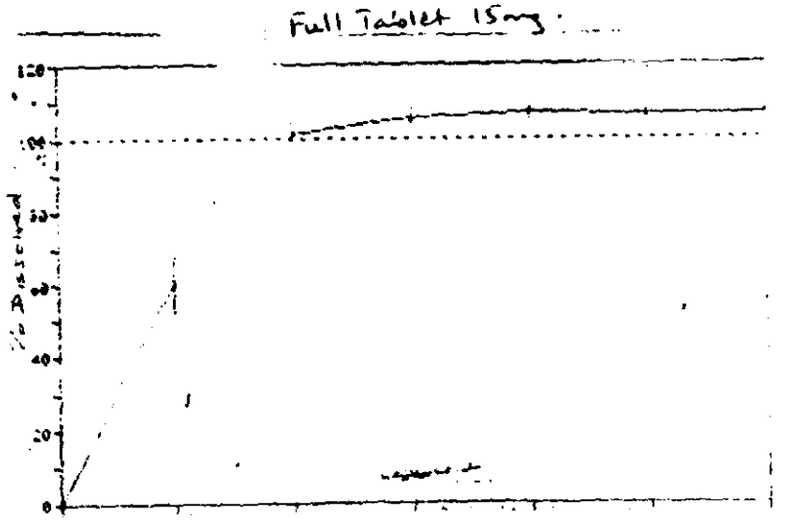
1) Dissolution profile of tablet halves 1-6
Batch no. 923001
7.5mg Tablet (Half)



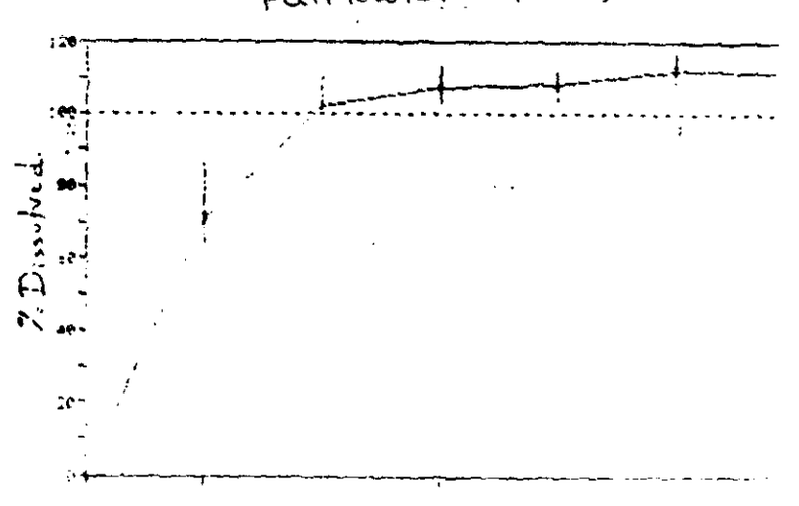
2) Dissolution profile of tablet halves 7-12
batch no. 923001
7.5mg Tablet (Half).

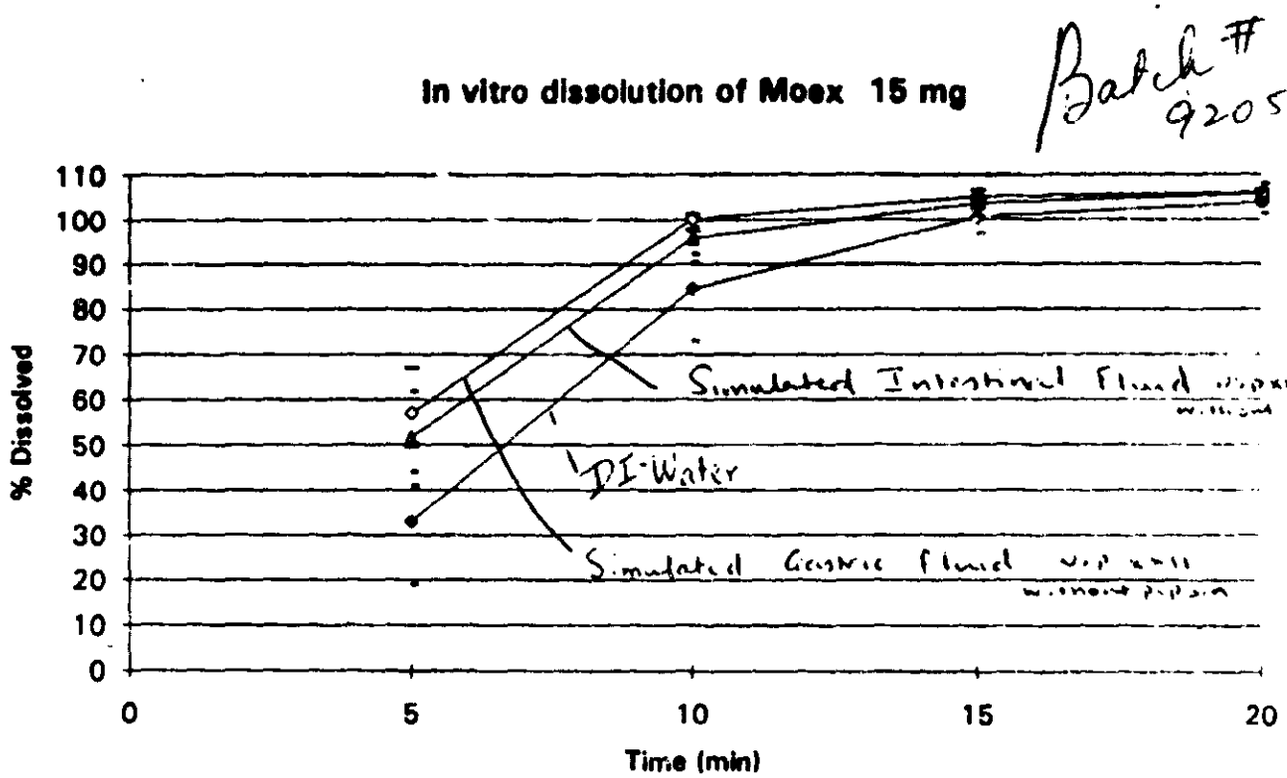


Full Tablet 15mg:



Full Tablet 7.5mg.





(from original record) [illegible]

K. B.
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NDA: 20-312 **Submission Date:** 12-18-92, 4-30-93, 5-17-93 and 7-7-93
Moexipril HCl Tablet, 7.5 and 15 mg.
Brand Name: Moex™
Sponsor: Besselaar **Reviewer: Rajendra S. Pradhan**
Type of Submission: Original NME Priority: 1S

Synopsis: The sponsor has adequately studied the pharmacokinetics (single and multiple dose), metabolism and excretion of prodrug moexipril and its active metabolite moexiprilat. Pharmacokinetics was studied over the dose range proposed in the package insert. Acceptable studies have also been performed in renally impaired patients and cirrhotic patients. Drug interaction between moexipril or moexiprilat and hydrochlorothiazide, digoxin, warfarin and nifedipine were studied. The sponsor has attempted to correlate plasma drug concentration to ACE-inhibition (a pharmacodynamic marker). An acceptable dissolution data has been provided on different strengths but not on broken tablets.

Recommendation: The sponsor's NDA 20-312 appears to be acceptable for meeting the biopharmaceutics requirements, provided that the comments are addressed satisfactorily by the sponsor.

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Appendix II
Individual Subject Data on Studies Listed Under Appendix I
Annotated Package Insert

Background: Moexipril hydrochloride is ethylester of moexiprilat, a long acting, non-sulfhydryl, nonpeptide angiotensin-converting enzyme (ACE) inhibitor. Moexipril hydrochloride is white to off-white powder. At room temperature it is about 10% W/V soluble in distilled water. Moexipril is a **prodrug**; following oral administration, it is bioactivated by hydrolysis of ethylester to moexiprilat. The sponsor is proposing to market coated tablets containing 7.5 mg and 15 mg of moexipril hydrochloride for oral administration. The sponsor has submitted 25 studies in support of the NDA. The first 13 studies listed under Appendix I are considered as important studies while others as supportive information. The recommended dosing is 7.5 to 60 mg/day administered in a single daily dose one hour prior to meals. It is recommended that dosage should be adjusted to blood pressure response.

Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics:
I. Bioavailability and Bioequivalence:
Absolute bioavailability for moexiprilat was not determined.

The to be marketed tablet formulation (15 mg), was bioequivalent to capsule formulation (15 mg), used in clinical studies except without a 5% overage. (Note: The clinical trial capsule and the capsule used in the bioequivalence study were made from the same blend. The bio study capsule batch was filled 5% less in weight than the clinical trial capsule). Considering the allowable tolerance limits for content uniformity for moexipril in the tablet (5% acceptable/Dr. Piechocki HFD 110) and based on all the available pharmacodynamic data it was concluded that 15.75 mg dose strength was not pharmacodynamically different from 15 mg dose of moexipril. The to be marketed tablet formulation (7.5 mg), is compositionally proportional to 15 mg tablet. Both tablets are scored.

II. Pharmacokinetics:
Absorption: The absorption of moexipril from the tablet and capsule formulations was rapid. For fasting conditions, the mean Tmax occurred between 0.6 and 1.5 hr. The absolute bioavailability of moexiprilat was not determined but for moexipril it was 22%. Both the rate and the extent of absorption were decreased when moexipril was administered (single dose) after a standard high fat breakfast. The AUC and Cmax for moexiprilat were reduced by 55% and 80% respectively after administration of moexipril postprandially.

Metabolism: The metabolite profiles in plasma and urine were determined by administering C^{14}-moexipril orally and by iv. After oral dosing, the metabolite profile for plasma showed moexipril to be the major radiolabelled component at 1 hr after dosing. The other metabolites present in the plasma were diketopiperazine moexiprilat, moexiprilat, diketopiperazine moexipril

and an unknown metabolite P4. All these metabolites were also seen in urine indicating that they are also at least partially eliminated renally (about 15% of total radioactivity). About 74% of total radioactivity was excreted in feces which included moexipril, moexiprilat, diketopiperazine moexiprilat in addition to unknown metabolites F1, F2, F3, F4, F5 and F6. On multiple oral dosing, the plasma radioactivity, moexipril or moexiprilat concentration time profile did not change. The urinary and fecal metabolite profile also remained the same on day one and day six of multiple dose administration (15 mg QD).

After intravenous administration of C^{14}-moexipril, plasma metabolic profile (10 min after administration) consisted of moexipril, moexiprilat and diketopiperazine moexiprilat. No P4 was observed after iv dosing. The urinary profile after iv dosing showed significant amounts of moexipril and moexiprilat but small amounts of diketopiperazine moexiprilat (about 65% of total radioactive dose). Moexiprilat, to lesser amount diketopiperazine moexiprilat and unknown metabolite F3 contributed to most of the radioactivity in faeces (about 26% of total radioactive dose). Up to five other minor metabolites were seen in faeces in addition to traces of moexipril.

Total recovery of radioactivity over 96 hours, both for oral and iv routes was about 90%. The radioactivity half life ranged from 1 to 4 hr.

Distribution: Both moexipril and moexiprilat bind mainly to plasma albumin. The binding can be considered as moderate (over concentration range 0.3 to 10 μg/ml). In young healthy subjects (under 45 yr) protein binding for moexipril was 88.2% (SD 1.8) and for moexiprilat 60.3 (SD 6.2). In elderly healthy subjects (over 65 yr) protein binding decreases ($\sim$ 48%). The volume of distribution (V_d), was determined to be 64 liters and the clearance from plasma (CL_p), was 419 ml/min for moexipril (after administration of the 5 mg iv dose to healthy young males).

Elimination: Unchanged moexipril is eliminated mainly in the urine, and moexiprilat is eliminated in both the urine and feces. The mean values for elimination half-life for moexipril ranged from 0.6 hr to 1.7 hr for all the studies of normal subjects. The $t_{1/2}$ of moexipril did not depend on dose. The mean values for elimination half-life for moexiprilat ranged from 0.8 hr to 53 hr for all the studies of normal subjects. The intersubject variation seen in $t_{1/2}$ of moexiprilat could be due to variation in binding of moexiprilat with ACE. The mean elimination $t_{1/2}$ for moexiprilat calculated using urine data was 4.3 hr in elderly subjects and 3.2 hr in younger subjects.

Multiple-Dose Kinetics: Comparison of single dose and multiple dose pharmacokinetics was studied in two different studies. Moexiprilat showed moderate accumulation (Accumulation ratio of about 1.3) on multiple (15 mg) QD dosing for five days, in both normal younger subjects and normal elderly subjects. There appeared a trend for an increase in the ratio of moexipril to moexiprilat on day 5. In the second study, which had a small number of subjects per group (4) and a parallel design, twice daily administration (BID) of 120 mg of moexipril for 15 days, did not show any moexiprilat accumulation, however, BID administration of 60 mg showed 100% accumulation (note: the latter is not a recommended dose in the labelling).

III. Dose and Dosage Form Proportionality:

In a study where 3.75, 7.5, 15 and 30 mg moexipril doses were administered to healthy subjects in a crossover design, lower doses showed higher bioavailability than higher doses (15 and 30

mg). This probably is due to dose independent contribution of the terminal phase of moexiprilat to AUC. It has been shown that the terminal phase due to the residual binding of drug to ACE has half life greater than 30 hr. This phase can certainly contribute more to AUC of small doses than AUC of large doses. There was an increasing trend in dose normalized Cmax with dose.

IV. Special Populations:

Renal Impairment: It was shown that $t_{1/2}$ values for moexipril and moexiprilat increased with decreasing renal function. Upon administration of single 15 mg dose the $t_{1/2}$ value for moexipril increased from 1.1 (SD 0.2) hr for subjects with creatinine clearance (CrCl) > 90 ml/min to 2.2 (SD 0.7) hr for subjects with CrCl from 10 to 40 ml/min. The AUC for moexipril increased from 60 to 70 ng hr/ml. The $t_{1/2}$ value for moexiprilat increased from 1.5 (0.5) hr for subjects with creatinine clearance (CrCl) > 90 ml/min to 5.3 (SD 3.6) hr for subjects with CrCl from 10 to 40 ml/min. The AUC for moexiprilat increased from 150 to 268 ng hr/ml. Accumulation of moexipril and moexiprilat is not expected for the recommended doses in patients with mild to moderate renal impairment (CrCl >40 ml/min). With CrCl $\leq$ 40 ml/min, dosage reduction should be considered.

Hepatic Impairment: In a cross study comparison it was seen that, for moexipril (single 15 mg dose), dose normalized Cmax was about 1.5 times higher and dose normalized AUC was about 1.5 to 2 times nigher for cirrhotic subjects than for the normal subjects. For moexiprilat, dose normalized Cmax was lower ($\simeq$ by 25%) for the cirrhotic subjects, but dose normalized AUC was about 2 to 2.5 times higher. The $t_{1/2}$ was longer for moexipril and moexiprilat for the cirrhotic subjects. Thus, pharmacokinetics of moexipril and moexiprilat were significantly altered in cirrhotic subjects compared with normal subjects, but plasma concentrations in cirrhotic subjects returned to levels similar to those in normal volunteer between 12 and 24 hr postdosing. Accumulation of moexipril and moexiprilat is not expected at this dose in cirrhotic subjects. However, since the pharmacokinetics across the recommended dose range has not been established in these patients, caution should be exercised at higher doses in these patients. OK

Elderly: The mean elimination $t_{1/2}$ for moexiprilat calculated using urine data was 4.3 hr in elderly subjects and 3.2 hr in younger subjects. In elderly healthy subjects (over 65 yr) protein binding was lower ($\sim$ 48%). Following 15 mg QD moexipril administration, the mean Cmax and $AUC_{0\text{-}24}$ for both moexipril and moexiprilat were approximately 30 % higher in the elderly group than in the younger group on day one and on day five. The total body clearance for moexipril and moexiprilat were lower in the elderly group than in the younger group. OK

V. Drug Interactions:

The results of moexipril interaction studies (hydrochlorothiazide HCTZ, digoxin, cimetidine and nifedipine retard) are summarized below.

Study No.	Dosage Form	Dose (mg)	Moexipril				Moexiprilat			
			C_{max} (ng/mL)	T_{max} (hr)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)
GHBA 625R	Capsule	30	248	1.2	487	-	71	1.6	209	-
		30 + HCTZ	241	0.8	416	-	69	1.6	215	-
GHBA 626	Capsule	30	130	0.9	296	-	52	1.6	169	-
		30 + digoxin	152	1.0	239	-	57	1.8	177	-
GHBA 627	Capsule	30	254	0.9	406	0.6	68	1.5	226	0.9
		30 + cimetidine	206	1.0	378	0.6	82	1.6	255	0.8
GHBA 693	Capsule	15	100	1.0	150	0.8	18	1.7	89	0.9
		15 + nifedipine	122	1.0	193	0.7	25	1.5	71	0.9

Neither HCTZ, digoxin, cimetidine nor nifedipine (given as CR) had any significant effect on the pharmacokinetics of either moexipril or moexiprilat. Administration of moexipril did not affect mean total urinary excretion of HCTZ; mean Cmax, AUC or Tmax for digoxin and mean Cmax, AUC or $t_{1/2}$ for nifedipine. Mean Tmax for nifedipine administered together with moexipril occurred earlier 1.3 (SD 0.7) than nifedipine administered alone 2.4 (SD 2.1).

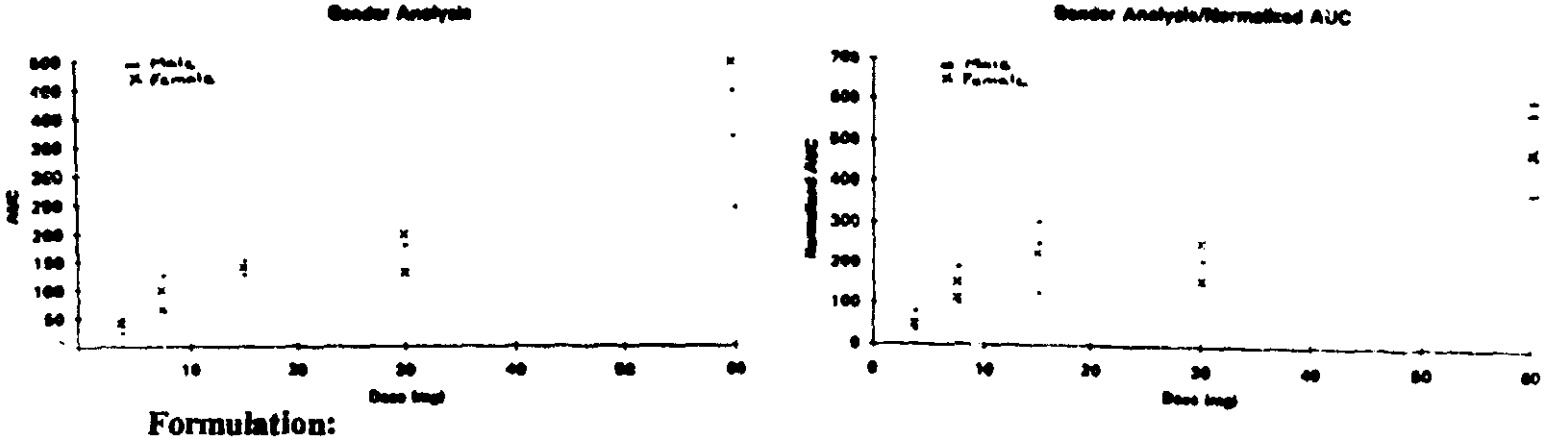
The following table shows that coadministration of moexipril with warfarin had no demonstrable effects on plasma warfarin concentrations.

Parameters	50 mg Warfarin	15 mg Moexipril + 50 mg Warfarin
Warfarin (S)		
Cmax (μg/ml)	2.85 ± 0.35	2.79 ± 0.37
Tmax (hr)	1.8 ± 0.9	2.5 ± 3.4
$AUC_{(0-t)}$ (μg hr/ml)	94.8 ± 15.7	95.3 ± 18.4
Warfarin (R)		
Cmax (μg/ml)	2.80 ± 0.42	2.81 ± 0.34
Tmax (hr)	2.1 ± 1.1	2.5 ± 3.4
$AUC_{(0-t)}$ (μg hr/ml)	124 ± 21	125 ± 28

There was no effect on the anticoagulant effects of warfarin for 5 days, as measured by elongation of the prothrombin time. Medical officer should note the increased number of adverse effects (headache and dizziness) associated with concomitant administration of moexipril and warfarin.

VI. Pharmacokinetic/Pharmacodynamic Relationship:
The sponsor has used ACE inhibition as a marker for drug activity and compared it with moexiprilat concentration using simple Emax model. The EC50 was calculated to be 0.4 ng/ml for moexiprilat. However it was seen that ACE inhibition was still more than 50% when blood pressure had returned to predose value, implying that in addition to plasma ACE inhibition, other factors may contribute to the lowering of blood pressure.

VII. Gender Analysis:
The firm did not submit any gender analysis. Based on the study which had sufficient female subjects (about 50% of male subjects), it was concluded by this reviewer, that there is no gender difference in moexiprilat pharmacokinetics over a dose range of 3.75 to 30 mg. The figures below show that at 60 mg dose, the female subject had the highest exposure. When corrected for weight, however, the AUC for this subject was lower. (In the following fig on the right AUC was normalized to a reference body weight of 60 kg). This comparison was non-statistical due to limited subjects per dose group.



Formulation:
The tablet formulation 7.5 mg is compositionally proportional to 15.0 mg tablet.

Dissolution:
The sponsor has proposed dissolution method of USP XXII apparatus II at 50 rpm, in 900 ml water at 37°C, with sampling time at 15 min and a specification of at least dissolved in 15 min according to USP <711> dissolution acceptance table.

This specification is not acceptable and after reviewing the in vitro dissolution data, Division of Biopharmaceutics recommends a Q of not less than in 15 min.

General Comments (Need not be sent to the firm):
The sponsor has not studied the pharmacokinetics in patients with CHF.

The drug interaction study with nifedipine utilizes a controlled release formulation of nifedipine. Upon coadministration of 20 mg nifedipine with 15 mg moexipril, there was a marginal increase (16% for mean AUC and 15% for mean Cmax) in moexipril plasma levels. Higher doses of moexipril with immediate release nifedipine may have potential for interaction.

Comments to the Pharmacologist: Under Carcinogenesis, Mutagenesis, Impairment of Fertility section of labeling, the firm claims that mice and rats were exposed to doses 150 times higher than human dose. Based on a comparison between rats and humans and using area under radioactivity versus time curve as an exposure parameter and considering 60 mg as highest human dose, 75 mg/kg/day produces only about 2 fold higher exposure to animals. This statement is based on linear extrapolation of exposure from 15 mg to 60 mg dose in humans. Although the animal doses were several fold higher than humans, due to different disposition the exposure scale in animals translated to only about two times that of the humans.

Comments to be Sent to the Firm:
The dissolution specification proposed by the firm is not acceptable. The Division of Biopharmaceutics recommends a Q of not less than in 15 min.

The firm is requested to submit in vitro dissolution data in deionized water on half Moex™ tablet (7.5 and 15 mg/broken at the score) using the same dissolution method conditions used for the full tablet. The data should be provided to Division of Biopharmaceutics in a format where comparison can be made between in vitro dissolution of full and half Moex™ tablet.

The firm should attempt an in vitro characterization of enzymes involved in moexipril metabolism.

Labeling Comments:

1. The statement 'The extent of absorption may be reduced when MOEX™ tablets are administered with high fat breakfast' should be replaced by following statement.
   'Upon single dose administration of 15 mg MOEX™ with a high fat breakfast to normal volunteers, the area under the plasma concentration versus time curve (AUC) and peak plasma concentration (Cmax) of moexiprilat is reduced by up to 50% and 80% respectively'.

2. The statement 'The serum protein binding of moexipril is about 90% and that of moexiprilat about 75%, as measured by equilibrium dialysis at 25°C; on the basis of in vitro studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, renal dysfunction or concentration (over concentration range of 0.3 - 10 μg/ml)' should be replaced by following statement.
   'The serum protein binding of moexipril is about 90% and that of moexiprilat about 65%, as measured by equilibrium dialysis at 25°C. On the basis of in vitro studies, the degree of protein binding was unaffected by hepatic dysfunction or concentration (over concentration range of 0.3 - 10 μg/ml). In healthy elderly subjects over 65 years of age, moexiprilat protein binding was 48%'.

3. The statement ' In elderly male subjects (65-80 year old) with clinically normal renal and hepatic function, there appear to be no difference in pharmacokinetic parameters compared to those of younger subjects (19-42 years old)' should be replaced by following statement.
'In elderly male subjects (65-80 year old) the AUC and Cmax of moexiprilat tends to be about 30% higner than in younger subjects (19-42 years old)'.

4. The statement 'The kinetics of moexipril have been shown to be dose-proportional within the range of 3.75 mg to 30 mg' should be replaced by following statement:
'In the dose range of 3.75 to 30 mg, the pharmacokinetics of moexipril may be considered dose proportional. Highest dose, however, was not evaluated'.

5. The firm should state 'Moexiprilat showed moderate accumulation upon multiple dosing of moexipril'.

6. The firm should replace the paragraph, under 'Pharmacokinetics and Metabolism', on effective half life by the following:
'Based on multiple dose administration of 15 mg QD for 5 days to healthy young and elderly subjects, the mean effective half life was estimated to be about 12 hr'.

7. The firm should replace the statement in the 'Precaution' section under Impaired Liver Function with 'In patients with hepatic dysfunction due to cirrhosis, a single 15 mg dose study showed moderate increases in AUC values of moexipril and moexiprilat. Caution should be exercised in dosing these patients'.

8. Under 'Pharmacokinetics and Metabolism' section regarding hepatic cirrhosis patients, state: 'Patients with hepatic cirrhosis showed moderate increases in AUCs as compared to normal subjects when a single 15mg dose was administered'.

9. In the 'Drug Interaction' section, the firm should specify that nifedipine was administered as a controlled release formulation.

10. The ingredients for the tablet coat should be listed in the labelling.

11. Under 'Dosage Adjustment in Renal Impairment', 'Pharmacokinetics and Metabolism' sections the cut off point for creatinine clearance should be change from $\leq$30 ml/min to $\leq$40 ml/min. Also in 'Precaution' section the statement 'In patients with glomerular filtration rate $\leq$ 30 ml/min, peak moexipril level and half life increase, and time to steady state may be delayed' should be replaced by following statement:
'In patients with creatinine clearance $\leq$ 40 ml/min, moexiprilat half life increase, and time to steady state may be delayed'.

12. In 'Pharmacokinetic and Metabolism' section, the statement regarding the site of absorption should be deleted since a conclusive study has not been conducted.

9/30/93

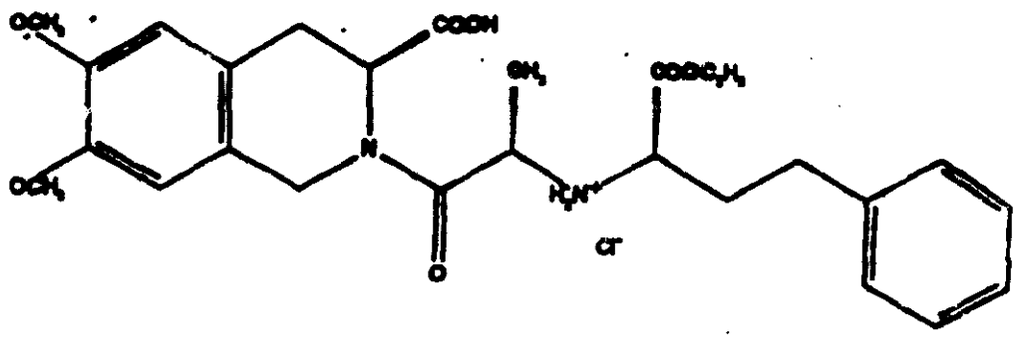
Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics

RD Initialed by Ameeta Parekh, Ph.D. Ameeta Parekh 9/30/93

Biopharm Day: Collins, Fleischer, Hepp, Ludden, Parekh, Pradhan.

cc NDA 20-312, HFD 110, HFD 426 (Fleischer/Pradhan) Reviewer, Chron, Drug, FOI (HFD-19), HFD 340 (Viswanathan), Food, Metabolism.

APPENDIX I



Moexipril hydrochloride

Appearance: Fine white to off-white powder
Odor: Odorless to slightly characteristic
Polymorphism: Without relevance because high water solubility (> 10% w/v at RT).
pH: The pH of a 10% w/v solution in water is 1.8.

Composition and Dosage Form

The description and quantitative composition of Moexipril HCl Tablets 7.5mg strength are:

Description: biconvex, 6 mm, round pink film coated tablets with score and engravure "M/7.5" on one side and the engravure "SP" on the other side.

COMPONENT	STANDARD	MG PER TABLET	
		THEORETICAL	ACTUAL
CORE:			
moexipril HCl	Schwarz Pharma	7.50	7.500
lactose	NF XVII		
crospovidone	NF XVII		
magnesium oxide	USP XXII		
gelatin	NF XVII		
magnesium stearate	NF XVII		
purified water*	USP XXII		
FILM COAT:			
hydroxypropyl methyl cellulose	USP XXII		
hydroxypropyl cellulose	NF XVII		
titanium dioxide	USP XXII		
polyethylene glycol 6000	NF XVII		
magnesium stearate	NF XVII		
ferric oxide	NF XVII		
purified water*	USP XXII		

The description and quantitative composition of Moexipril HCl Tablets 15mg strength are:

Description: biconvex, 8mm, round, indian red film coated tablet with score and engravure "M/15" on one side and engravure "SP" on the other side.

COMPONENT	STANDARD	MG PER TABLET	
		THEORETICAL	ACTUAL
CORE:			
moexipril HCl	Schwarz Pharma	15.00	15.000
lactose	NF XVII		
crospovidone	NF XVII		
magnesium oxide	USP XXII		
gelatin	NF XVII		
magnesium stearate	NF XVII		
purified water*	US XXII		
FILM COAT:			
hydroxypropyl methyl cellulose	USP XXII		
hydroxypropyl cellulose	NF XVII		
titanium dioxide	USP XXII		
polyethylene glycol 6000	NF XVII		
magnesium stearate	NF XVII		
ferric oxide	NF XVII		
purified water*	USP XXII		

ASSAY VALIDATION

Study No.	Study Title	Site	Date	Procedure
Pivotal Studies				
GHBA 628	Metabolic Profile			GC-MS
GHBA 621	Efficacy and PK study for singl rising dose		01/04/88	GC-ECD
925-3,4,6	Identification of ME-Dose and efficacy			GC-ECD
PHAKI 794	Bioequivalence Formu.4A and Formu Syntex		3/13/92-7/17/92	GC-MS
PHAKI 792	Bioequivalence Formu.4 and Formu Syntex		3/15/91-5/10/91	GC-MS
GHBA 637	Influence of Age		7/15/92-9/16/92	GC-MS
GHBA 629	Renal Impairment		3/18/91-3/18/92	GC-MS
GHBA 636	Hepatic Cirrhosis		2/21/92-03/12/92	GC-MS
GHBA 625R	Drug Interaction		7/30/91-10/10/91	GC-MS
GHBA 626	Drug Interaction		3/15/91-5/10/91	GC-MS
GHBA 627	Drug Interaction		5/27/91-8/1/91	GC-MS
GHBA 631	Drug Interaction		6/19/91	HPLC
GHBA 633	Drug Interaction		10/17/91 11/22/91	GC-MS
PHAKI 796	Food Interaction		3/15/91-5/10/91	GC-MS

Site /	Instrument	Analyte	Bio. Matrix	Int.Std.	Linear Range/LQL	Inj. Vol.
		Moexipril and Moexipril-at	**Plasma**	Quinapril	5-500 ng/ml 5 ng/ml	1.6 µl
		Moexipril and Moexipril-at	Plasma	Quinapril	10-1000 ng/ml 10 ng/ml	1.0 µl
		Moexipril-at	Plasma	NA	7-57ng/ml on Logit-log scale/ 7 ng/ml	50 µl Plasma
		Moexipril	Plasma	Quinapril	0.5-50.0 ng/ml 0.5 ng/ml	1.0 µl
		Moexipril and Moexipril-at	Plasma and Urine	Quinapril and Quinaprilat	0.5-300ng/ml and (0.5) 50-15000 ng/ml,(50)	1.0 µl
		Moexipril and Moexipril-at	Plasma and Urine	Quinapril and Quinaprilat	0.5-100ng/ml and 0.5ng/ml 5-500 ng/ml and 5 ng/ml	1.0 µl

Investigation of Bioequivalence of Two Different Formulations of Moexipril

Study No: PHAKI-794 Volume: 1.56 to 1.58 Pages: 1 of 1.56 to end of 1.58

Investigator and Site:

Objectives: To determine bioavailability and pharmacokinetic parameters of two different moexipril hydrochloride preparations following oral administration.

Formulations: Moexipril 15 mg coated tablet, Batch #920512
Moexipril 15 mg capsule, Batch #913168

Study Design: This was an open, randomized two-way cross-over design with 37 healthy male non-smoker subjects.
Washout: One week.
Treatment A: 30 mg moexipril once as two tablets (test formulation).
Treatment B: 30 mg moexipril once as two capsule (reference formulation).

Specimens: Blood, 40 ml pre-dose and 8 ml at 5, 10, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr post administration.

Assay (moexipril and moexiprilat): GC-MS
Plasma:
Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 300 ng/ml.
Precision: Interday for moexipril ranged from 2.49% at 0.5 ng/ml to 1.04% at 300 ng/ml. Intraday for moexipril ranged from 2.83% at 0.5 ng/ml to 2.45% at 50 ng/ml. Interday for moexiprilat ranged from 3.9% at 0.5 ng/ml to 2.31% at 300 ng/ml. Intraday for moexiprilat ranged from 1.99% at 0.5 ng/ml to 2.48% at 50 ng/ml.
Accuracy: Interday for moexipril ranged from 1.88% at 0.5 ng/ml to 0.44% at 300 ng/ml. Intraday for moexipril ranged from 4% at 0.5 ng/ml to 0.1% at 50 ng/ml. Interday for moexiprilat ranged from 10.41% at 0.5 ng/ml to 1.72% at 300 ng/ml. Intraday for moexiprilat ranged from 4% at 0.5 ng/ml to 0.4% at 50 ng/ml.

Data Analysis: $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, Cmax, Tmax, $t_{1/2}$, and K_e were determined by model independent methods. Concentration dependent parameters were evaluated after logarithmic transformation by ANOVA and by 90% confidence interval approach. The Koch's non-parametric test was used to evaluate Tmax.

Note For the statistical part, only data from subject #9 was not used, as subject #9 under went a dental therapy between period 1 and 2 during which he was administered antiphlogistic preparation.

Estimation of terminal rate constant (K_e) for moexipril was not reliable for 8 subjects due to lack of data points in terminal phase. This resulted in unreliable estimates for $AUC_{(0-\infty)}$ for 8 subjects.

For moexiprilat 27 out of the 36 subjects showed pre-dose concentration above 0.5 ng/ml in period 2. Since a reliable estimate for the true terminal half-life was not available, measured moexiprilat data for period 2 could not be corrected for carry-over in any resonable way.

The bias thus generated however does not influence the between treatment comparison because of completely balanced study design.

Results: The mean (± SD) values for pharmacokinetic parameters are shown in the following table.

Parameter	Treatment: [illegible] dose	
	2 x 15-mg tablet	[illegible] 15-mg capsule
Moexipril		
$AUC_{0-\infty}$ (ng·hr/mL)	346 ± 146	326 ± 195
C_{max} (ng/mL)	183 ± 73	182 ± 82
T_{max} (hr)	1.0 ± 0.3	1.0 ± 0.3
k_e (hr^{-1})	0.46 ± 0.13	0.50 ± 0.14
$t_{1/2}$ (hr)	1.6 ± 0.5	1.5 ± 0.5
Moexiprilat		
$AUC_{0-\infty}$ (ng·hr/mL)	175 ± 50	171 ± 43
C_{max} (ng/mL)	47 ± 17	50 ± 24
T_{max} (hr)	1.6 ± 0.4	1.7 ± 0.3
k_e (hr^{-1})	0.08 ± 0.02	0.09 ± 0.02
$t_{1/2}$ (hr)	8.9 ± 2.5	8.3 ± 1.7

The statistical parameters for moexipril and moexiprilat for two treatments are shown in appendix II. The mean plasma concentration time profile for moexipril and moexiprilat is shown in fig 1 and 2.
The following table shows the 90% confidence intervals for pharmacokinetic parameters of moexipril and moexiprilat.

	Parameters	90% CI
Moexipril	$AUC_{(0-t)}$	85.87-112.21
	$AUC_{(0-24)}$	85.89-112.02
	$AUC_{(0-\infty)}$	88.65-112.99
	Cmax	88.01-112.86
	$t_{1/2}$	105.45-126.80
	Tmax (non-parametric)	87.50-125.00
Moexiprilat	$AUC_{(0-t)}$	88.46-111.02
	$AUC_{(0-\infty)}$	89.49-109.79
	Cmax	84.19-112.24
	$t_{1/2}$	96.48-115.12
	Tmax (non-parametric)	83.33-116.67

Conclusion: The test formulation was bioequivalent to reference formulation with respect to the parent compound and the active metabolite moexipril.

Figure 1:

Plasma Levels of Moexipril

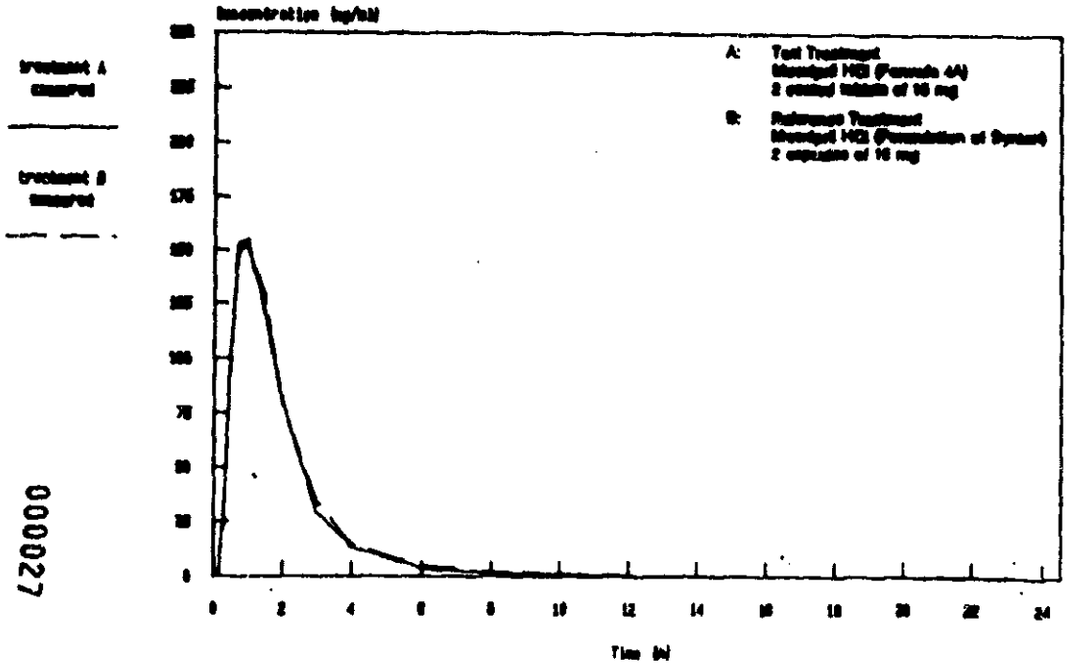


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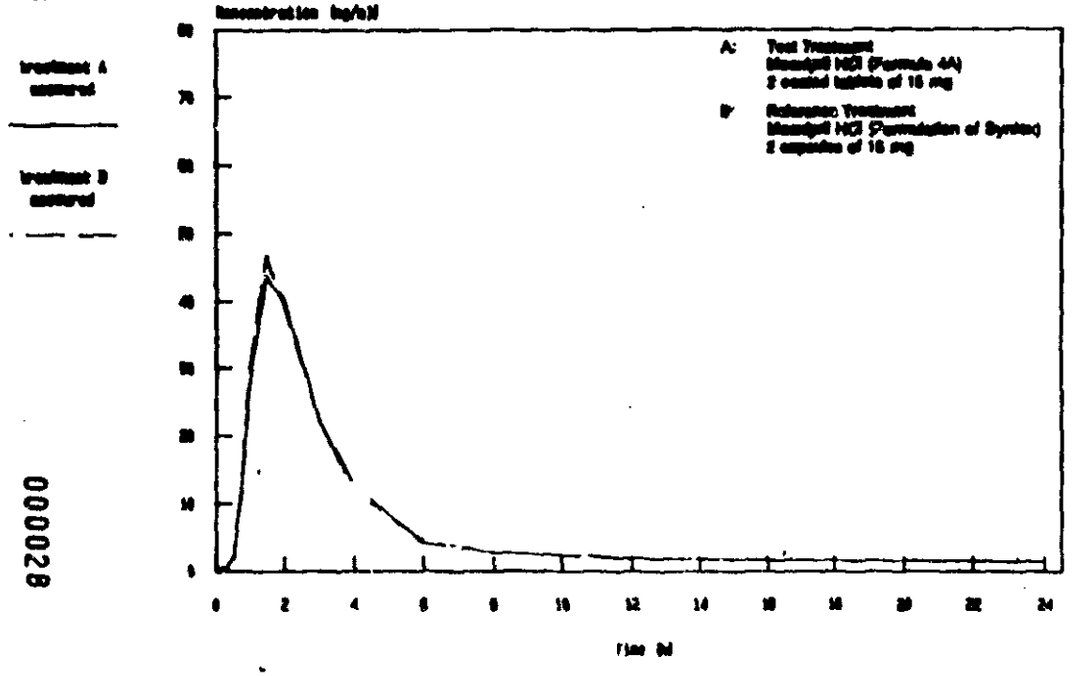
Figure 2:

Plasma Levels of Moexiprilat



000028

Drug Disposition Study of ^{14}C-Labelled Moexipril

Study No. GHBA-628 Volume: 1.52 Pages: 41-163
Investigator and site:

Objectives: To compare the drug disposition and pharmacokinetics of a single oral, single intravenous and multiple oral dose of radiolabelled moexipril. To examine the extent of ACE inhibition over time.

Formulation: ^{14}C-Moexipril, Batch # CFQ.6611 and Moexipril capsules, Batch # 912118. Radiolabelled formulations were prepared fresh for each dose occasion.

Study Design: This was open-label, drug disposition study. Group I (N=4) referred as Panel A received a single oral dose (15 mg/ 40 μCi) of ^{14}C-moexipril (phase 11) followed by a single IV infusion dose of (5 mg/ 17 μCi) ^{14}C-moexipril (phase 1). There was a wash-out period of 3 weeks between doses. A further group of four volunteers (Panel B) received a single oral dose of (15 mg/ 28.5 μCi) ^{14}C-moexipril on day 1, followed by daily doses of non-radiolabelled moexipril (days 2-5) and a second ^{14}C-moexipril dose (15 mg/ 28.5 μCi) on day 6.
All subjects fasted 10 hr prior and 4 hr after dosing.

Specimens: Blood (12 ml)
Panel A, Phase I: Pre dose, 0 hr (end of 15 min infusion), 5, 10, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12 hr after the end of infusion.
Panel A, Phase II: 0 hr (pre dose), 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12 and 24 hr post dose.
Panel B: 0 hr (pre dose), 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12 and 24 hr post dose on days 1 and 6.
Urine and faeces were collected at the following intervals after each dose of ^{14}C-moexipril:
Urine: 0 hr (pre dose), 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hr.
Faeces: 0 hr (pre dose), 0-12, 12-24, 24-48, 48-72 and 72-96 hr.

Assay: Radioactivity was measured for 2 to 10 min using a liquid scintillation counter with facilities for computing quench-corrected disintegrations per min. Efficiency correlation curves were routinely checked by the use of ^{14}C-n-hexadecane standards.

Plasma ACE activity was determined at using a commercially available kit (procedure no.

Plasma samples were analyzed for moexipril and moexiprilat using a GC-MS method. Linearity: Satisfactory. Standard curve from 0.5 to 50 ng/ml.
Sensitivity: Satisfactory. LQL = 0.5 ng/ml.
Accuracy: Interday ranged from 0.9 to 3.0%, intraday ranged from 3.2 to 8.0% for moexipril. Interday ranged from 0.2 to 15%, intraday ranged from 7.4 to 8.0% for moexiprilat.
Precision: Interday ranged from 14.8% at 50 ng/ml to 29.2% at 1.0 ng/ml, intraday ranged from 6.5% at 0.5 ng/ml to 10% at 50 ng/ml for moexipril. Interday ranged from 42.5% at 1.0 ng/ml to 14.5% at 50 ng/ml, intraday ranged from 7.3% at 50 ng/ml to 17.4% at 0.5 ng/ml for moexiprilat.

HPLC with UV detection 254 nm/ radioactivity monitor with liquid scintillant was used to study the metabolite profiling.

Data Analysis: Terminal half life of elimination, $AUC_{0-\infty}$, Cmax, and time (tmax) to reach Cmax, total clearance and volume of distribution using radioactivity concentrations. ACE activity and degree of inhibition. PK profile of moexipril and moexiprilat were analyzed. Plasma, urine and faecal metabolites were also analyzed.

Results:

	$AUC_{0-\infty}$ ng equivalents·hr/ml	Cmax ng equivalents/ml	Tmax (hr)	$t_{1/2}$ (hr)	TUE %	TFE %
I (ra)	870 ± 390	270.7 ± 125.6	1.06 ± 0.31	2.535	15.17	73.74
II (ra)	475.2 ± 119.7	566.8 ± 103.5	NA	1.023	64.92	25.96
III (ra)	759.4 ± 356.7	279.0 ± 100.5	1.19 ± 0.37	1.711	14.30	76.76
IV (ra)	657.6 ± 293.8	253.0 ± 88.6	0.88 ± 0.14	1.929	13.35	73.97
I (ML)	139.9 ± 68.1	74.0 ± 60.0	1.00 ± 0.35	0.826	1·7	1·49
II (ML)	207.0 ng·hr/ml ± 47.7	579.9 ng/ml ± 106.9	NA	1.340	17·83	0·53
III (ML)	140.8 ± 56.51	92.13 ± 52.12	0.93 ± 0.43	1.316	1.68	—
IV (ML)	100.7 ± 51.15	65.88 ± 33.55	0.69 ± 0.12	1.059	1·01	—
I (MT)	98.87 ± 42.74	26.1 ± 18.1	2.12 ± 0.95	4.42	5·9	51·64
II (MT)	177.5 ± 47.43	98.4 ± 31.3	0.81 ± 0.12	3.44	38·87	15·24
III (MT)	128.8 ± 32.62	23.63 ± 15.09	1.75 ± 0.29	11.32	7·09	55·03
IV (MT)	122.8 ± 35.67	28.18 ± 11.10	1.37 ± 0.25	5.03	6·61	54.23

I - Single oral dose of ^{14}C-moexipril 15 mg.
II - Single intravenous infusion (over 15 min) of ^{14}C-Moexipril 5 mg.
III- Oral dose of ^{14}C-Moexipril 15 mg 1 st day of QD for 6 days phase.
IV - Oral dose of ^{14}C-moexipril 15 mg 6 th day of QD for 6 days phase.
Concentration expressed in (ra)- radioactivity, (ML)- moexipril and (MT) moexiprilat.
TUE- Total urinary excretion, TFE- total faecal excretion. (Expressed as % of Dose)
Moexipril clearance (Cl_p) of 418.5 ± 92.89 ml/min and volume of distribution (V_d) of 63.98 ± 44.46 L were calculated.

Metabolic profile: Fig. 1 to 4 show mean plasma radioactivity concentrations versus time profile for panel A and B. Fig. 5 to 8 show mean plasma concentrations of moexipril and moexiprilat versus time profile for panel A and B. The HPLC chromatogram of reference standards is shown

in appendix II along with HPLC profiles of radioactivity in plasma, urine and faeces for oral and iv doses of moexipril.

Following a single oral administration, plasma radio-HPLC profile showed presence of moexipril, moexiprilat, diketopiperazine moexipril and diketopiperazine moexiprilat in addition to unknown metabolites referred as PI, P2 and P3. Urine radio-HPLC profile showed presence of moexipril, moexiprilat, diketopiperazine moexipril and diketopiperazine moexiprilat in addition to unknown metabolites referred as U1, U2, U3, U4 and U5. Faecal radio-HPLC profile showed presence of moexipril, moexiprilat, diketopiperazine moexiprilat in addition to unknown metabolites referred as Fl, F2, F3, F4, F5 and F6. Following multiple dose administration metabolic profiles for day 1 and day 6 were similar to following a single dose administration.

Following single intravenous administration of ^{14}C-moexipril, plasma radio-HPLC profile showed presence of moexipril, moexiprilat, diketopiperazine moexiprilat in addition to P2. Urine radio-HPLC profile showed presence of moexipril, moexiprilat, diketopiperazine moexipril and diketopiperazine moexiprilat in addition to unknown metabolites referred as Ul, U2, U3 and U4. Faecal radio-HPLC profile showed presence of moexipril, moexiprilat, diketopiperazine moexipril and diketopiperazine moexiprilat in addition to unknown metabolites referred as F2, F3, F4 and F5.

Recovery: The total radioactivity recovered was 88.91% for 15 mg oral dose (panel A), 90.88% for 5 mg iv dose (panel A), 91.06% for 15 mg oral dose on day one (panel B) and 87.32% for 15 mg on day six (panel B).

ACE activity and inhibition: The mean percent ACE inhibition reached maximum (>90%) in 2 hr and dropped to 50% by 96 hrs.

Conclusion

After single oral or iv doses of ^{14}C-moexipril to healthy male volunteers at dose levels of 15 or 5 mg respectively, plasma ACE inhibition appeared to correlate well with plasma profile of moexiprilat. Moexipril was mainly renally excreted and moexiprilat eliminated by both renal and hepatic mechanisms. The pharmacokinetics of moexipril and moexiprilat did not change upon multiple daily oral administration.

Figure 8.4 1

Mean plasma radioactivity concentrations following a single oral administration of (^{14}C)-moexipril to male volunteers at a nominal dose level of 15 mg/subject

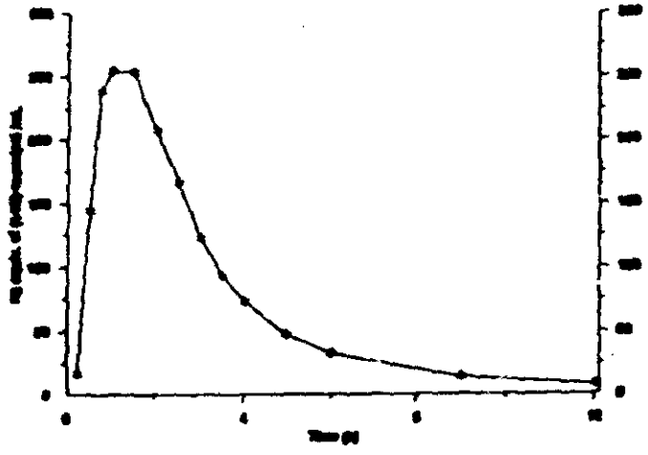


Figure 8.4 2

Mean plasma radioactivity concentrations following a single intravenous administration of (^{14}C)-moexipril to male volunteers at a nominal dose level of 5 mg/subject

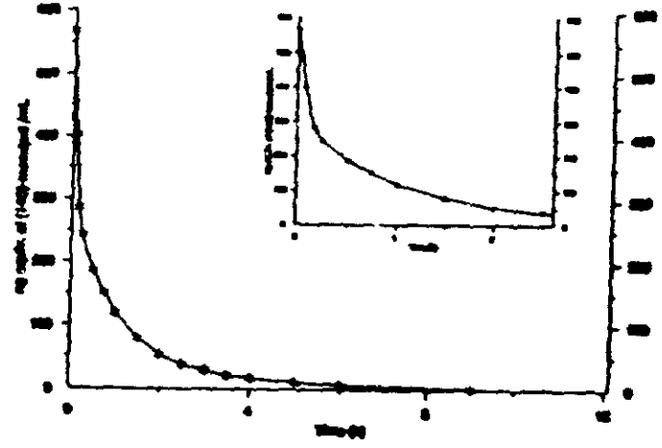
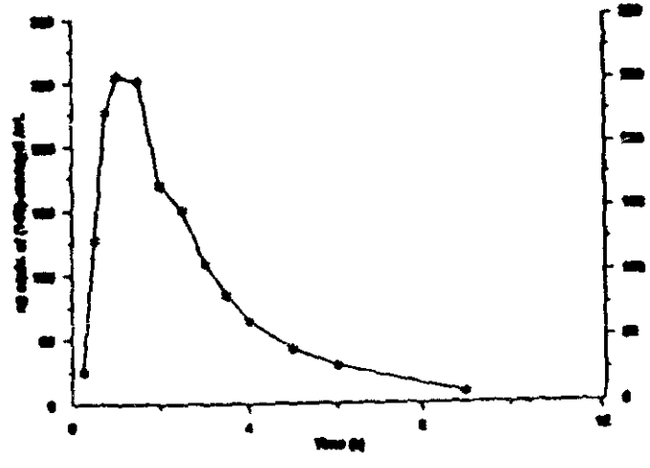


Figure 8.4 3

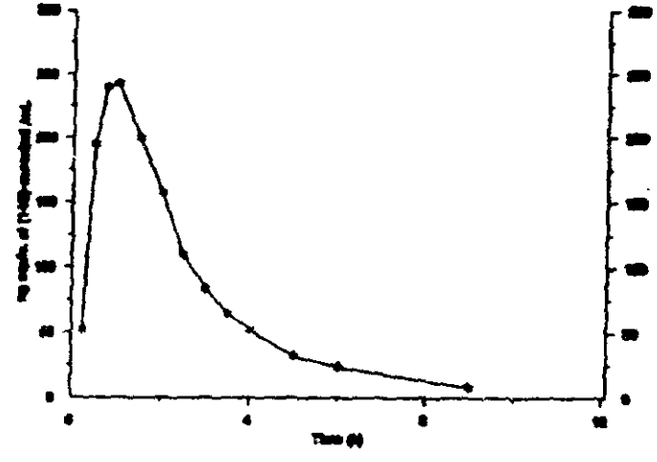
Mean plasma radioactivity concentrations following the first of six daily oral administrations of moexipril and (^{14}C)-moexipril* to male volunteers at a nominal dose level of 15 mg/subject



* (^{14}C)-moexipril administered on days 1 and 6

Figure 8.4 4

Mean plasma radioactivity concentrations following the last of six daily oral administrations of moexipril and (^{14}C)-moexipril* to male volunteers at a nominal dose level of 15 mg/subject



* (^{14}C)-moexipril administered on days 1 and 6

Figure 5

Mean plasma concentrations of moexipril and moexiprilat following a single oral administration of (^{14}C)-moexipril to male volunteers at a nominal dose level of 15 mg/subject

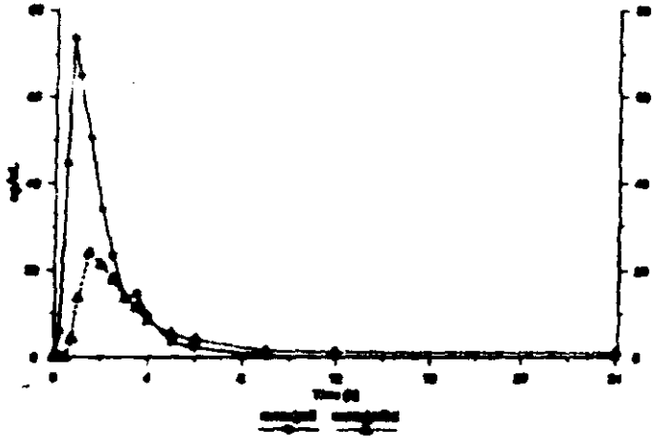


Figure 6

Mean plasma concentrations of moexipril and moexiprilat following a single intravenous administration of (^{14}C)-moexipril to male volunteers at a nominal dose level of 5 mg/subject

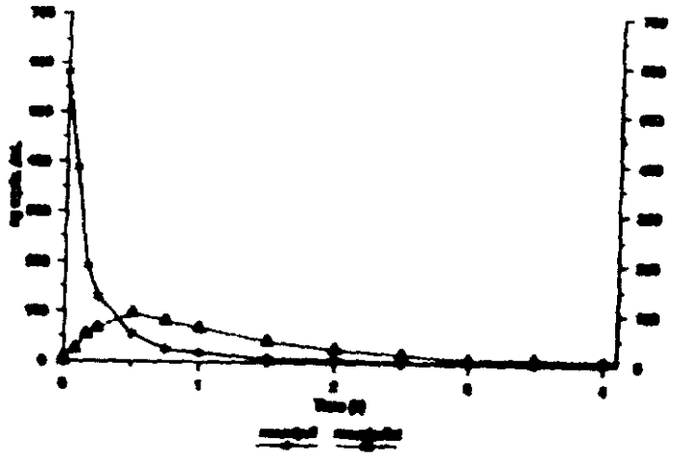
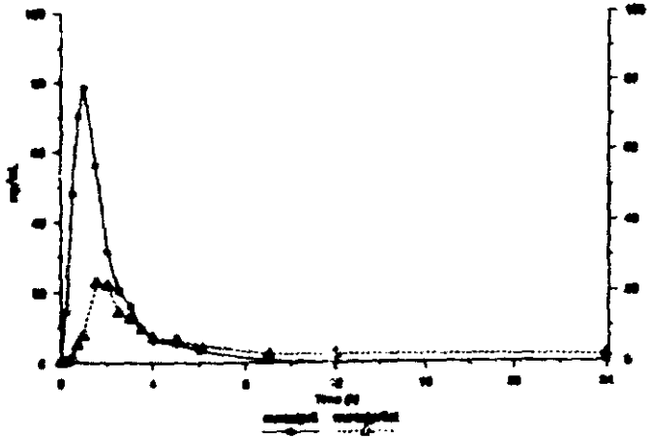


Figure 7

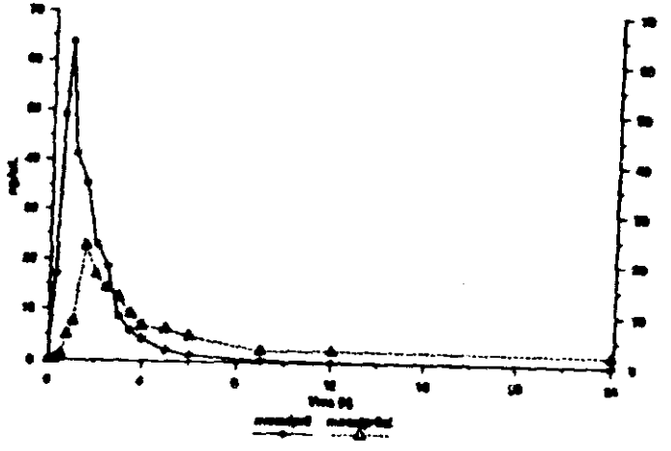
Plasma concentrations of moexipril and moexiprilat following the first of six daily oral administrations of moexipril and (^{14}C)-moexipril* to male volunteers at a nominal dose level of 15 mg/subject



* (^{14}C)-moexipril administered on days 1 and 6

Figure 8

Mean plasma concentrations of moexipril and moexiprilat following the last of six daily oral administrations of moexipril and (^{14}C)-moexipril* to male volunteers at a nominal dose level of 15 mg/subject



* (^{14}C)-moexipril administered on days 1 and 6

Effect of Food on Bioavailability of Moexipril and Moexiprilat

Study No: PHAKI 796 Volume: 1.99 to 1.101 Pages: 1 of 1.99 to end of 1.101

Investigator and Site:

Objective: To investigate the pharmacokinetics and bioavailability of a 15 mg moexipril hydrochloride coated tablet under fasting conditions as well as after food intake.

Formulation: Moexipril 15 mg coated tablet, Batch #920512.

Study Design: This was an open, randomized two-way crossover design with 24 healthy male subjects.
Washout period: One week.
Treatment A: One coated tablet under fasting conditions (fast for 10 hr before and 4 hr after administration).
Treatment B: One coated tablet 30 min after standardized breakfast (table 1).

Specimens: Blood, at predose and at 5, 10, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hr after administration.

Assay (moexipril and moexiprilat): GC-MS
Plasma:
Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 300 ng/ml.
Precision: Interday for moexipril ranged from 2.49% at 0.5 ng/ml to 1.04% at 300 ng/ml. Intraday for moexipril ranged from 2.83% at 0.5 ng/ml to 2.45% at 50 ng/ml. Interday for moexiprilat ranged from 3.9% at 0.5 ng/ml to 2.31% at 300 ng/ml. Intraday for moexiprilat ranged from 1.99% at 0.5 ng/ml to 2.48% at 50 ng/ml.
Accuracy: Interday for moexipril ranged from 1.88% at 0.5 ng/ml to 0.44% at 300 ng/ml. Intraday for moexipril ranged from 4% at 0.5 ng/ml to 0.1% at 50 ng/ml. Interday for moexiprilat ranged from 10.41% at 0.5 ng/ml to 1.72% at 300 ng/ml. Intraday for moexiprilat ranged from 4% at 0.5 ng/ml to 0.4% at 50 ng/ml.

Data Analysis: Cmax, Tmax, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, and $t_{1/2}$ were calculated by model independent method. The treatments were compared statistically only for $AUC_{(0-24)}$, Cmax and Tmax.

Note Estimates of terminal rate constant (k) calculated by log-linear regression (based on 2 hr and above concentration) may be are affected by residual ongoing absorption for moexipril.
There was a carry-over effect from period 1 to period 2 for moexiprilat.
Estimation for terminal rate constant (k) for moexiprilat was not possible since terminal half life could be as large as 5 days and plasma concentration data available was only up to 24 hrs.

Results: The mean (± SD) values for pharmacokinetic parameters are shown below.

Parameter	Treatment: 15-[illegible] dose	
	Fasting	Postprandial
Moexipril		
$AUC_{0-\infty}$ (ng·hr/mL)	188 ± 75	83 ± 43
C_{max} (ng/mL)	101 ± 45	42 ± 23
T_{max} (hr)	1.1 ± 0.4	1.4 ± 0.7
k_e (hr^{-1})	0.58 ± 0.14	0.62 ± 0.14
$t_{1/2}$ (hr)	1.3 ± 0.4	1.2 ± 0.3
Moexiprilat		
AUC_{0-24} (ng·hr/mL)	81 ± 24	38 ± 12
C_{max} (ng/mL)	19.9 ± 9.0	4.0 ± 2.2
T_{max} (hr)	1.7 ± 0.4	2.3 ± 0.9
k_e (hr^{-1})	0.039 ± 0.014	0.022 ± 0.010
$t_{1/2}$ (hr)	20.9 ± 8.6	37.4 ± 18.0

The following table shows the ratios of geometric means and corresponding 90% CI. The mean plasma concentration time profile for moexipril and moexiprilat is shown in fig 1 and 2.

	Parameters	Ratio of Geometric means (fed/fasted)	90% CI
Moexipril	$AUC_{(0-24)}$	43%	35-51
	$AUC_{(0-\infty)}$	42%	35-49
	Cmax	40%	33-49
Moexiprilat	$AUC_{(0-24)}$	46%	41-52
	Cmax	21%	16-26

Comments: For clinical use, it should be recommended that this dosage form should only be taken under fasting conditions.

Conclusion: The intake of food before drug administration reduced the bioavailability of moexipril. The bioavailability was only about 40% of that achieved during fasting condition.

Table 4: Standard Breakfast

Food	Quantity (g)	kcal	Protein (g)	Carbohydrate (g)	fat (g)
Roll	100	258	8	53	1.5
Bread	100	225	7	46	1.4
Butter	25	189	0.2	0.2	21
Bacon	50	167	8.5	0	17.5
Egg	60	96	7.7	0.4	7.0
Whole Milk	240	154	8	11.5	8.4
Σ	575	1089	39.4	111.1	56.8

Figure 1: Plasma Levels of Moexipril

mean over 24 subjects

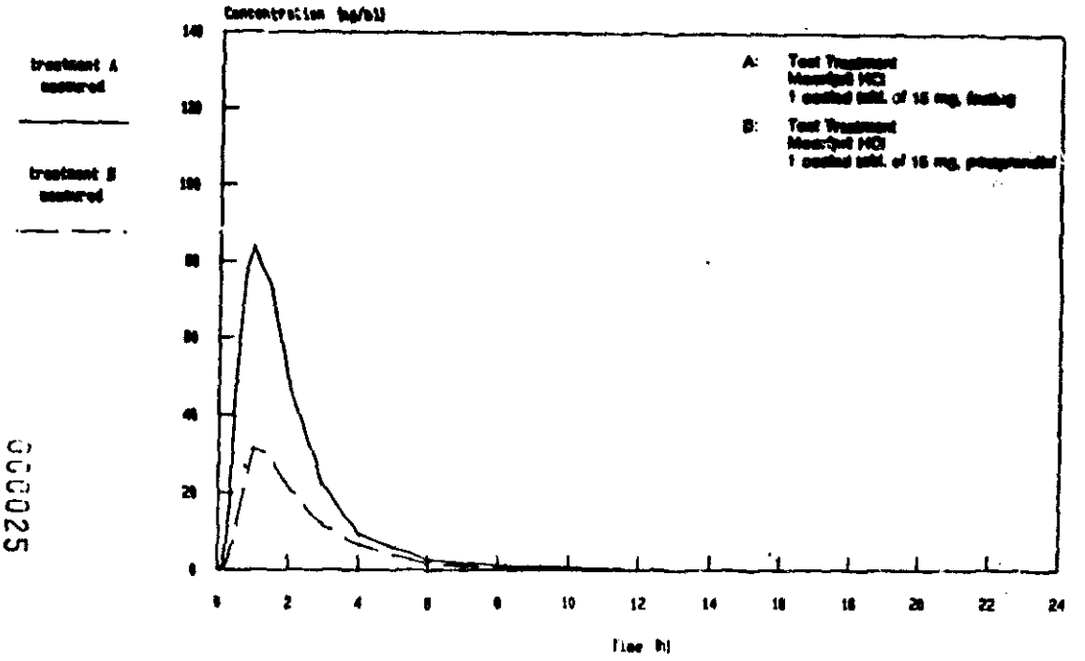


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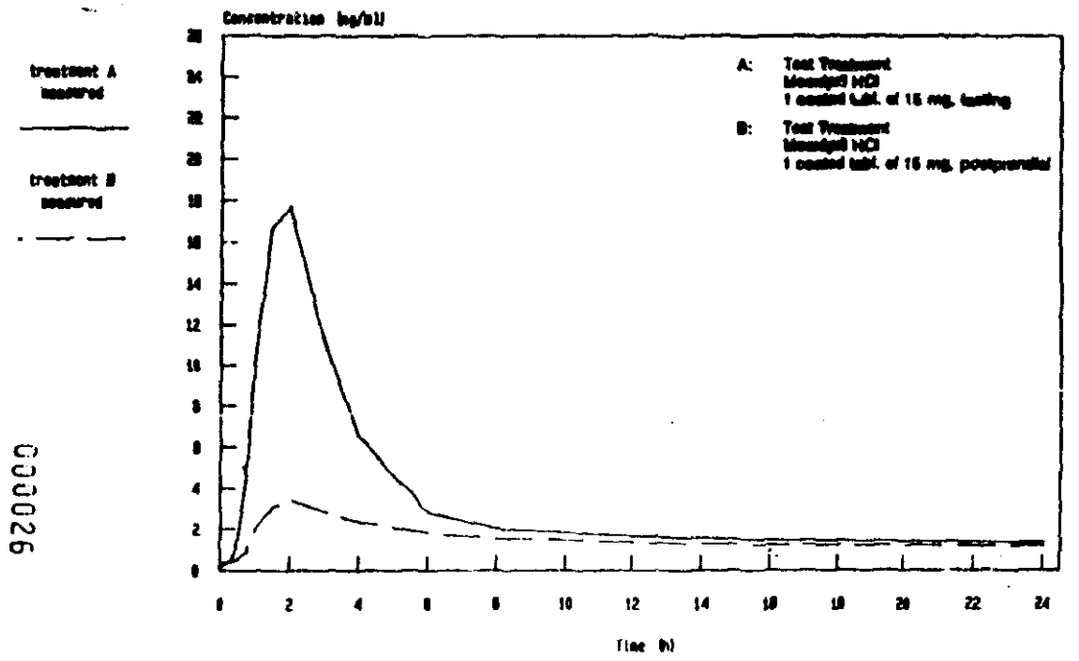
Figure 2: Plasma Levels of Moexiprilat

mean over 24 subjects



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Effect of Age on Moexipril and Moexiprilat Pharmacokinetics

Study No. GHBA-637 Volume: 1.73 to 1.75 Pages: 1-end
Investigator and site:

Objective To evaluate the effects of age on the pharmacokinetics of single and multiple doses of moexipril when given to healthy elderly male subjects (65 to 80 years) and younger male subjects (18 to 45 years).

Formulations Moexipril 15 mg capsule, batch # 912118.

Study Design The study was carried out in 24 healthy volunteers.
12 elderly subjects = 65-80 years
12 younger subjects ≤ 45 years
This was an open-label study and moexipril was administered once daily (15 mg/day) over a period of 5 days. All doses were administered with 150 ml water and same quantity of water was administered 2, 4, 6, and 8 hr after dosing on day 1 and day 5. Subjects fasted for 10 hr prior and 2 hr post dosing.

Specimens Blood (10 ml)
On day 1 and day 5 prior to administration, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hrs after administration. 10 ml blood was also drawn prior to administration on day 3 and day 4 and 48 hr after the last administration.
Urine was collected -1 to prior to administration (-1 to 0) and 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 hr after administration of moexipril on day 1 to day 5.

Assay Plasma samples were analyzed for moexipril and moexiprilat using a GC-MS method.
Linearity: Satisfactory. Standard curve from 0.5 to 300 ng/ml.
Sensitivity: Satisfactory. LQL = 0.5 ng/ml.
Precision: Interday for moexipril was 5.08% at 0.5 ng/ml and 0.84% at 300 ng/ml and for moexiprilat 5.46% at 0.5 ng/ml and 2.24% at 300 ng/ml. Intraday for moexipril was 2.83% at 0.5 ng/ml and 2.45% at 50 ng/ml and for moexiprilat 1.99% at 0.5 ng/ml and 2.47% at 50 ng/ml.
Accuracy: Interday for moexipril was 0.06% at 0.5 ng/ml and 0.39% at 300 ng/ml and for moexiprilat 8.82% at 0.5 ng/ml and 1.64 at 300 ng/ml. Intraday for moexipril was 3.84% at 0.5 ng/ml and 0.2% at 50 ng/ml and for moexiprilat 3.84 at 0.5 ng/ml and 0.4% at 50 ng/ml.

Urine samples were analyzed for moexipril and moexiprilat using a GC-MS method.
Linearity: Satisfactory. Standard curve from 5 to 2000 ng/ml.
Sensitivity: Satisfactory. LQL = 5.0 ng/ml.
Precision: Interday for moexipril was 8.80% at 5 ng/ml and 0.88% at 2000 ng/ml and for moexiprilat 6.22% at 10 ng/ml and 5.15% at 2000 ng/ml. Intraday for moexipril was 5.57% at 50 ng/ml and 2.99% at 1000 ng/ml.
Accuracy: Interday for moexipril was 1.2% at 5.0 ng/ml and 0.71% at 2000 ng/ml and for

moexiprilat 1.13% at 10 ng/ml and 1.04% at 2000 ng/ml. Intraday for moexipril was 9.17 % at 50 ng/ml and 2.4% at 1000 ng/ml and for moexiprilat 0.4% at 50 ng/ml and 4.2% at 1000 ng/ml.

Data Analysis AUC(0-t) (calculated up to the final value of estimation), Cmax, Tmax, total urinary excretion (Amax), total urinary excretion (TUE), clearance (Cl) were also calculated.

Results

Safety: No subjects were prematurely discontinued from the study.

Pharmacokinetics:

	Parameter Mean ± SD	Elderly Sub.	Younger Sub.
Pharmacokinetics of moexipril - Day 1	Cmax (ng/ml)	139.6 ± 48.5	119.4 ± 63.8
	Tmax (hr)	1.1 ± 0.3	0.9 ± 0.3
	$AUC_{(0-t)}$ (ng.h/ml)	294.2 ± 151.0	237.8 ± 156.9
	TUE (mcg)	142.9 ± 47.9	158.7 ± 74.8
Pharmacokinetics of moexipril - Day 5	Cmax (ng/ml)	124.0 ± 66.5	94.3 ± 42.2
	Tmax (hr)	1.3 ± 0.5	0.9 ± 0.3
	$AUC_{(0-t)}$ (ng.h/ml)	261.4 ± 172.7	191.9 ± 119.3
	TUE (mcg)	119.3 ± 56.7	166.2 ± 70.9
Pharmacokinetics of moexiprilat - Day 1	Cmax (ng/ml)	24.3 ± 7.8	17.2 ± 15.5
	Tmax (hr)	1.9 ± 0.2	1.6 ± 0.4
	$AUC_{(0-t)}$ (ng.h/ml)	102.3 ± 28.0	74.8 ± 43.9
	TUE (mcg)	338.8 ± 172.3	326.2 ± 267.6
Pharmacokinetics of moexiprilat - Day 5	Cmax (ng/ml)	30.6 ± 11.6	23.7 ± 11.4
	Tmax (hr)	1.9 ± 0.4	1.5 ± 0.3
	$AUC_{(0-t)}$ (ng.h/ml)	134.7 ± 23.2	100.9 ± 30.2
	TUE (mcg)	472.8 ± 143.9	614.0 ± 346.1
Oral clearance Cl/F	moexipril (ml/min)	1311 ± 721	1829 ± 1113
Oral clearance Cl/F	moexiprilat (ml/min)	1910 ± 343	2697 ± 844

Results of ANOVA are summarized below.

parameter		Young & Old	p
C_{max}	moexipril	day 1	0.394
auc(0-t)	moexipril	day 1	0.368
C_{max}	moexipril	day 5	0.205
auc(0-t)	moexipril	day 5	0.258
C_{max}	moexiprilat	day 1	0.166
auc(0-t)	moexiprilat	day 1	0.081
C_{max}	moexiprilat	day 5	0.158
auc(0-t)	moexiprilat	day 5	0.006
amount	moexipril	day 1	0.544
amonut	moexipril	day 5	0.087
amount	moexiprilat	day 1	0.892
amount	moexiprilat	day 5	0.205

The mean plasma concentration data for moexipril and moexiprilat are summarized in Fig 1. Note: Pre moexipril administration creatinine clearance (CrCl) in elderly and younger subjects were 70.78 ml/min and 115.37 ml/min respectively.

Comments: The ANOVA carried out on Cmin values of 3 rd, 4 th and 5 th dose show that steady state was achieved in elderly subjects earlier than in young subjects. However individual Cmin values showed high variation over day 3 to 5 (Table 1 and 2). Moexipril/Moexiprilat ratio decreases considerably from day 1 to day 5 in young and elderly subjects (table 3).

Conclusions

Moexipril is rapidly absorbed and then converted to moexiprilat. It was seen that greater percentage of the prodrug was activated after repeated dosing. Mean Cmax and $AUC_{(0\text{-}24)}$ for both moexipril and moexiprilat were approximately one third greater in the elderly group than they were in the younger group on both day 1 and day 5. The difference was significant only for $AUC_{(0\text{-}24)}$ on day 5 with respect to moexiprilat. Moexiprilat showed moderate accumulation (Accumulation ratio of about 1.3) on multiple QD dosing.

Fig 1.

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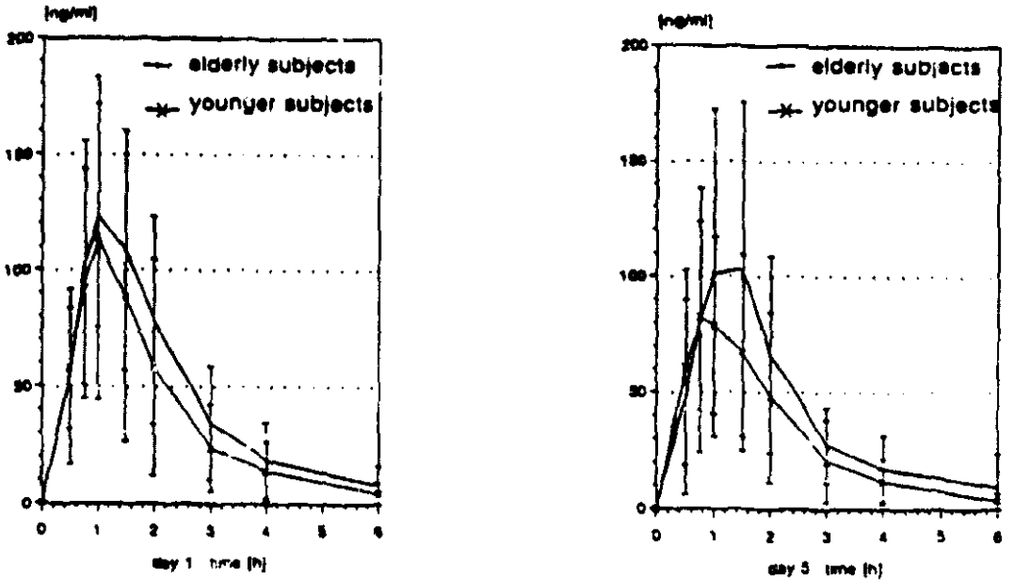
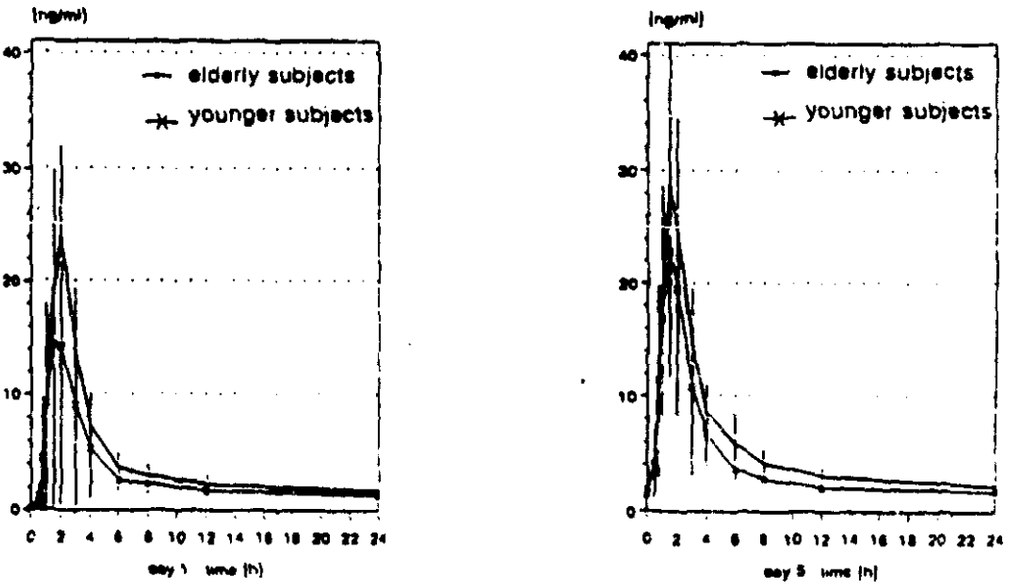
Moexipril plasma concentrations (mean+/- SD)



BIOMAT165/93/21

Moexiprilat plasma concentrations (mean+/- SD)



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BIOMAT165/93/22

	Study GHBA-637/Steady State Determination				Cmin		
Younger/Macrolar							
Time →	24	48	72	96	120	hr	
	1.3	1.25	1.27	1.26	1.34		
	1.79	1.96	1.83	2.22	2.35		
	1.43	1.8	1.69	2	1.96		
	0.73	0.72	0.79	0.79	0.88		
	1.34	1.33	1.28	1.15	1.15		
	1.59	1.56	1.5	1.27	2.28		
	1.16	1.11	1.47	1.75	1.58		
	1.25	1.34	1.52	1.17	1.31		
	1.2	1.27	1.32	1.3	2.21		
	1.17	1.42	1.31	1.37	1.96		
	1.72	1.62	1.61	1.58	1.6		
	1.39	1.54	1.59	1.66	2.41		
	Anova: Two-Factor Without Replication						
	Summary	*Count*	*Sum*	*Average*	*Variance*		
	Row 1	3	3.87	1.29	0.0019		
	Row 2	3	6.4	2.133333	0.073233		
	Row 3	3	5.65	1.883333	0.028433		
	Row 4	3	2.46	0.82	0.0027		
	Row 5	3	3.58	1.193333	0.005633		
	Row 6	3	5.05	1.683333	0.280233		
	Row 7	3	4.8	1.6	0.0199		
	Row 8	3	4	1.333333	0.031033		
	Row 9	3	4.83	1.61	0.2701		
	Row 10	3	4.64	1.546667	0.129033		
	Row 11	3	4.79	1.596667	0.000233		
	Row 12	3	5.66	1.886667	0.206633		
72	Column 1	12	17.18	1.431667	0.071306		
96	Column 2	12	17.52	1.46	0.158782		
120	Column 3	12	21.03	1.7525	0.264202		
	ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*	
	Rows	4.096231	11	0.372385	6.109395	0.000162	2.258517
	Columns	0.757172	2	0.378586	6.211138	0.007268	3.443361
	Error	1.340961	22	0.060953			
	Total	6.194364	35				

Study GHBA-637/Steady State Determination				Cmin		
Elderly /Moexiprilat						
24	48	72	96	120	hr	
1.46	1.48	1.5	1.17	1.42		
1.36	1.35	1.47	2.35	2.19		
1.9	2.42	2.29	1.86	2.1		
2.18	2.69	2.28	2.32	2.21		
2.65	2.56	1.94	2.2	2.89		
1.64	1.6	2.49	3.15	2.58		
1.72	1.56	1.94	2.01	1.92		
2.24	2.02	1.86	1.61	2.08		
1.19	1.38	1.73	1.76	3.33		
1.31	1.36	2.08	1.63	1.39		
1.56	1.57	2.45	2.44	3.11		
1.9	1.73	1.81	2.86	1.68		
Anova: Two-Factor Without Replication						
Summary	*Count*	*Sum*	*Average*	*Variance*		
Row 1	3	4.09	1.363333	0.029633		
Row 2	3	6.01	2.003333	0.219733		
Row 3	3	6.25	2.083333	0.046433		
Row 4	3	6.81	2.27	0.0031		
Row 5	3	7.03	2.343333	0.241033		
Row 6	3	8.22	2.74	0.1281		
Row 7	3	5.87	1.956667	0.002233		
Row 8	3	5.55	1.85	0.0553		
Row 9	3	6.82	2.273333	0.837633		
Row 10	3	5.1	1.7	0.1227		
Row 11	3	8	2.666667	0.147433		
Row 12	3	6.35	2.116667	0.418633		
Column 1	12	23.84	1.986667	0.116006	72	
Column 2	12	25.36	2.113333	0.311061	96	
Column 3	12	26.9	2.241667	0.394779	120	
ANOVA						
e of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Rows	4.926522	11	0.447866	2.395133	0.03908	2.258517
Columns	0.390156	2	0.195078	1.043253	0.369095	3.443361
Error	4.113778	22	0.18699			
Total	9.430456	35				

Moexipril/Moexiprilat Ratio for Day 1 and Day 5

Sub #	MX AUC(0–24)	MXM AUC(0–24)	MX	MXM	MX/MXM Day 1	MX/MXM Day 5
7	275.6	98.9	319.7	147.5	2.79	2.17
3	201.5	70.6	250.1	146.4	2.85	1.71
9	178.2	72	98.8	110.7	2.48	0.89
10	265.3	129.5	277.1	150.7	2.05	1.84
11	229.4	135.2	164.9	135.9	1.70	1.21
12	694.5	124	684.2	173	5.60	3.95
13	276.6	122.6	156.5	110.5	2.26	1.42
14	357.5	102.2	499.6	141.2	3.50	3.54
15	488.3	84.7	100.3	97	5.77	1.03
16	118	61.3	164.4	115.1	1.92	1.43
17	278.4	83.6	341.2	162.8	3.33	2.10
18	228.9	143	139.1	125.3	1.60	1.11
				AVG	2.99	1.87
				SD	1.33	0.93
1	173.5	48.7	82.5	61.1	3.56	1.35
2	145.5	76.8	59.7	85.9	1.89	0.69
3	74.8	39.5	142	85.3	1.89	1.66
4	243.4	39	437.5	94	6.24	4.65
5	470.8	196.3	349.3	163.9	2.40	2.13
6	296.9	81.7	143.5	104.9	3.63	1.37
19	308.1	89	197.1	124.2	3.46	1.59
20	49.4	34.5	81.6	58.8	1.43	1.39
21	112.4	67.5	123.2	121.9	1.67	1.01
22	344.8	103.1	276.3	121.2	3.34	2.28
23	548.9	66.4	309	75.9	8.27	4.07
24	118.9	54.9	134	113.8	2.17	1.18
				AVG	3.33	1.95
				SD	1.95	1.16

MX – Moexipril, MXM – Moexiprilat

Examination on Dose Linearity of Moexipril

Study No. PHAKI-795R Volume: 2.2 to 2.4 Pages: 1 of vol 2 to 451 of vol 4
Investigator and site:

Objectives: To examine the dose linearity of moexipril hydrochloride following oral administration at doses 3.75, 7.5, 15 and 30 mg.

Formulation: Solution of Moexipril hydrochloride (Batch # 20248-P105)

Study Design: This was open randomized 4 was cross-over study with wash-out phase of 1 week in between. Twenty-four healthy male volunteers, non-smokers were included into this study.

Specimens: Blood (8 ml), at 0 (prior to administration), 5, 10, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hr.

Assay: GC-MS
Linearity: Satisfactory. Standard curve from 0.5 to 300 ng/ml.
Sensitivity: Satisfactory. LQL = 0.5 ng/ml.
Precision: Intraday ranged from 6.5% at 0.5 ng/ml to 1.1% at 300 ng/ml, intraday ranged from 2.8% at 0.5 ng/ml to 2.4% at 50 ng/ml for moexipril. Interday ranged from 6.6% at 0.5 ng/ml to 1.9% at 300 ng/ml, intraday ranged from 1.9% at 0.5 ng/ml to 2.5% at 50 ng/ml for moexiprilat.

Data Analysis: AUC_{0-24}, $AUC_{0-\infty}$, Cmax and Tmax.

Results: The following table summarizes the pharmacokinetic parameters for moexipril and moexiprilat at 4 different doses.

Pharmacokinetic Parameters/moexipril	Treatment A mean	sdev	Treatment B mean	sdev	Treatment C mean	sdev	Treatment D mean	sdev
$AUC_{0-\infty}$ (hxng/ml)	88.15	38.94 (n=6)	150.26	55.69 (n=6)	243.29	111.00 (n=13)	346.82	178.00 (n=21)
AUC(0-24) (hxng/ml)	54.26	30.17	91.58	50.99	205.38	102.40 (n=23)	326.18	176.72
C_{max} (m) (ng/ml)	31.88	15.26	56.66	27.59	114.29	53.57	184.04	79.80
T_{max} (m) (h)	0.88	0.36	0.70	0.19	0.86	0.21	0.78	0.31
$t_{½}$ (h)	2.27	2.12 (n=6)	1.60	0.45 (n=6)	1.45	0.45 (n=13)	1.58	0.53 (n=21)
k (1/h)	0.444	0.199 (n=6)	0.460	0.122 (n=6)	0.512	0.132 (n=13)	0.479	0.134 (n=21)

Pharmacokinetic Parameters/moexiprilat	Treatment A mean	sdev	Treatment B mean	sdev	Treatment C mean	sdev	Treatment D mean	sdev
$AUC_{0-\infty}$ (hxng/ml)	-	-	-	-	98.29	25.51 (n=8)	167.60	50.32 (n=18)
AUC(0-24) (hxng/ml)	30.18	12.39	43.59	13.73 (n=23)	77.78	23.28 (n=23)	138.00	52.99
C_{max} (m) (ng/ml)	2.98	1.32	6.36	3.57	20.19	11.05	42.15	20.99
T_{max} (m) (h)	1.66	0.85	1.50	0.42	1.71	0.53	1.50	0.29
$t_{½}$ (h)	30.06	28.83	33.46	43.45 (n=22)	12.71	7.34	8.95	3.17
k (1/h)	0.032	0.016	0.036	0.018 (n=22)	0.064	0.021	0.086	0.026

Dose Corrected Geometric Mean	3.75 mg	7.5 mg	15 mg	30 mg
Moexipril $AUC_{(0-24)}$ (ng.h/ml)	190.24	161.37	176.79	140.9
Moexipril Cmax (ng/ml)	114.66	101.69	102.94	83.13
Moexiprilat $AUC_{(0-24)}$ (ng.h/ml)	109.54	83.24	73.49	64.07
Moexiprilat Cmax (ng/ml)	10.83	11.14	17.30	18.26

Fig 1 and 2 shows the mean plasma concentration time data for moexipril and for moexiprilat respectively.

Discussion: The dose normalized values of $AUC_{(0-24)}$ and Cmax for moexiprilat do not indicate dose proportionality.

Periods 2,3 and 4 show period effect due to moexiprilat lingering in body for long time. This is due to tight binding of moexiprilat with ACE. It was also observed that $t_{1/2}$ of moexiprilat has a tendency to decrease with increase in dose. This can be explained by considering relative free fraction of moexiprilat available in body. For low doses fraction bound to ACE relative to total drug in body could be significant and this translates in extending the plasma half life at low doses. For ACE-inhibitors using urine data may be more helpful to calculate effective $t_{1/2}$ than using plasma data.

Since periods 2,3 and 4 show considerable carry-over effect, interpretation of results was done subjectively. **The influence of carry-over effect is more on lower doses than higher doses.** Figures 3 and 4 show dose adjusted $AUC_{(0-24)}$ and Cmax profile of moexiprilat versus moexipril dose, respectively. The dose of 15 mg moexipril was used as standard dose. The $AUC_{(0-24)}$ for dose 3.75 is more confounded by carry-over effect than Cmax. Fig 5 shows $AUC_{(0-24)}$ of moexiprilat versus moexipril dose for first period only (no carry-over effect). It can be said from these plots that moexiprilat $AUC_{(0-24)}$ increases in a linear fashion from moexipril doses 3.75 to 30 mg. Moexiprilat Cmax however, does show a trend towards nonlinearity. The statistical analysis carried out by the firm is of secondary importance, because of carry-over effect and high variability. Fig 6 shows a cross study dose proportionality comparison for Cmax (data was included for 1 st period only).

Conclusion: Moexipril and moexiprilat do not exhibits dose proportionality over the dose range (3.75 to 30 mg). There is a tendency of disproportionate increase in Cmax for moexiprilat at higher doses of moexipril.

Figure 1

Plasma Levels of Moexipril

mean over 24 subjects

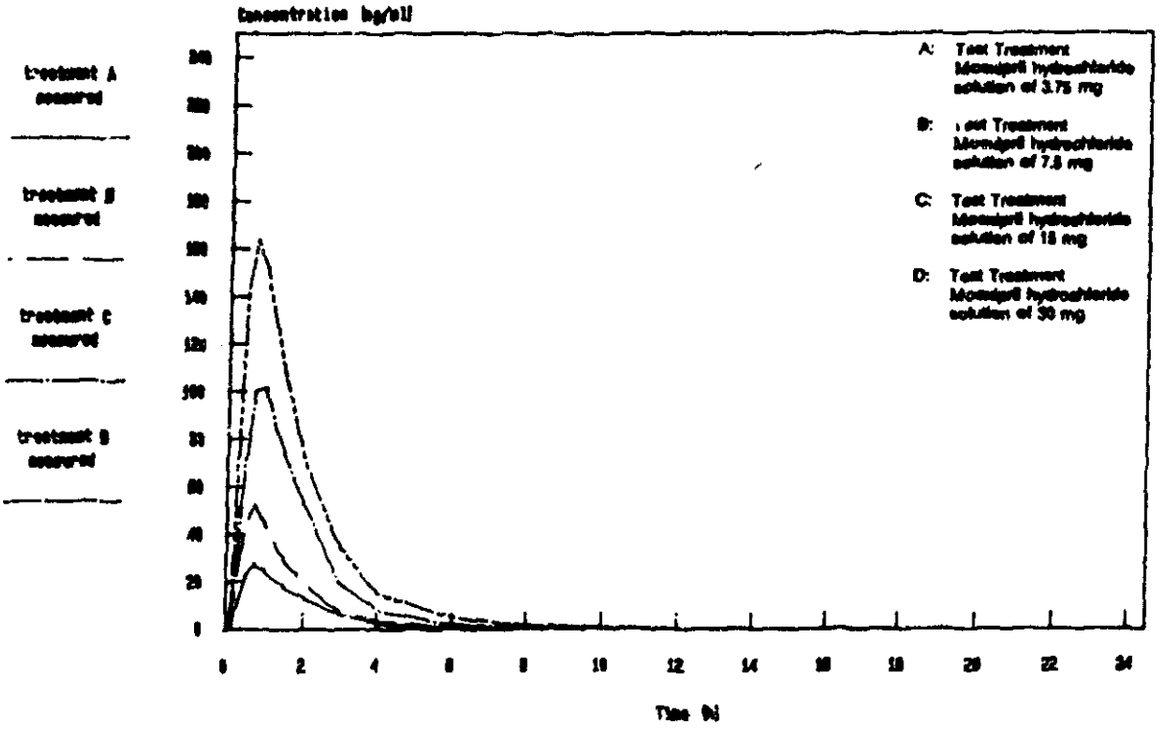


Figure 2

Plasma Levels of Moexiprilat

mean over 24 subjects

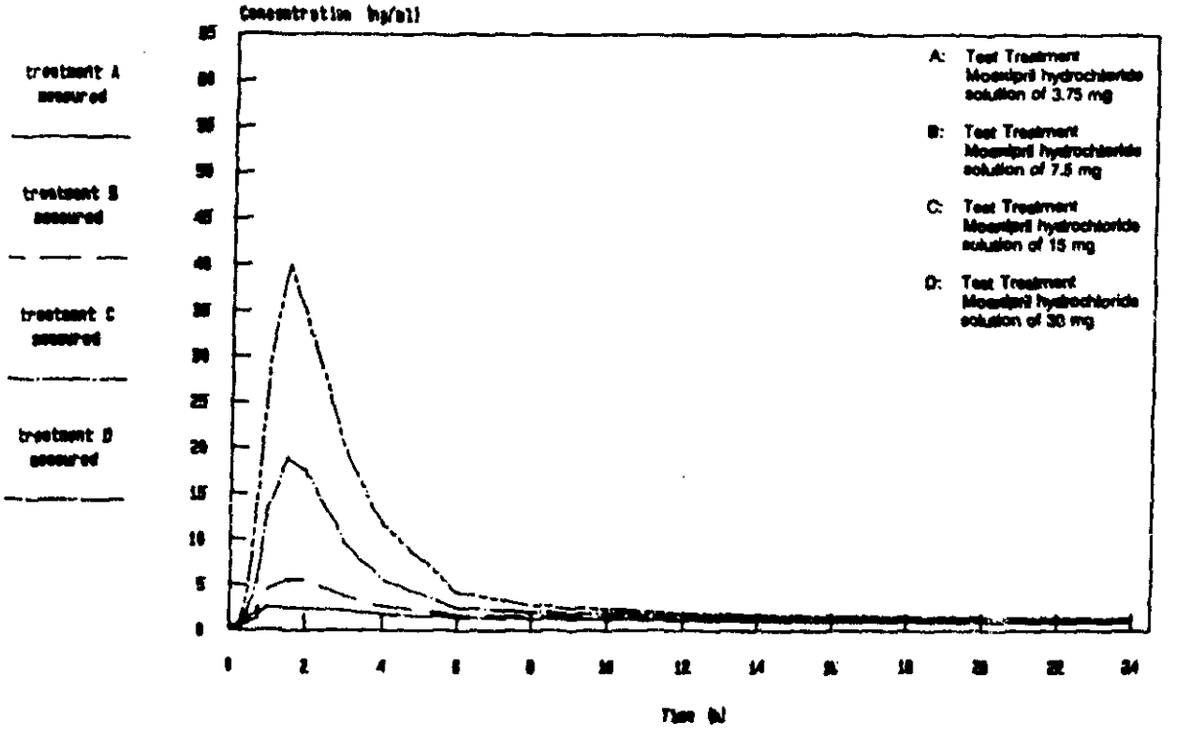


Fig3. **Dose-Proportionality/Dose Normalized Value**

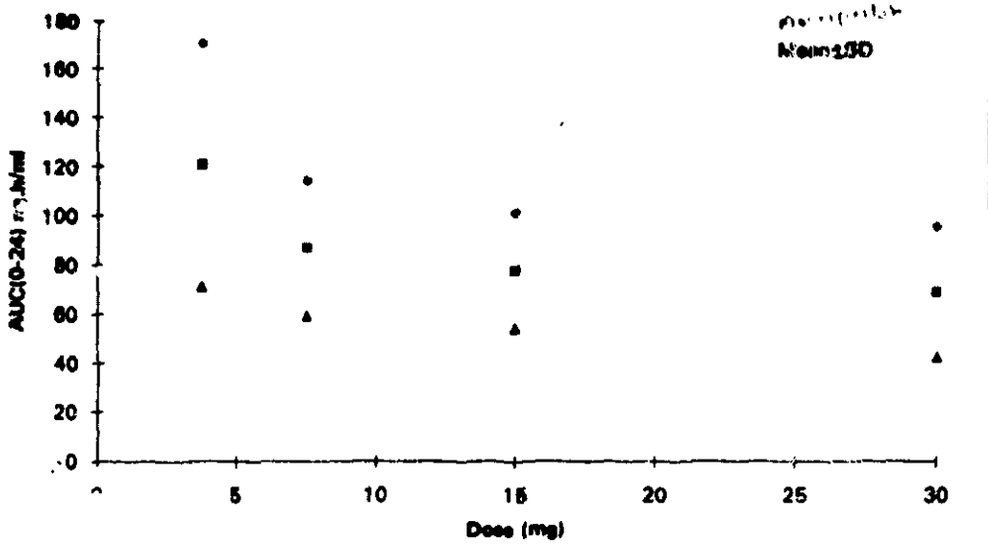


Fig4. **Dose-Proportionality/Dose normalized value**

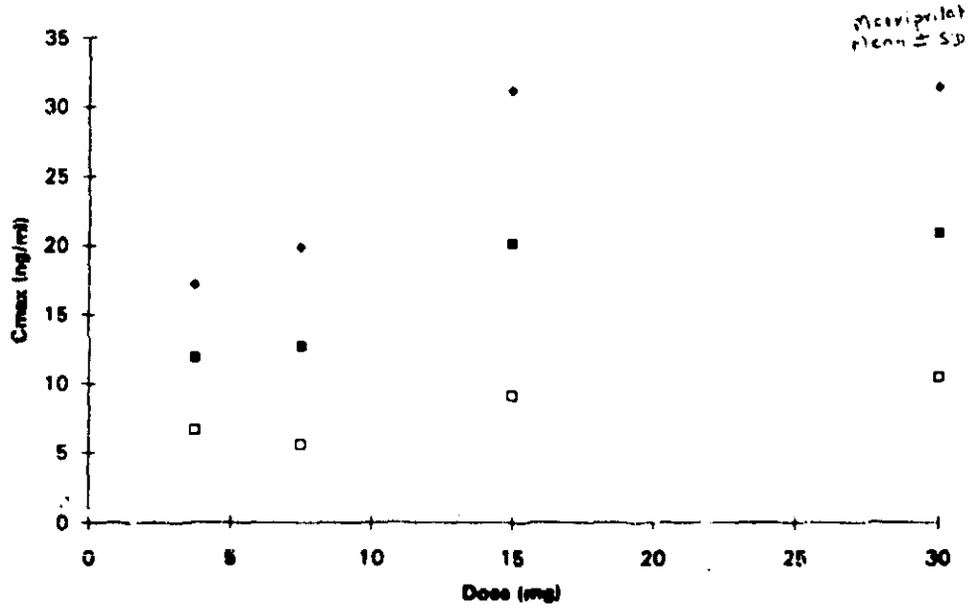


Fig 5 Cross-Study 1 st Period Dose-Proportionality

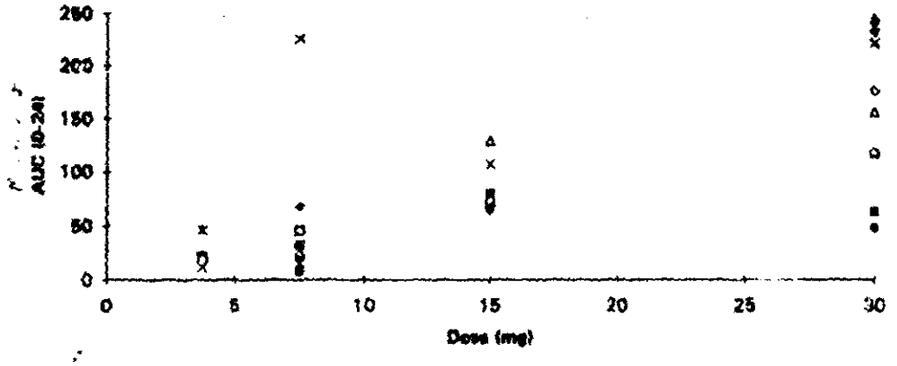
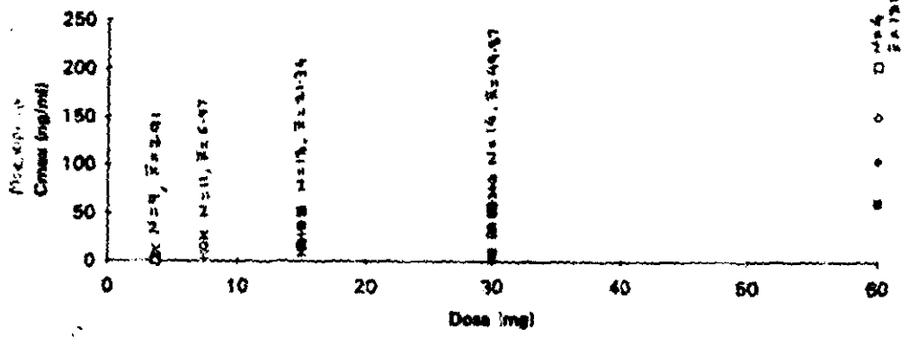


Fig 6 Dose Proportionality/Data Pooled from Studies: GHBA 621, PHAK 795, 795R



Effect of Renal Insufficiency on Single Dose Pharmacokinetics

Stud No: GHBA-629 Volume: 1.76 to 79 Pages: 1.76/1 to 1.79/374

Investigator and Site:
1.

2.

Objectives: To investigate the effect of different level of renal function on the safety, tolerability and pharmacokinetics of moexipril and its active metabolite moexiprilat.

Formulation: Site 1: 15 mg capsule (Batch # 902512)
Site 2: 15 mg capsule (Batch # 910534)

Study Design: Open label PK study in normal and patients with different levels of renal impairment.

Dose administered = 15 mg moexipril capsule.
The study had 7 day pre-study screening period and 5 day post evaluation period.
The 21 subjects were divided into four groups according to creatinine clearance rates (CrCl):
1. Normal renal function: CrCl > 90 ml/min. (N = 4)
2. Mild renal insufficiency: CrCl 90 -60 ml/min. (N = 4)
3. Moderate renal insufficiency: CrCl 65-41 ml/min. (N = 5)
4. Severe renal insufficiency: CrCl 40-10 ml/min. (N = 8)

Specimen: Blood, on day of administration, 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8,10, 12, 16, 24, 48, 72 and 96 hr following drug administration.
Urine, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hr after administration of moexipril.

Assay: GC-MS.
Plasma:
Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 100 ng/ml.
Precision: Interday for moexipril ranged from 8.6% at 0.5 ng/ml to 6.4% at 100 ng/ml. Intraday for moexipril ranged from 14.1% at 0.5 ng/ml to 4.1% at 100 ng/ml. Interday for moexiprilat ranged from 11.5% at 0.5 ng/ml to 7.5% at 100 ng/ml. Intraday for moexiprilat ranged from 11.6% at 0.5 ng/ml to 3.3% at 100 ng/ml.
Accuracy: Interday for moexipril ranged from 2% at 0.5 ng/ml to 4.6% at 100 ng/ml. Intraday for moexipril ranged from 12% at 0.5 ng/ml to 4.2% at 100 ng/ml. Interday for moexiprilat ranged from 6% at 0.5 ng/ml to 4.4% at 100 ng/ml. Intraday for moexiprilat ranged from 12% at 0.5 ng/ml to 1.77% at 100 ng/ml.

Urine:
Linearity: Satisfactory. Standard curve range: 2 to 500 ng/0.1 ml.
Precision: Interday for moexipril ranged from 17.4% at 2 ng/0.1 ml to 1.3% at 500 ng/0.1 ml. Intraday for moexipril ranged from 2% at 5 ng/0.1 ml to 1.7% at 500 ng/0.1 ml. Interday for moexiprilat ranged from 20.8% at 2 ng/0.1 ml to 0.4% at 500 ng/0.1 ml. Intraday for moexiprilat ranged from 3.9% at 5 ng/0.1 ml to 2.1% at 500 ng/0.1 ml.

Accuracy: Interday for moexipril ranged from 15% at 2 ng/ml to 3.2% at 500 ng/ml. Intraday for moexipril ranged from 2% at 5 ng/ml to 3.8% at 500 ng/ml. Interday for moexiprilat ranged from 20% at 2 ng/ml to 1.7% at 500 ng/ml. Intraday for moexiprilat ranged from 2% at 5 ng/ml to 3% at 500 ng/ml.

Data Analysis: Cmax, Tmax and $AUC_{(0-t)}$ (AUC up to the last concentration greater than zero). The total urinary excretion (TUE) and terminal elimination half life ($t_{1/2}$) were calculated from urinary data.

Results: The following table shows the calculated PK parameters for all the groups.

Parameter	Creatinine Clearance (mL/min)			
	> 90	66 - 90	41 - 65	10 - 40
Moexipril (Mean ± SD)				
C_{max} (ng/mL)	46 ± 16	42 ± 11	38 ± 21	40 ± 13
T_{max} (hr)	0.8 ± 0.2	1.0 ± 0.4	1.1 ± 0.3	1.1 ± 0.6
AUC_{0-t} (ng·hr/mL)	60 ± 26	60 ± 13	65 ± 26	72 ± 28
$t_{1/2}$ (hr)	1.1 ± 0.2	1.2 ± 0.1	1.9 ± 0.9	2.2 ± 0.7
TUE (μg)	203 ± 105	152 ± 37	116 ± [illegible]	98 ± 61
Moexiprilat (Mean ± SD)				
C_{max} (ng/mL)	17 ± 10	24 ± 10	18 ± [illegible]	26 ± 18
T_{max} (hr)	1.6 ± 0.3	1.8 ± 0.3	1.9 ± 0.2	2.8 ± 1.6
AUC_{0-t} (ng·hr/mL)	150 ± 57	148 ± 31	166 ± 38	268 ± 152
$t_{1/2}$ (hr)	1.5 ± 0.6	2.9 ± 1.2	5.0 ± 4.1	5.3 ± 3.6
TUE (μg)	53 ± 338	628 ± 122	479 ± 226	621 ± 374

The mean plasma concentration profile for moexipril and moexiprilat is depicted in fig 1 to 8.
The mean Cmax values of unchanged moexipril decreased slightly where as mean Tmax and AUC values increased slightly from group 1 to 4. AUC showed non-significant difference between the groups (ANOVA, p=0.868).

The Cmax, Tmax and AUC of moexiprilat increased from group 1 to 4 AUC showed non-significant difference between the groups (ANOVA, p=0.154).

The TUE values for moexipril decreased progressively from group 1 to group 4 in relation to the degree of renal function. The TUE values for moexiprilat were relatively constant for all four groups. The TUE values for moexipril and moexiprilat showed non-significant difference between the groups (ANOVA, p=0.810 and p=0.817 respectively). The elimination half life $t_{1/2}$ were significantly different across 4 groups for moexipril ($p < 0.05$) but not for moexiprilat (p=0.204).

Comment: There was no indication from the safety and tolerability data in this single dose study that the changes seen in the PK parameters are of clinical significance. This probably can be evaluated with a multiple dose study in such study population.

Conclusions: In subjects with a calculated creatinine clearance of greater than 40 ml/min, the degree of the change in plasma pharmacokinetic parameters was not clinically important. It appears that reduction of the initial dose of moexipril is required in patients with severe renal impairment (CrCl < 40 ml/min), however this needs to be substantiated in a multiple dose study in patient with renal dysfunction.

mean moexipril plasma concentrations - group I - BIOMAT 114/91

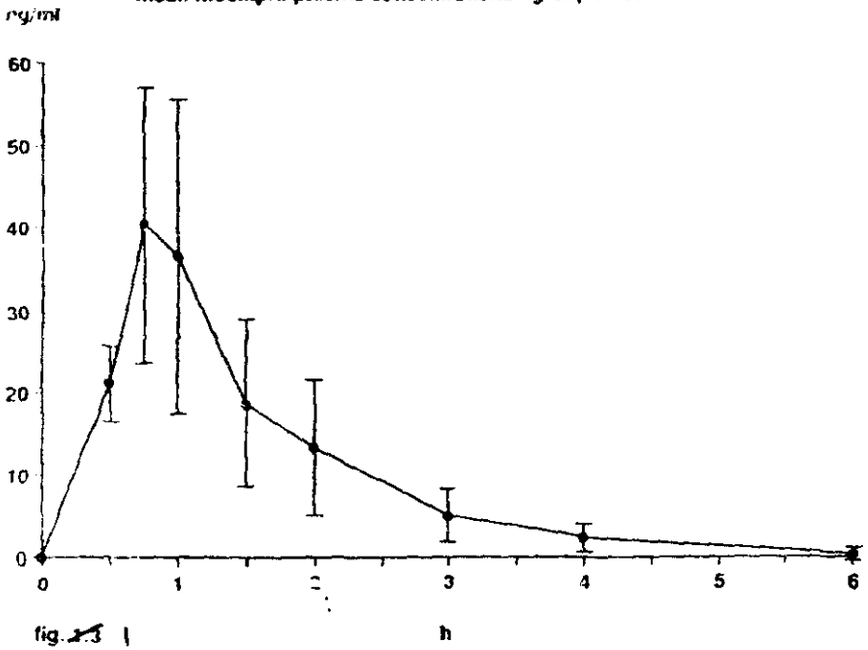


fig. 1

mean moexipril plasma concentrations - group II - BIOMAT 114/91

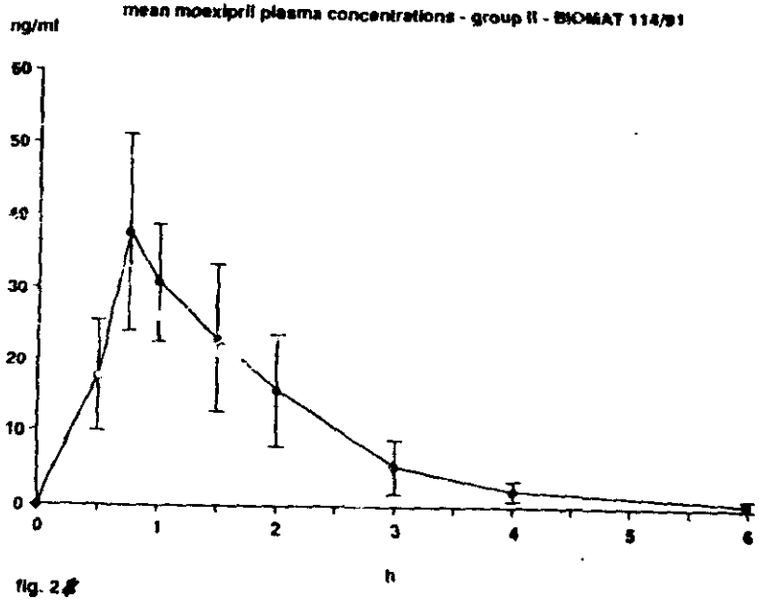


fig. 2

mean moexipril plasma concentrations - group III - BIOMAT 114/91

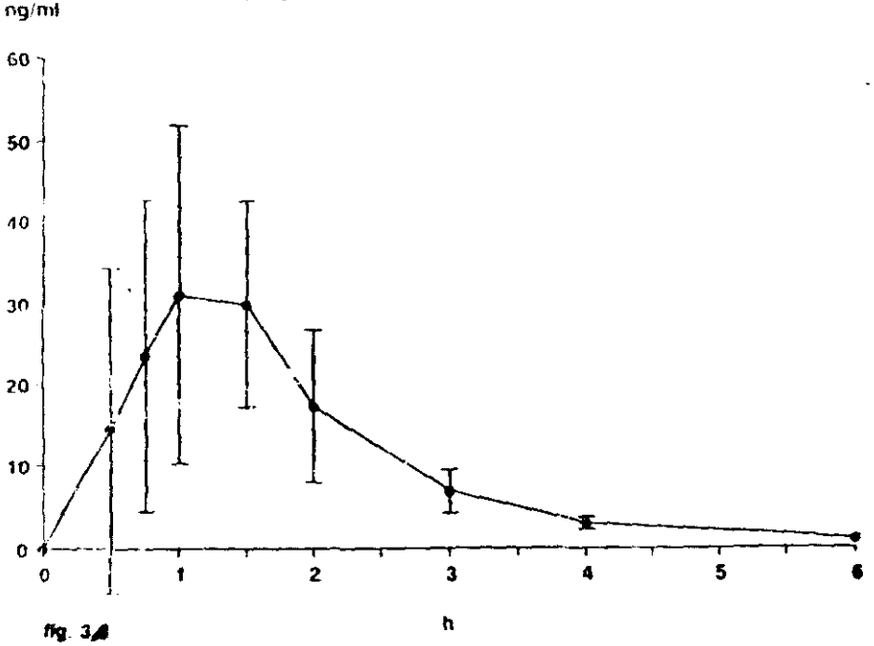


fig. 3

mean moexipril plasma concentrations - group IV - BIOMAT 114/91

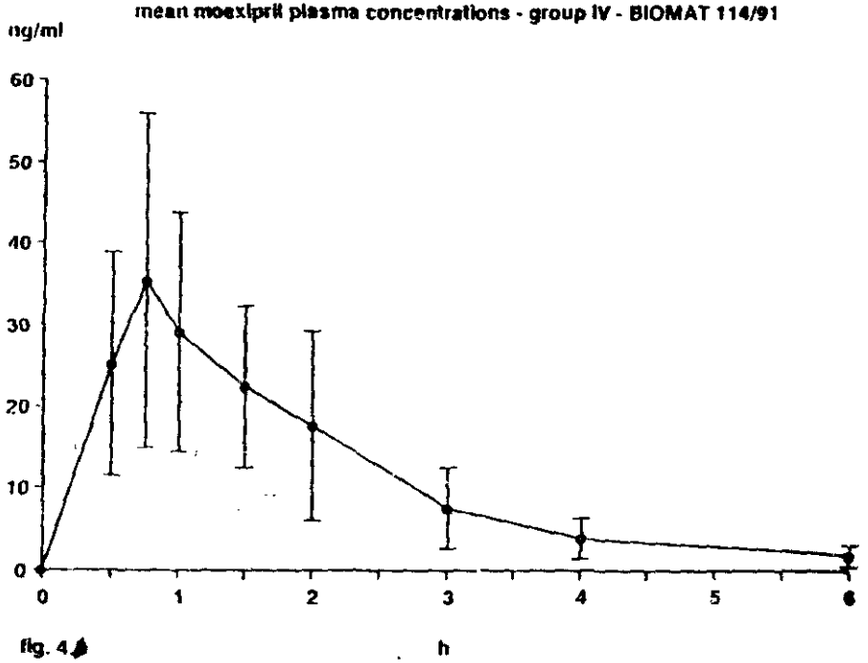


fig. 4

mean moexiprilat plasma concentrations - group I - BIOMAT 114/91

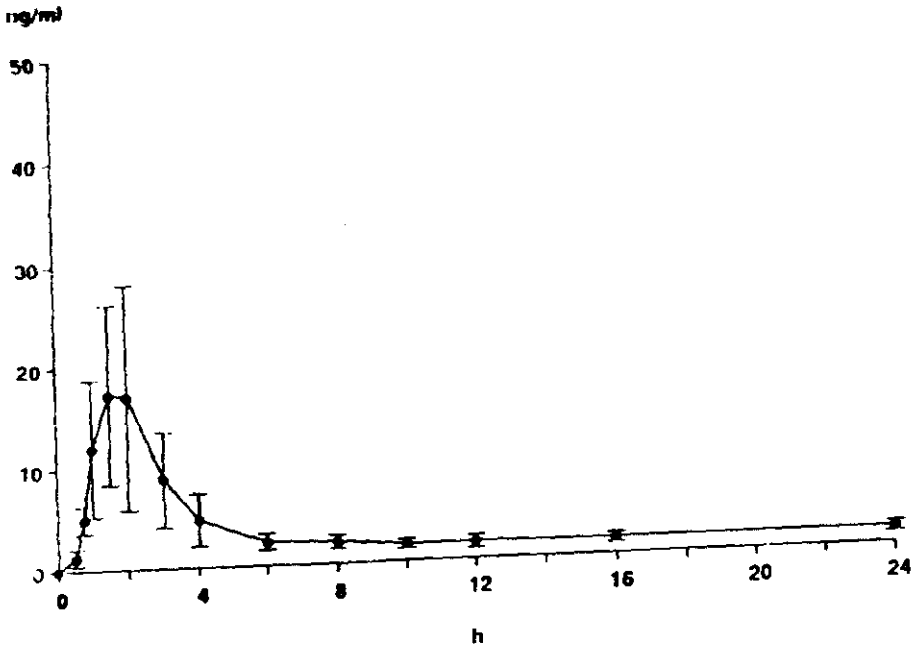


fig. 5

mean moexiprilat plasma concentrations - group II - BIOMAT 114/91

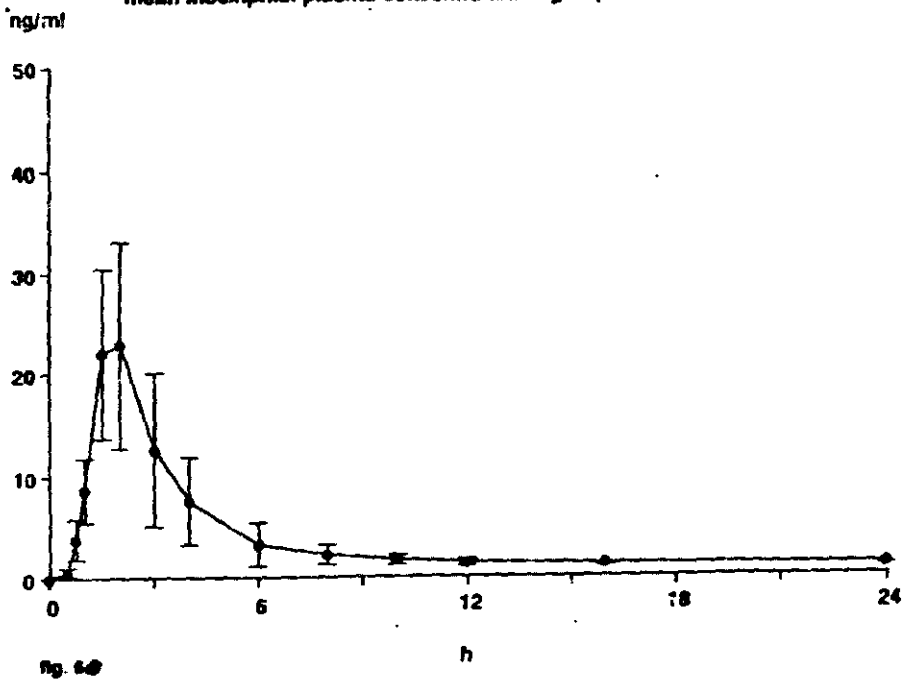


fig. 6

mean moexiprilat plasma concentrations - group III - BIOMAT 114/91

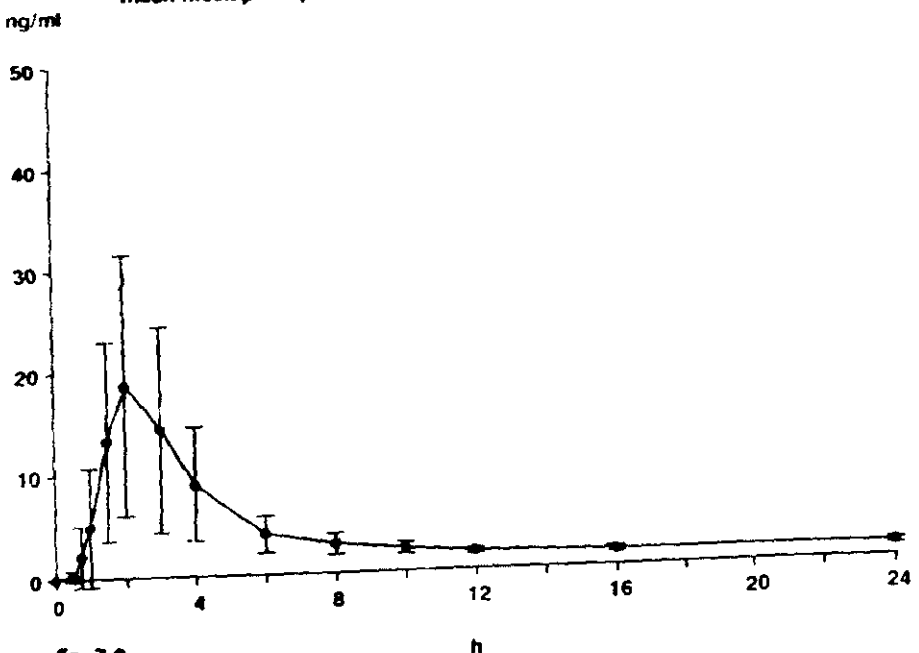


fig. 7

mean moexiprilat plasma concentrations - group IV - BIOMAT 114/91

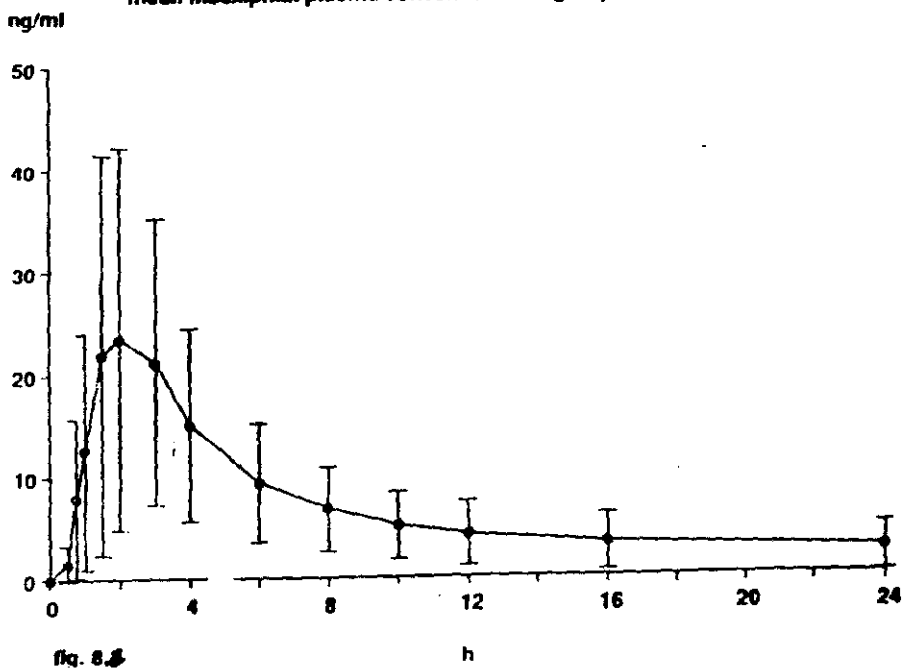


fig. 8

Effect of Hepatic Cirrhosis on Single Dose Pharmacokinetics

Study No: GHBA-636 Volume: 1.80 to 1.81 Pages: 1 of 1.80 to 481 of 1.81

Investigator and Site:

Objectives: To investigate the effect of cirrhosis on the safety, tolerability and pharmacokinetics of moexipril and its active metabolite moexiprilat.

Formulation: Moexipril capsule (15 mg).

Study Design: This was an open-label pharmacokinetic study in subjects with hepatic cirrhosis (N=12, 5 males and 7 female) (biopsy-confirmed hepatic alcoholic cirrhosis). The study consisted of a 14 day prestudy screening period and a 4 day post dosing evaluation period.

Specimen: Blood, prior to administration, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72 and 96 hr after administration of moexipril.

Urine, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hr after administration of moexipril.

Assay: GC-MS

Plasma:

Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 300 ng/ml.

Precision: Interday for moexipril ranged from 2.49% at 0.5 ng/ml to 1.04% at 300 ng/ml. Intraday for moexipril ranged from 2.83% at 0.5 ng/ml to 2.45% at 50 ng/ml. Interday for moexiprilat ranged from 3.9% at 0.5 ng/ml to 2.31% at 300 ng/ml. Intraday for moexiprilat ranged from 1.99% at 0.5 ng/ml to 2.47% at 50 ng/ml.

Accuracy: Interday for moexipril ranged from 1.88% at 0.5 ng/ml to 0.44% at 300 ng/ml. Intraday for moexipril ranged from 4% at 0.5 ng/ml to 0.1% at 50 ng/ml. Interday for moexiprilat ranged from 10.41% at 0.5 ng/ml to 1.72% at 300 ng/ml. Intraday for moexiprilat ranged from 4% at 0.5 ng/ml to 0.4% at 50 ng/ml.

Urine:

Linearity: Satisfactory. Standard curve range: 50 to 15000 ng/ml.

Precision: Interday for moexipril ranged from 6.64% at 50 ng/ml to 0.9% at 15000 ng/ml. Intraday for moexipril ranged from 5.05% at 50 ng/ml to 2.97% at 10000 ng/ml. Interday for moexiprilat ranged from 3.35% at 50 ng/ml to 1.54% at 15000 ng/ml. Intraday for moexiprilat ranged from 2.47% at 50 ng/ml to 6.19% at 10000 ng/ml.

Accuracy: Interday for moexipril ranged from 5.22% at 50 ng/ml to 0.3% at 15000 ng/ml. Intraday for moexipril ranged from 8.44% at 50 ng/ml to 3.34% at 10000 ng/ml. Interday for moexiprilat ranged from 0.69% at 50 ng/ml to 0.81% at 15000 ng/ml. Intraday for moexiprilat ranged from 0.4% at 50 ng/ml to 9.08% at 10000 ng/ml.

Data Analysis: Cmax, Tmax and $AUC_{(0-t)}$ (AUC up to the last concentration greater than zero). The total urinary excretion (TUE) and terminal elimination half life ($t_{1/2}$) were calculated from urinary data. The ANOVA was chosen to compare moexipril/moexiprilat pharmacokinetics in

hepatic cirrhosis with historical normal volunteer data from studies GHBA-625R, GHBA-627 and GHBA-633 by SAS procedure.

Results: The pharmacokinetic parameters for moexipril and moexiprilat are shown in the following table.

Parameter	Mean ± SD	Range
Moexipril		
C_{max} (ng/mL)	154 ± 60	
T_{max} (hr)	0.9 ± 0.3	
AUC_{0-t} (ng·hr/mL)	324 ± 180	
$t_{1/2}$ (hr)	1.7 ± 0.7	
TUE (μg)	469 ± 277	
Moexiprilat		
C_{max} (ng/mL)	16 ± 9	
T_{max} (hr)	2.5 ± 1.9	
AUC_{0-t} (ng·hr/mL)	228 ± 70	
$t_{1/2}$ (hr)	3.5 ± 2.3	
TUE (μg)	439 ± 273	

The following table shows the dose adjusted PK parameters of moexipril in subjects with cirrhosis and normal subjects.

Parameter	GHBA-636 N=12	GHBA-625R N=12	GHBA-627 N=12	GHBA-633 N=11	ANOVA
Cmax/Dose	10.3±4.0	8.2 ± 2.1	8.5 ± 3.8	6.6 ± 2.9	p = 0.090
$AUC_{(0-0)}$/Dose	21.6±12.0	14.6 ± 5.9	13.5 ± 6.0	10.0 ± 4.8	p = 0.007

The mean Cmax of moexipril in cirrhotic subjects was higher than in all three normal subject groups; however overall ANOVA did not reach statistical significance (p=0.09). Dose-adjusted mean AUC in cirrhotics was 1.5 to two fold that in normal subjects and statistically significant (p=0.007). Fig 1 shows the dose-adjusted moexipril plasma concentration profile for cirrhotic subjects and normal subjects.

The following table shows the dose adjusted PK parameters of moexiprilat in subjects with cirrhosis and normal subjects.

Parameter	GHBA-636 N=12	GHBA-625R N=12	GHBA-627 N=12	GHBA-633 N=11	ANOVA
Cmax/Dose	1.08±0.58	2.36 ± 1.05	2.26 ± 0.84	1.19 ± 0.74	p < 0.001
$AUC_{(0-0)}$/Dose	15.2±4.6	6.8 ± 2.5	7.5 ± 2.0	3.9 ± 2.1	p < 0.001

The mean Cmax of moexiprilat in cirrhotic subjects was lower than in all three normal subject groups and statistically significant ($p < 0.001$). Dose-adjusted AUC in cirrhotics was 2 to 4 fold that in normal subjects and statistically significant ($p < 0.001$). Fig 2 shows the dose-adjusted moexiprilat plasma concentration profile for cirrhotic subjects and normal subjects.

The following table shows dose-adjusted mean total urinary excretion (TUE) and $t_{1/2}$ el for moexipril and moexiprilat in cirrhotic subjects and normal subjects.

Parameter	GHBA-636 N=12	GHBA-625R N=12	GHBA-627 N=12	GHBA-633 N=11	ANOVA
Moexipril TUE (μg)	31.3±18.5	11.1 ± 4.5	16.0 ± 12.6	11.5±7.1	$p < 0.001$
Moexipril $t_{1/2}$ (h)	1.65±0.69	Not available	1.02 ± 0.5	0.73±0.17	$p < 0.001$
Moexiprilat TUE (μg)	31.9±16.4	40.2±22.4	47.6 ± 20.3	26.8±16.2	$p = 0.062$
Moexiprilat $t_{1/2}$ (h)	3.51±2.33	Not available	1.48 ± 0.41	1.48±0.73	p=0.0019

Comments: Moexipril was well tolerated during the study. The changes observed in baseline blood-pressure and pulse rate were similar for cirrhotic subjects and normal subjects. However it is not known that, the same will hold true with hypertensive subjects with or without cirrhosis. Although plasma elimination half-life of both moexipril and moexiprilat is lengthened in cirrhotic subjects, plasma levels of both compounds are similar to those in normal subjects by 12 hr post moexipril dosing, so that a drug accumulation on a once daily dosing schedule is not evident.

Conclusions: As drug accumulation should not occur in cirrhotic subjects on a 15 mg QD dosing schedule, a downward dose adjustment is not considered necessary at 15 mg QD. However, at higher doses caution should be exercised.

Figure A: Dose-Adjusted* Moexipril Plasma Concentration-Time Curve in Subjects with Cirrhosis and Normal Subjects. (*Adjusted to 15 mg moexipril dose).

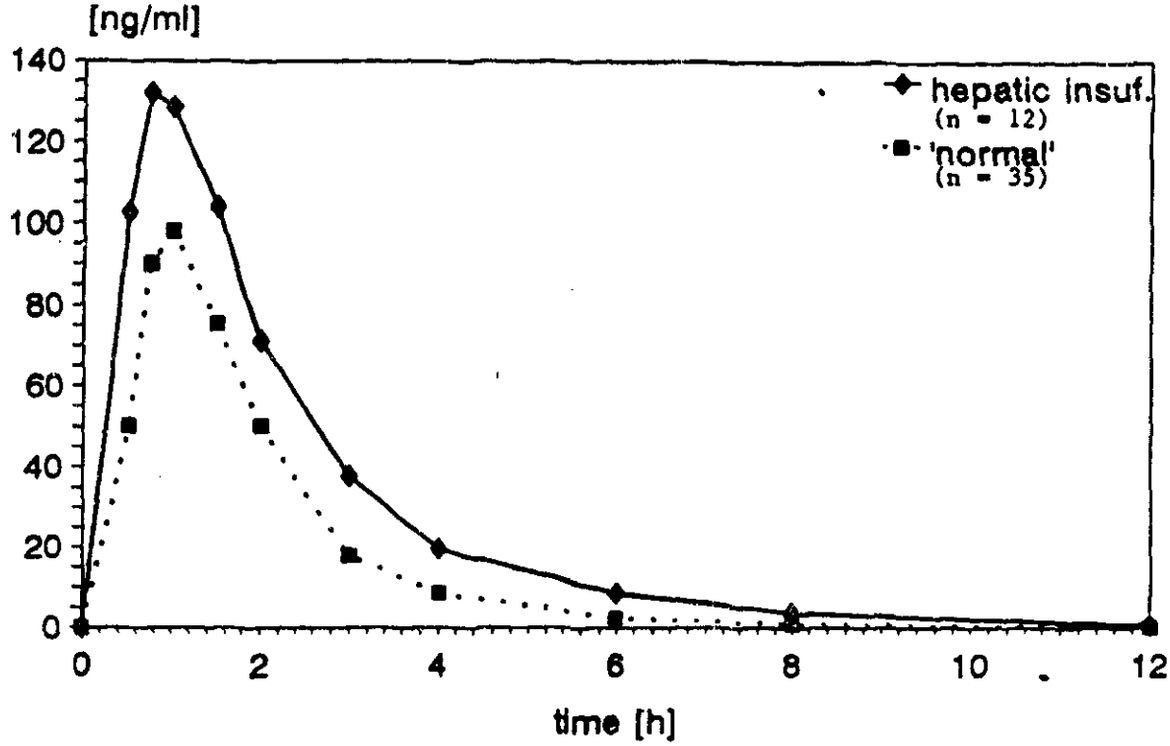
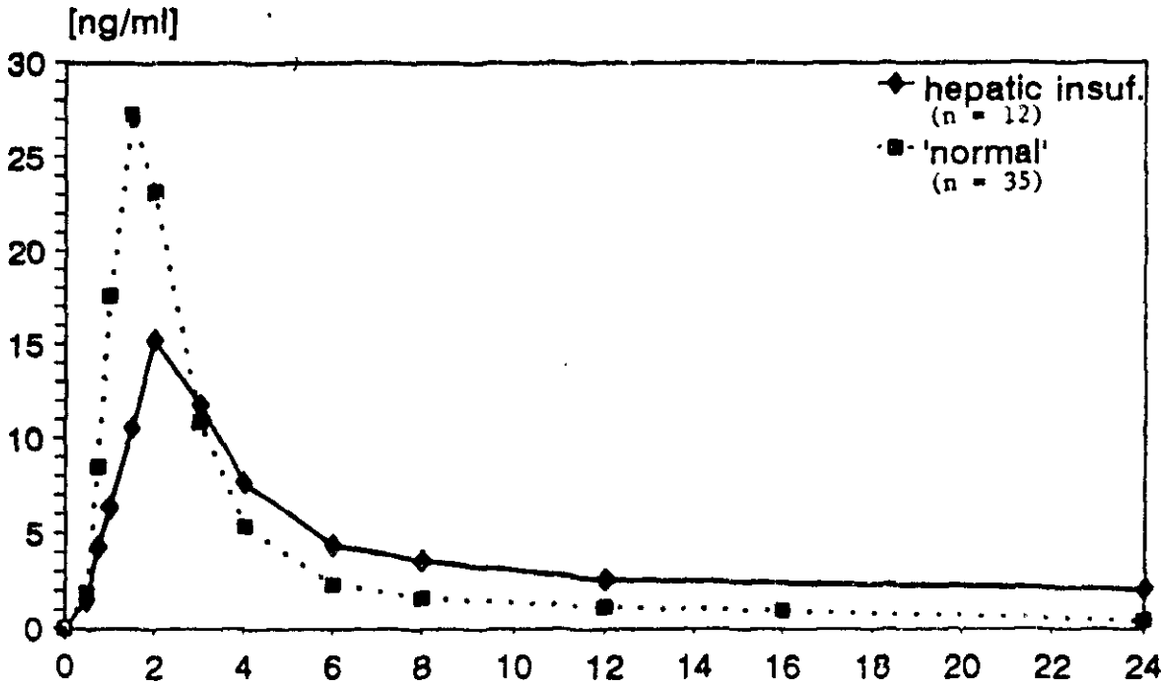


Figure B: Dose Adjusted* Moexiprilat Plasma Concentration-Time Curve in Subjects with Cirrhosis and Normal Subjects. (*Adjusted to 15 mg moexipril dose).



Evaluation of Drug Interaction of Moexipril with Hydrochlorothiazide

Study No: GHBA-625R Volume: 1.82 to 85 Pages: 1 of 1.82 to end of 1.85
Investigator and Site:

Objectives: To determine the effect, of co-administration of moexipril and hydrochlorothiazide (HCTZ) on plasma concentrations and urinary excretion of moexipril and its principle metabolite moexiprilat and urinary excretion of HCTZ when administered alone and simultaneously.

Formulations: Moexipril 30 mg capsule Batch # 903549.
HCTZ 25 mg tablet Batch # WE10142 (Merk Sharp and Dohme)

Study Design: This was a randomized, single-dose, open-label, three-way cross-over study in which 12 male subjects received single oral doses of each of the following treatments:
1. moexipril 30 mg
2. HCTZ 25 mg
3. moexipril 30 mg and HCTZ 25 mg

Each dose was separated by a seven day wash-out period.

Specimens: Blood, at pre dose and at hours 0.5, 0.75, 1.0, 2, 3, 4, 6, 8, 12, 16, 24 and 48 post-drug administration.

Urine samples were collected over following time intervals: 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24 and 24-48 hr after each dose.

Assay (moexipril and moexiprilat): GC-MS
Plasma:
Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 300 ng/ml.
Precision: Interday for moexipril ranged from 2.49% at 0.5 ng/ml to 1.04% at 300 ng/ml. Intraday for moexipril ranged from 2.83% at 0.5 ng/ml to 2.45% at 50 ng/ml. Interday for moexiprilat ranged from 3.9% at 0.5 ng/ml to 2.31% at 300 ng/ml. Intraday for moexiprilat ranged from 1.99% at 0.5 ng/ml to 2.48% at 50 ng/ml.
Accuracy: Interday for moexipril ranged from 1.88% at 0.5 ng/ml to 0.44% at 300 ng/ml. Intraday for moexipril ranged from 4% at 0.5 ng/ml to 0.1% at 50 ng/ml. Interday for moexiprilat ranged from 10.41% at 0.5 ng/ml to 1.72% at 300 ng/ml. Intraday for moexiprilat ranged from 4% at 0.5 ng/ml to 0.4% at 50 ng/ml.

Urine:
Linearity: Satisfactory. Standard curve range: 50 to 15000 ng/ml.
Precision: Interday for moexipril ranged from 6.64% at 50 ng/ml to 0.9% at 15000 ng/ml. Intraday for moexipril ranged from 5.05% at 50 ng/ml to 2.97% at 10000 ng/ml. Interday for moexiprilat ranged from 3.35% at 50 ng/ml to 1.54% at 15000 ng/ml. Intraday for moexiprilat ranged from 2.47% at 50 ng/ml to 6.19% at 10000 ng/ml.
Accuracy: Interday for moexipril ranged from 5.22% at 50 ng/ml to 0.3% at 15000 ng/ml. Intraday for moexipril ranged from 8.44% at 50 ng/ml to 3.34% at 10000 ng/ml. Interday for moexiprilat ranged from 0.69% at 50 ng/ml to 0.81% at 15000 ng/ml. Intraday for moexiprilat

ranged from 0.4% at 50 ng/ml to 9.08% at 10000 ng/ml.

Assay (HCTZ): HPLC with UV detector (275 nm).
Linearity: Satisfactory. Standard curve over 1 to 100 μg/ml.
Precision: Interday was 2.9% at 1 μg/ml and 2.8% at 9 μg/ml. Intraday was 4.4% at 1 μg/ml and 1.6% at 40 μg/ml.
Accuracy: Not reported.

Data Analysis: Cmax, Tmax, $AUC_{(0-t)}$ (up to the last concentration greater than zero) and total urinary excretion (TUE). ANOVA was chosen to compare the possible interaction between moexipril and HCTZ.

Results: The following table summarizes the pharmacokinetic parameters for moexipril and moexiprilat. Fig 1 to 4 show mean plasma concentration time profile for moexipril and moexiprilat.

Parameter	Treatment	
	30 mg Moexipril	30 mg Moexipril + 25 mg HCTZ
Moexipril		
C_{max} (ng/mL)	245 ± 64	241 ± 85
T_{max} (hr)	1.2 ± 0.3	0.8 ± 0.2
AUC_{0-t} (ng·hr/mL)	437 ± 177	416 ± 173
TUE (µg)	334 ± 134	453 ± 295
Moexiprilat		
C_{max} (ng/mL)	71 ± 32	69 ± 34
T_{max} (hr)	1.6 ± 0.4	1.6 ± 0.5
AUC_{0-t} (ng·hr/mL)	203 ± 74	215 ± 71
TUE (µg)	1205 ± 673	1462 ± 796

The TUE for HCTZ was 15.2 ± 2.1 mg after administration of HCTZ alone and was 15.1 ± 1.8 mg after concomitant administration of moexipril and HCTZ.

The following table summarizes the ANOVA for possible pharmacokinetic interaction between HCTZ and moexipril.

Drug	Parameter	Sequence	Treatment
Moexipril (with co-mod HCTZ)	Cmax	0.853	0.888
Moexiprilat	Cmax	0.603	0.907
Moexipril	$AUC_{(0-t)}$	0.745	0.782
Moexiprilat	$AUC_{(0-t)}$	0.979	0.712
Moexipril	TUE	0.083	0.196
Moexiprilat	TUE	0.154	0.392
HCTZ	TUE	0.282	0.961

Conclusion: There was no evidence of any effect on model-independent parameters of pharmacokinetics between moexipril and HCTZ and no influence of administration sequence was evident.

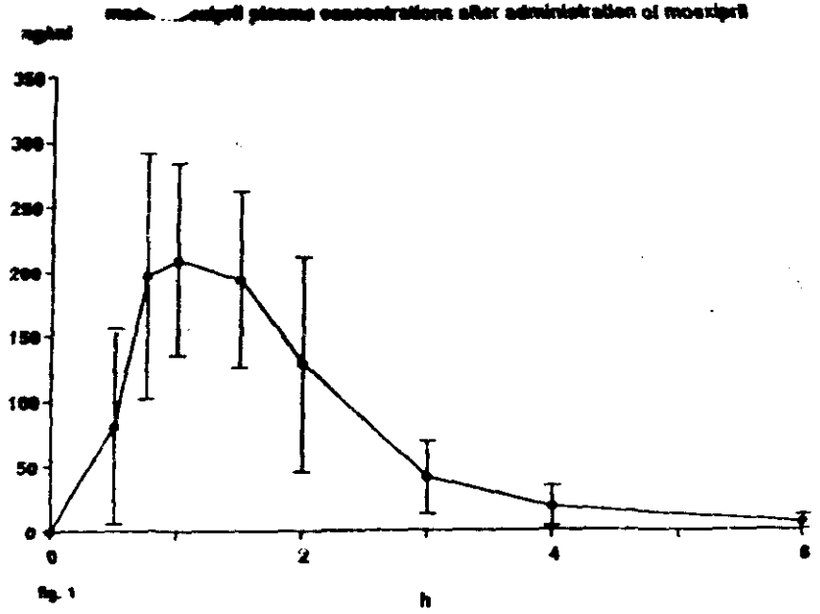


fig. 1

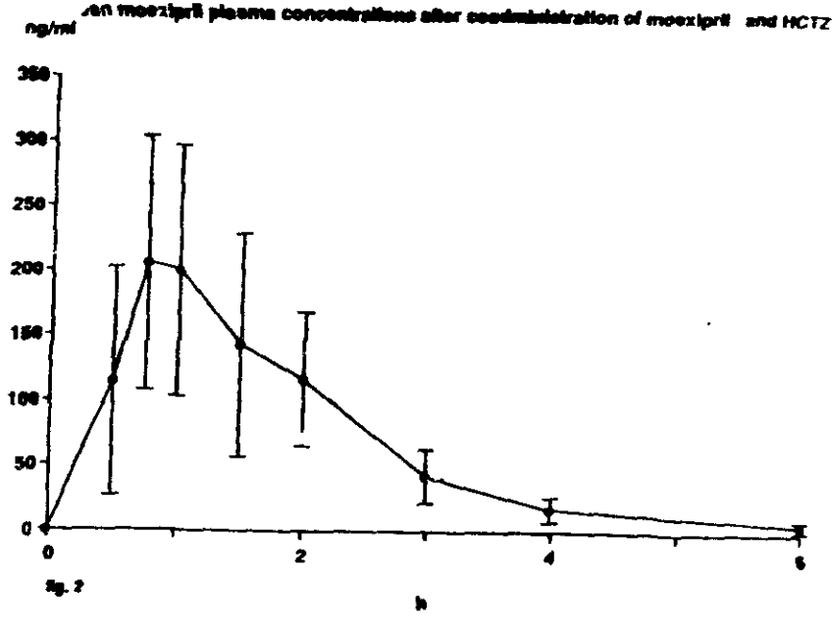


fig. 2

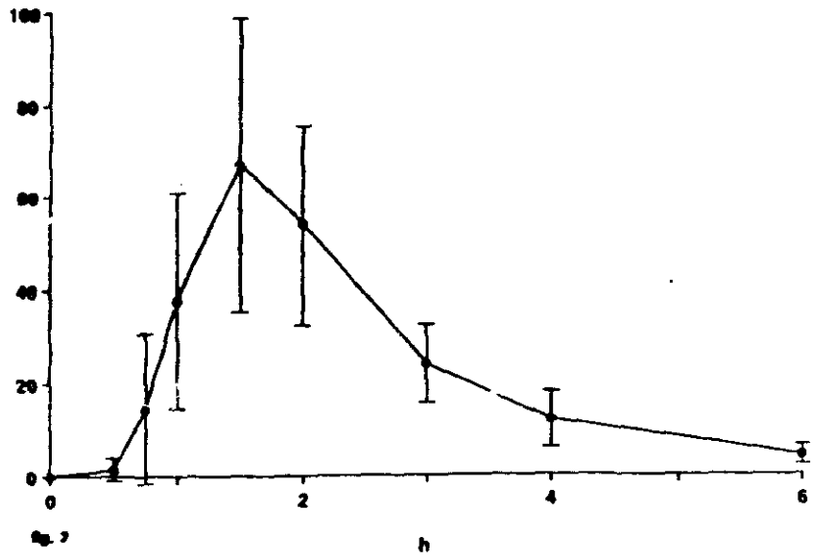


fig. 3

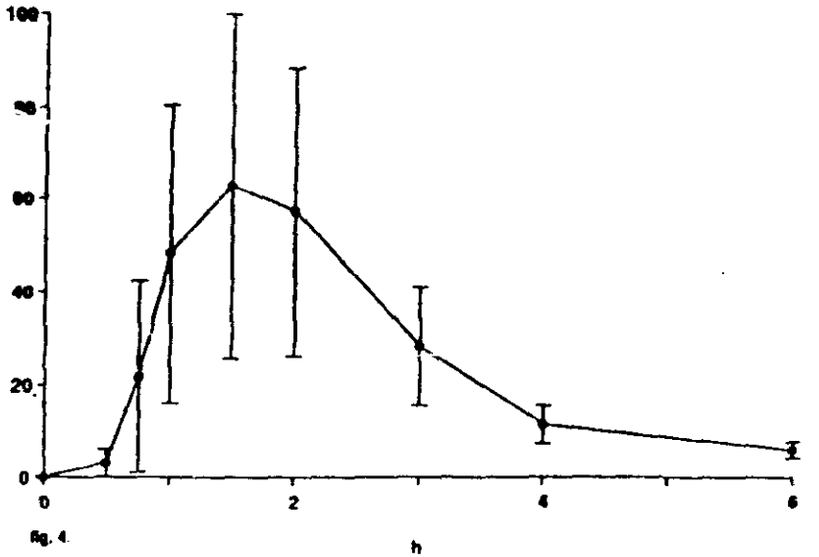


fig. 4

Evaluation of Drug Interaction of Moexipril with Cimetidine

Study No: GHBA-627 Volume: 1.89 to 1.92 Pages: 1 of 1.89 to end of 1.92

Investigator and Site:

Objective: To determine the effect, of co-administration of moexipril and cimetidine on plasma concentrations and urinary excretion of moexipril and its principal metabolite, moexiprilat, by comparison of pharmacokinetic profiles of each drug when administered alone and simultaneously.

Formulations: Moexipril 30 mg capsule, Batch #903549.
Cimetidine 400 mg tablet, Batch #WE10141 (Tagamet®).

Study Design: This was an open-label study in which 12 normal, adult, male subjects were randomly assigned to one of two treatment sequences A or B. The study design is summarized in the following table.

STUDY DESIGN					
SUBJECT NUMBERS	TREATMENT ASSIGNMENTS				
SEQUENCE A 2, 4, 5, 7, 10, 13, a 12,b	DAY 1 moexipril 30mg	DAYS 4-7 cimetidine 400mg TID	DAY 8 moexipril * 30mg plus cimetidine 400mg TID	DAYS 9-10 cimetidine 400mg TID	
SEQUENCE B 1, 6, 8, 11, 14, 16, a 3, 9, b	DAYS 1-4 cimetidine 400mg TID	DAY 5 moexipril * 30mg plus cimetidine 400mg TID	DAYS 6-7 cimetidine 400mg TID	DAYS 8-11 WASHOUT PERIOD	DAY 12 moexipril 30mg

TID = Three times daily (every 8 hours)
* = Moexipril given with morning dose of cimetidine.
a = Subjects completing all treatments
b = Subjects who were prematurely withdrawn

Specimens: Blood, at pre-dose and at 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hr after each dose of moexipril for determination of plasma concentration of moexipril and moexiprilat. A pre-dose and total urine collection was made for 48 hr after each dose of moexipril.

Plasma samples for cimetidine assay were obtained pre-dose on day 4 for sequence A and on day 1 for sequence B, and on the third, fourth and fifth days of cimetidine administration, before the morning dose (trough samples), at -48, -24 and 0 hr before co-administration of moexipril and cimetidine. These Cmin samples were to establish that a steady-state plasma concentration had been achieved.

Assay (moexipril and moexiprilat): GC-MS
Plasma:
Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 300 ng/ml.
Precision: Interday for moexipril ranged from 2.49% at 0.5 ng/ml to 1.04% at 300 ng/ml. Intraday for moexipril ranged from 2.83% at 0.5 ng/ml to 2.45% at 50 ng/ml. Interday for moexiprilat ranged from 3.9% at 0.5 ng/ml to 2.31% at 300 ng/ml. Intraday for moexiprilat ranged from 1.99% at 0.5 ng/ml to 2.48% at 50 ng/ml.
Accuracy: Interday for moexipril ranged from 1.88% at 0.5 ng/ml to 0.44% at 300 ng/ml. Intraday for moexipril ranged from 4% at 0.5 ng/ml to 0.1% at 50 ng/ml. Interday for moexiprilat ranged from 10.41% at 0.5 ng/ml to 1.72% at 300 ng/ml. Intraday for moexiprilat ranged from 4% at 0.5 ng/ml to 0.4% at 50 ng/ml.

Urine:
Linearity: Satisfactory. Standard curve range: 50 to 15000 ng/ml.
Precision: Interday for moexipril ranged from 6.64% at 50 ng/ml to 0.9% at 15000 ng/ml. Intraday for moexipril ranged from 5.05% at 50 ng/ml to 2.97% at 10000 ng/ml. Interday for moexiprilat ranged from 3.35% at 50 ng/ml to 1.54% at 15000 ng/ml. Intraday for moexiprilat ranged from 2.47% at 50 ng/ml to 6.19% at 10000 ng/ml.
Accuracy: Interday for moexipril ranged from 5.22% at 50 ng/ml to 0.3% at 15000 ng/ml. Intraday for moexipril ranged from 8.44% at 50 ng/ml to 3.34% at 10000 ng/ml. Interday for moexiprilat ranged from 0.69% at 50 ng/ml to 0.81% at 15000 ng/ml. Intraday for moexiprilat ranged from 0.4% at 50 ng/ml to 9.08% at 10000 ng/ml.

Cimetidine: HPLC with UV detection (228 nm)
Linearity: Satisfactory. Standard curve from 0.025 μg/ml to 2 μg/ml.
Precision: Interday for cimetidine was 1% at 0.25 μg/ml and 3.9% at 0.5 μg/ml. Intraday ranged from 8% at 0.075 μg/ml to 1.4% at 0.75 μg/ml.

Data Analysis: Cmax, Tmax, $AUC_{(0-t)}$ (up to the last concentration greater than zero), $t_{1/2}$ and total urinary excretion (TUE) for moexipril and moexiprilat.
Results: The following table shows the mean (± SD) cimetidine plasma concentrations 0, 24 and 48 hr prior to administration of moexipril. While considerable variation was seen, the cimetidine plasma concentrations before co-administration appeared to approximate steady-state conditions.

Time Relative to Co-administration With Moexipril	400 mg Cimetidine TID	
	Sequence A n = 6	Sequence B n = 6
Cimetidine C_{min} (μg/mL)		
48 hr before moexipril	0.32 ± 0.12	0.26 ± 0.14
24 hr before moexipril	0.31 ± 0.09	0.23 ± 0.06
0 hr before moexipril	0.46 ± 0.15	0.37 ± 0.11

The following table summarizes the mean (± SD) pharmacokinetic parameters for moexipril and moexiprilat.

Parameter	Treatment	
	30 mg Moexipril	30 mg Moexipril + 400 mg Cimetidine TID
Moexipril		
C_{max} (ng/mL)	254 ± 115	206 ± 85
T_{max} (hr)	0.9 ± 0.3	1.0 ± 0.3
AUC_{0-t} (ng·hr/mL)	406 ± 179	378 ± 123
$t_{1/2}$ (hr)	0.6 ± 0.1	0.6 ± 0.1
TUE (μg)	480 ± 380	379 ± 199
Moexiprilat		
C_{max} (ng/mL)	68 ± 25	82 ± 45
T_{max} (hr)	1.5 ± 0.4	1.6 ± 0.4
AUC_{0-t} (ng·hr/mL)	226 ± 59	255 ± 85
$t_{1/2}$ (hr)	0.9 ± 0.2	0.8 ± 0.4
TUE (μg)	1,429 ± 609	1,399 ± 570

Fig 1 to 4 show mean plasma concentration time profile of moexipril and moexiprilat. The following table summarizes the ANOVA for possible pharmacokinetic interaction between cimetidine and moexipril. The table shows p-values (comparison of PK parameters) for cimetidine and moexipril administered separately and concomitantly.

Parameter	Moexipril	Moexiprilat
Cmax	0.94	0.67
$AUC_{(0-t)}$	0.81	0.59
TUE	0.27	0.51

Comments: Analysis of individual subject data and cumulative urinary excretion of moexipril or moexiprilat plots showed that an error was made by the sponsor in titling these plots. Sponsor has titled these plots as individual plasma concentrations instead of individual cumulative urinary excretion.

Conclusion: The co-administration of moexipril and cimetidine had no demonstrable effect on pharmacokinetic parameters for moexipril and its active metabolite moexiprilat, as indicated by profiles of plasma moexipril and moexiprilat concentrations and total urinary excretion of moexipril and moexiprilat.

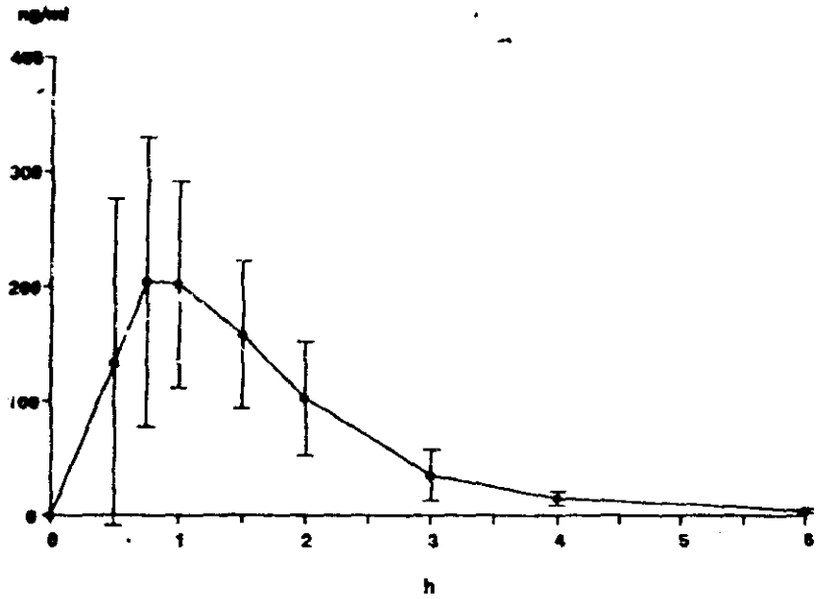


fig. 1: mean moexipril plasma concentrations after administration of moexipril - BIOMAT 118/91

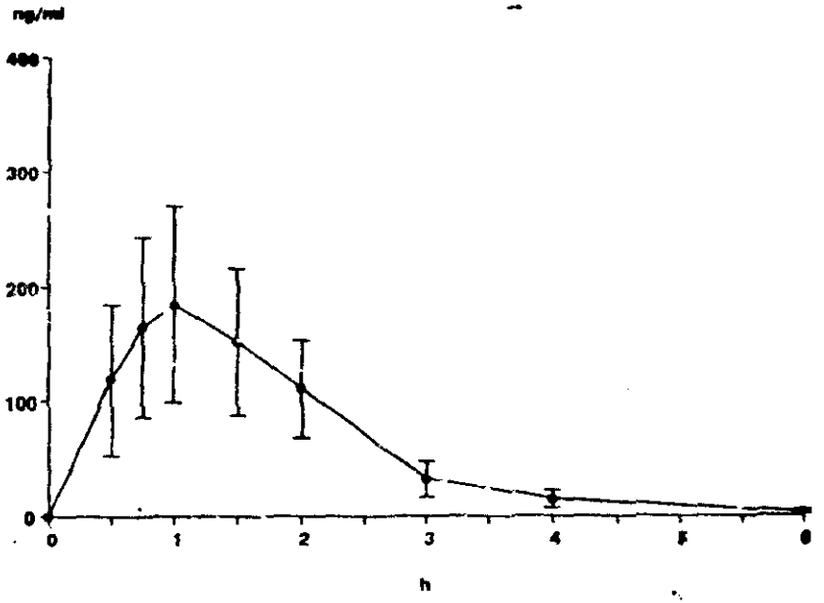


fig. 2: mean moexipril plasma concentrations after coadministration of moexipril and cimetidine BIOMAT 118/91

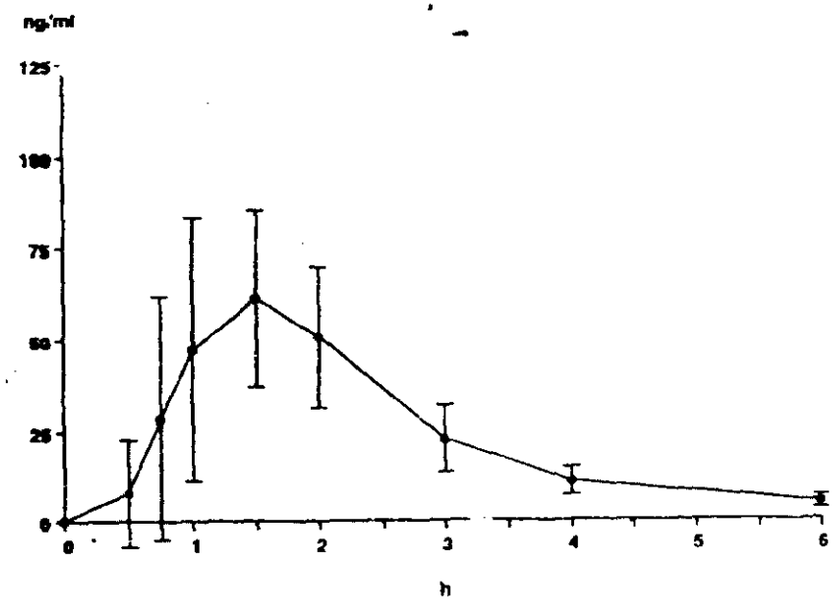


fig. 3: mean moexiprilat plasma concentrations after administration of moexipril - BIOMAT 118/91

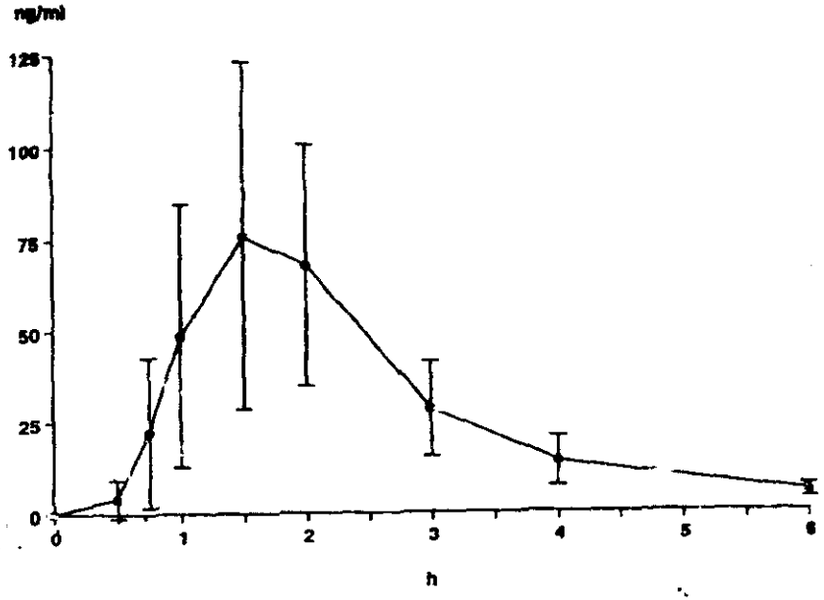


fig. 4: mean moexiprilat plasma concentrations after coadministration of moexipril and cimetidine BIOMAT 118/91

Evaluation of Drug Interaction of Moexipril with Digoxin

Study No: GHBA-626 Volume: 1.86 to 1.88 **Pages**: 1 of 1.86 to end of 1.88

Investigator and Site:

Objectives: To determine the effect, of co-administration of moexipril and digoxin on plasma concentrations and urinary excretion of moexipril and its principal metabolite, moexiprilat, and serum concentrations of digoxin, by comparison of pharmacokinetic profiles of each drug when administered alone and simultaneously.

Formulations: Moexipril 30 mg capsule, Batch #902513.
Digoxin 0.25 mg tablet, Batch #WE10115 (Lanoxin®).

Study Design: This was an open-label study in which 12 normal, adult, male subjects were randomly assigned to one of two treatment sequences A or B. The study design is summarized in the following table.

STUDY DESIGN

SUBJECT NUMBERS	TREATMENT SEQUENCE ***				
	Washout period Day 2 through to Day 7				
SEQUENCE A	DAY 1	DAY 8	DAYS 9-15	DAY 16	DAY 17
2,3,5,8,9,11	30mg moexipril **	0.25mg *Q6H digoxin	0.25mg daily digoxin	30mg moexipril plus 0.25mg digoxin **	0.25mg digoxin **
				Washout period Day 18 through to Day 22	
SEQUENCE B	DAY 1	DAY 2-8	DAY 9	DAY 10	DAY 23
1,4,6,7,10,12	0.25mg *Q6H digoxin	0.25mg, daily digoxin	30mg moexipril plus 0.25mg digoxin **	0.25mg digoxin **	30mg moexipril **

Specimens: Blood, pre-dose, 1, 2, 3, 4, 8, 12 and 24 hr after administration at day 15 and 16 for sequence A and at day 8 and 9 for sequence B of the administration of digoxin, to determine digoxin in plasma and Pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hr after administration of moexipril with or without digoxin to determine moexipril and moexiprilat in plasma.

Assay (moexipril and moexiprilat): GC-MS
Plasma:
Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 300 ng/ml.

Precision: Interday for moexipril ranged from 2.49% at 0.5 ng/ml to 1.04% at 300 ng/ml. Intraday for moexipril ranged from 2.83% at 0.5 ng/ml to 2.45% at 50 ng/ml. Interday for moexiprilat ranged from 3.9% at 0.5 ng/ml to 2.31% at 300 ng/ml. Intraday for moexiprilat ranged from 1.99% at 0.5 ng/ml to 2.48% at 50 ng/ml.
Accuracy: Interday for moexipril ranged from 1.88% at 0.5 ng/ml to 0.44% at 300 ng/ml. Intraday for moexipril ranged from 4% at 0.5 ng/ml to 0.1% at 50 ng/ml. Interday for moexiprilat ranged from 10.41% at 0.5 ng/ml to 1.72% at 300 ng/ml. Intraday for moexiprilat ranged from 4% at 0.5 ng/ml to 0.4% at 50 ng/ml.

Urine:
Linearity: Satisfactory. Standard curve range: 50 to 15000 ng/ml.
Precision: Interday for moexipril ranged from 6.64% at 50 ng/ml to 0.9% at 15000 ng/ml. Intraday for moexipril ranged from 5.05% at 50 ng/ml to 2.97% at 10000 ng/ml. Interday for moexiprilat ranged from 3.35% at 50 ng/ml to 1.54% at 15000 ng/ml. Intraday for moexiprilat ranged from 2.47% at 50 ng/ml to 6.19% at 10000 ng/ml.
Accuracy: Interday for moexipril ranged from 5.22% at 50 ng/ml to 0.3% at 15000 ng/ml. Intraday for moexipril ranged from 8.44% at 50 ng/ml to 3.34% at 10000 ng/ml. Interday for moexiprilat ranged from 0.69% at 50 ng/ml to 0.81% at 15000 ng/ml. Intraday for moexiprilat ranged from 0.4% at 50 ng/ml to 9.08% at 10000 ng/ml.

Digoxin: [17]
Linearity: 0.8 - 2.4 ng/ml.
Precision: Interday for digoxin was 9.6% at 0.5 ng/ml and 7.8% at 9.7 ng/ml. Intraday for digoxin was 25.2% at 0.5 ng/ml and 5.8% at 9.7 ng/ml.
Accuracy: Interday for digoxin was 20% at 0.5 ng/ml and 3% at 9.7 ng/ml. Intraday for digoxin was 15.8% at 1.9 ng/ml and 6.2% at 9.7 ng/ml.

Data Analysis: Cmax, Tmax, $AUC_{(0-t)}$ (up to the last concentration greater than zero) ($AUC_{(0-24)}$ for digoxin and $AUC_{(0-48)}$ for moexipril and moexiprilat) and total urinary excretion (TUE) for moexipril and moexiprilat. ANOVA was chosen to compare the possible interaction between moexipril and digoxin.

Results: The following table summarizes the mean pharmacokinetic parameters for moexipril, moexiprilat and digoxin.

Parameter	Treatment	
	30 mg Moexipril	30 mg Moexipril + 0.25 mg Digoxin
Moexipril		
C_{max} (ng/mL)	130 ± 75	152 ± 72
T_{max} (hr)	0.9 ± 0.3	1.0 ± 0.4
AUC_{0-t} (ng·hr/mL)	236 ± 177	239 ± 108
TUE (μg)	325 ± 202	375 ± 156
Moexiprilat		
C_{max} (ng/mL)	52 ± 31	57 ± 33
T_{max} (hr)	1.6 ± 0.3	1.8 ± 0.3
AUC_{0-t} (ng·hr/mL)	169 ± 69	177 ± 71
TUE (μg)	1,119 ± 389	1,405 ± 605

Parameter	Treatment	
	0.25 mg Digoxin	[illegible] mg Moexipril + 0.25 mg Digoxin
Digoxin		
C_{max} (ng/mL)	1.46 ± 0.59	1.57 ± 0.41
T_{max} (hr)	1.3 ± 0.5	1.3 ± 0.5
AUC_{0-t} (ng·hr/mL)	13.5 ± 4.9	14.3 ± 3.5

Fig 1 to 6 show mean plasma concentration time profile for digoxin, moexipril and moexiprilat when digoxin and moexipril were administered separately and concomitantly.

The following table summarizes the analysis of variance for possible pharmacokinetic interaction between digoxin and moexipril. The table shows p-values (comparison of PK parameters) for digoxin and moexipril administered separately and concomitantly.

Parameter	Digoxin	Moexipril	Moexiprilat
Cmax	0.61	0.49	0.67
Tmax	0.67	0.23	0.21
$AUC_{(0-t)}$	0.64	0.98	0.78
TUE	-	0.21	0.51

Comments: Analysis of individual subject data showed that error was made by the sponsor in plotting TUE of moexipril and moexiprilat when moexipril was administered with or without digoxin. The legends in the figures were interchanged.

Conclusion: The co-administration of moexipril with digoxin had no demonstrable effect on pharmacokinetic parameters for digoxin, unchanged moexipril or the active metabolite moexiprilat.

mean digoxin concentrations in plasma after application of digoxin tablets

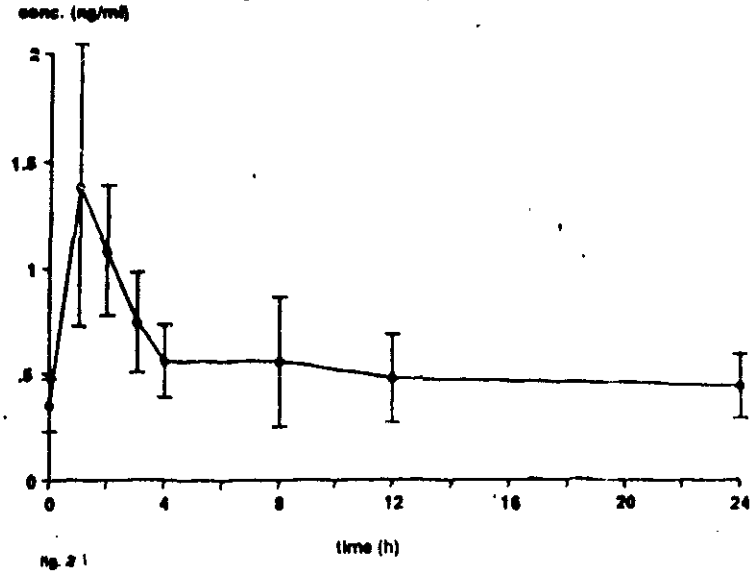


fig. 2.1

mean digoxin concentrations in plasma after coadministration of moexipril cap
...xin tablets

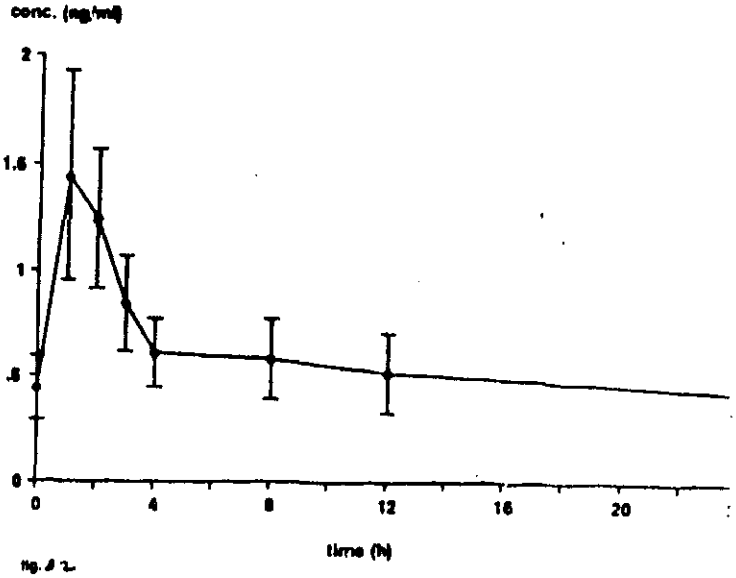


fig. 2.2

mean moexipril concentrations in plasma after application of moexipril capsules

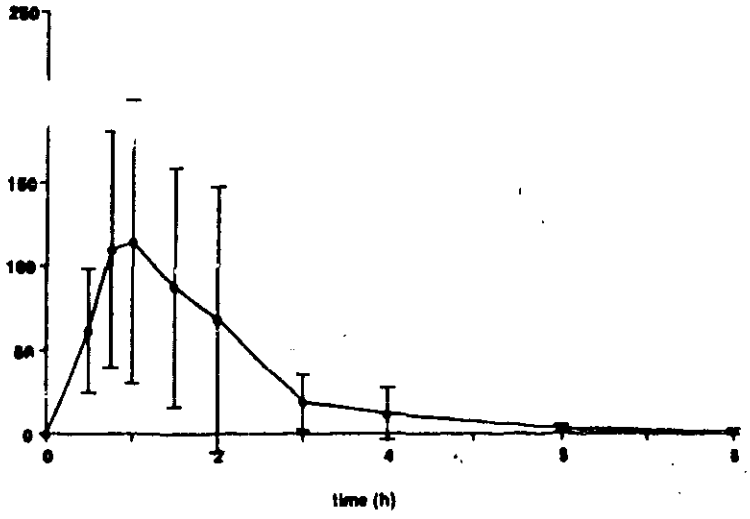


fig. 2.3

mean moexipril concentrations in plasma after coadministration of moexipril capsu...
digoxin tablets

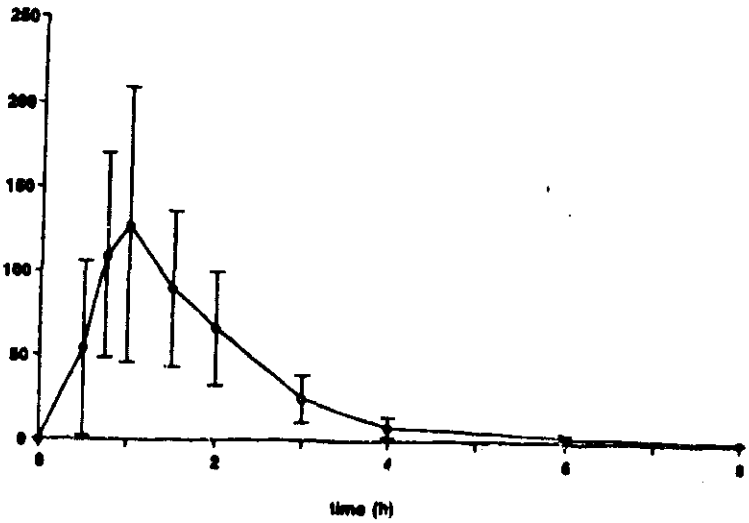


fig. 2.4

mean moexiprilat concentrations in plasma after application of moexipril capsules

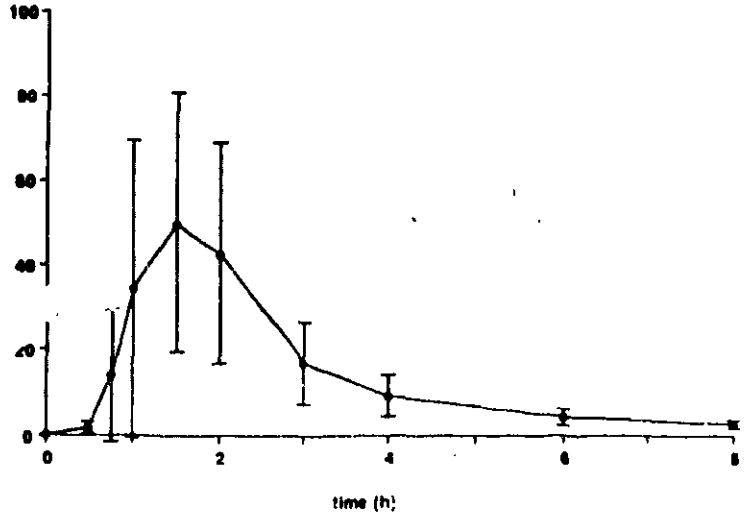


fig. 2.5

mean moexiprilat concentrations in plasma after coadministration of moexipril capsules ar
digoxin tablets

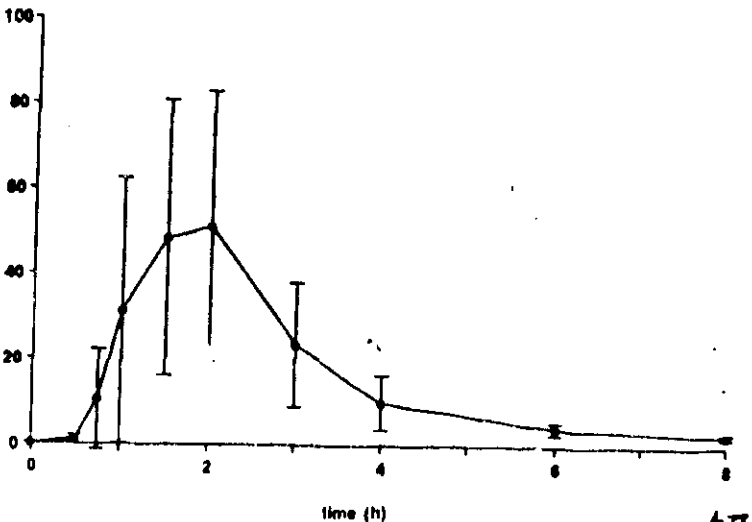


fig. 2.6

Evaluation of Drug Interaction of Moexipril with Nifedipine Retard

Study No: GHBA-633 Volume: 1.95 to 1.98 Pages: 1 of 1.95 to end of 1.98

Investigator and Site:

Objective: To determine the effect of co-administration of moexipril and nifedipine retard on plasma concentrations and urinary excretion of moexipril and moexiprilat and plasma concentrations of nifedipine, by comparison of pharmacokinetic profiles of each drug when administered alone and concomitantly.

Formulations: Moexipril 15 mg capsule, Batch #905041.
Nifedipine Retard 20 mg tablet, Batch #WE10219 (Adalat®).

Study Design: This was randomized, open-label, three-way crossover study in which 11 normal male subjects were administered single doses of moexipril, nifedipine and the two drugs simultaneously.

Treatments:	a.	moexipril	15 mg
	b.	nifedipine retard	20 mg
	c.	a and b together	
Washout period:	one week.		

Specimens: Following the administration of moexipril alone, nifedipine alone or co-administration of these two, blood specimens were obtained predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hr after drug administration.

Assay (moexipril and moexiprilat): GC-MS
Plasma:
Linearity: Satisfactory. Standard curve range: 0.5 ng/ml to 300 ng/ml.
Precision: Interday for moexipril ranged from 2.49% at 0.5 ng/ml to 1.04% at 300 ng/ml. Intraday for moexipril ranged from 2.83% at 0.5 ng/ml to 2.45% at 50 ng/ml. Interday for moexiprilat ranged from 3.9% at 0.5 ng/ml to 2.31% at 300 ng/ml. Intraday for moexiprilat ranged from 1.99% at 0.5 ng/ml to 2.48% at 50 ng/ml.
Accuracy: Interday for moexipril ranged from 1.88% at 0.5 ng/ml to 0.44% at 300 ng/ml. Intraday for moexipril ranged from 4% at 0.5 ng/ml to 0.1% at 50 ng/ml. Interday for moexiprilat ranged from 10.41% at 0.5 ng/ml to 1.72% at 300 ng/ml. Intraday for moexiprilat ranged from 4% at 0.5 ng/ml to 0.4% at 50 ng/ml.

Urine:
Linearity: Satisfactory. Standard curve range: 50 to 15000 ng/ml.
Precision: Interday for moexipril ranged from 6.64% at 50 ng/ml to 0.9% at 15000 ng/ml. Intraday for moexipril ranged from 5.05% at 50 ng/ml to 2.97% at 10000 ng/ml. Interday for moexiprilat ranged from 3.35% at 50 ng/ml to 1.54% at 15000 ng/ml. Intraday for moexiprilat ranged from 2.47% at 50 ng/ml to 6.19% at 10000 ng/ml.
Accuracy: Interday for moexipril ranged from 5.22% at 50 ng/ml to 0.3% at 15000 ng/ml.

Intraday for moexipril ranged from 8.44% at 50 ng/ml to 3.34% at 10000 ng/ml. Interday for moexiprilat ranged from 0.69% at 50 ng/ml to 0.81% at 15000 ng/ml. Intraday for moexiprilat ranged from 0.4% at 50 ng/ml to 9.08% at 10000 ng/ml.

Nifedipine: GC-ECD.
Linearity: Satisfactory, standard curve linear between 1 to 200 ng/ml.
Precision: Interday ranged from 5.66% at 1.09 ng/ml to 1.23% at 204 ng/ml and intraday ranged from 6.46% at 1.09 ng/ml to 2.76% at 204 ng/ml.
Accuracy: Interday ranged from 15.2% at 1.09 ng/ml to 3.9% at 204 ng/ml and intraday ranged from 16.5% at 1.09 ng/ml to 4.8% at 204 ng/ml.

Data Analysis: Cmax, Tmax, $AUC_{(0-t)}$ (up to the last concentration greater than zero), $AUC_{(0-16)}$ for moexipril, moexiprilat and nifedipine and total urinary excretion (TUE) for moexipril and moexiprilat. ANOVA was chosen to compare the possible interaction between moexipril and nifedipine.

Results: The mean and standard deviation values for the pharmacokinetic parameters are shown in the following table. The mean plasma concentration time profile for moexipril and moexiprilat is shown in fig 1 to 4 and for nifedipine in fig 5 and 6. The mean cumulative urinary excretion profile is shown in fig 7 to 10.

Parameter	Treatment	
	15 mg Moexipril	15 mg Moexipril + 20 mg Nifedipine
Moexipril		
C_{max} (ng/mL)	100 ± 44	122 ± 51
T_{max} (hr)	1.0 ± 0.2	1.0 ± 0.4
AUC_{0-t} (ng·hr/mL)	150 ± 71	193 ± 75
$t_{1/2}$ (hr)	0.8 ± 0.2	0.7 ± 0.2
TUE (μg)	173 ± 107	221 ± 98
Moexiprilat		
C_{max} (ng/mL)	18 ± 11	25 ± 15
T_{max} (hr)	1.7 ± 0.3	1.5 ± 0.3
AUC_{0-t} (ng·hr/mL)	59 ± 31	71 ± 29
$t_{1/2}$ (hr)	0.9 ± 0.4	0.9 ± 0.6
TUE (μg)	402 ± 244	496 ± 240

Parameter	Treatment	
	20 mg Nifedipine	15 mg Moexipril + 20 mg Nifedipine
Nifedipine		
C_{max} (ng/mL)	50 ± 18	62 ± 26
T_{max} (hr)	2.4 ± 2.1	1.3 ± 0.7
AUC_{0-t} (ng·hr/mL)	272 ± 92	316 ± 106
$t_{1/2}$ (hr)	3.4 ± 1.9	3.1 ± 1.5

There was no statistically significant effect of nifedipine retard co-administration on Cmax, $AUC_{(0-t)}$, $t_{1/2}$ or TUE of moexipril or moexiprilat. Similarly, co-administration of moexipril did not statistically significantly affect Cmax, $AUC_{(0-t)}$ or $t_{1/2}$ of nifedipine. The table below summarizes the possible pharmacokinetic interaction between nifedipine and moexipril.

Parameter	Drug	Treatment (p-values)
Cmax	moexipril	0.18
$AUC_{(0-t)}$	moexipril	0.29
TUE	moexipril	0.24
Cmax	moexiprilat	0.34
$AUC_{(0-t)}$	moexiprilat	0.24
TUE	moexiprilat	0.39
Cmax	nifedipine	0.32
$AUC_{(0-t)}$	nifedipine	0.22

Clinical adverse experiences: Mild in nature and resolved without treatment.

Comment to Medical Officer: The slight increase in Cmax and AUC seen with concomitant administration could be higher and significant with higher doses.

Conclusion: There was no interaction between nifedipine retard and moexipril on pharmacokinetic parameters.

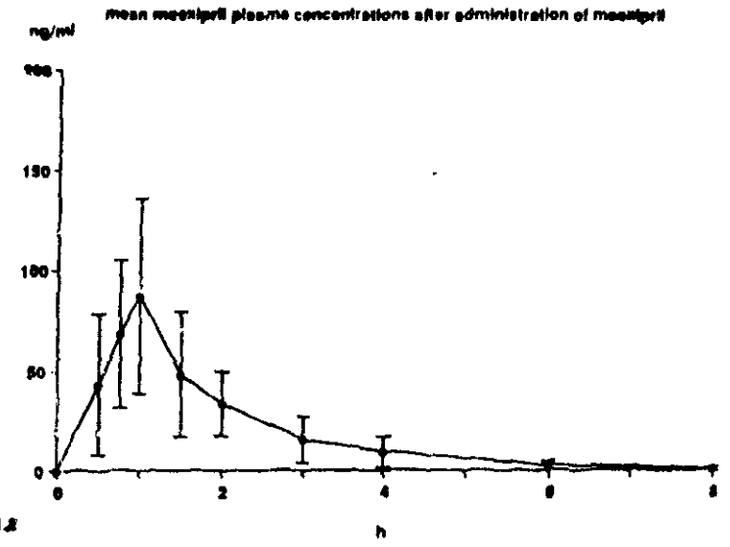


fig. 1.

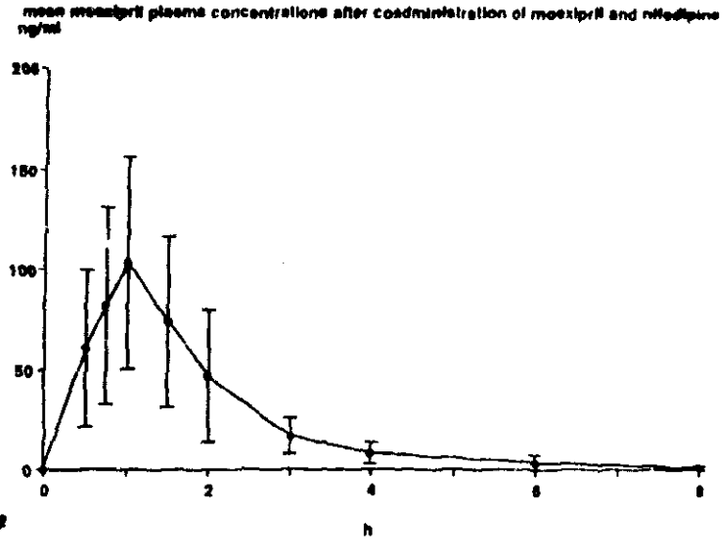


fig. 2.

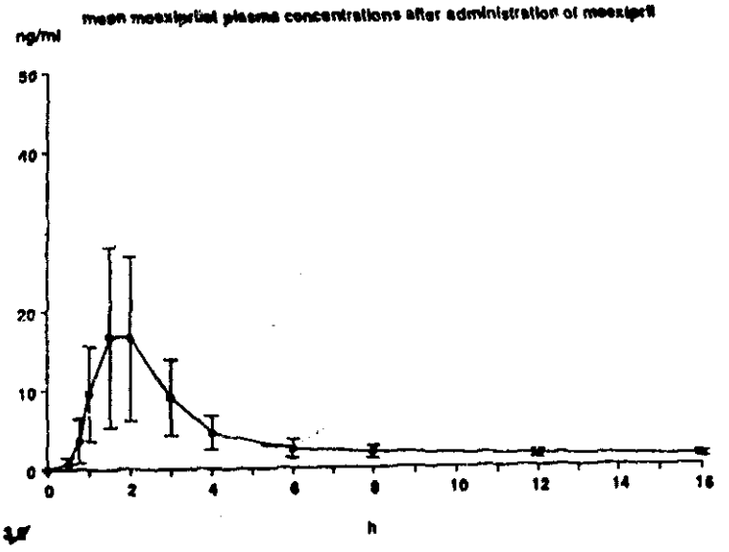


fig. 3.

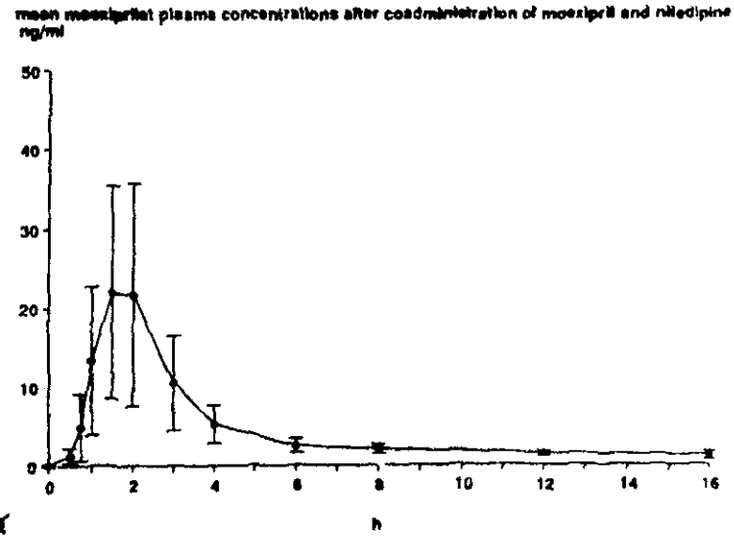


fig. 4.

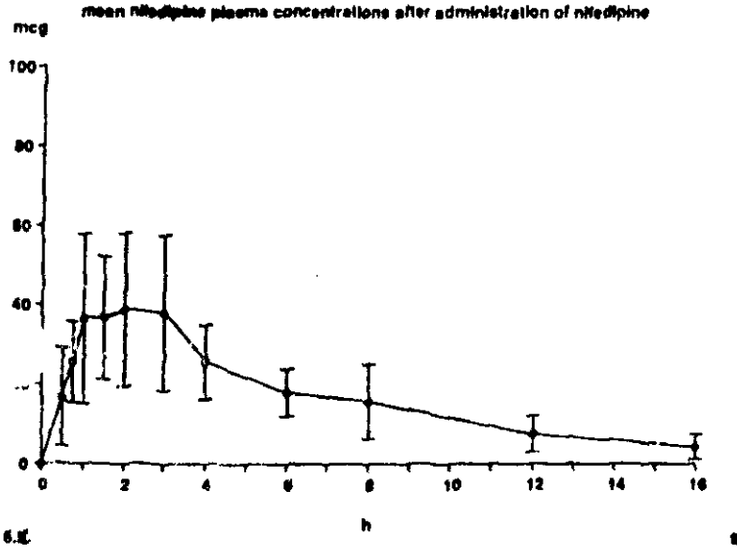


fig. 5.

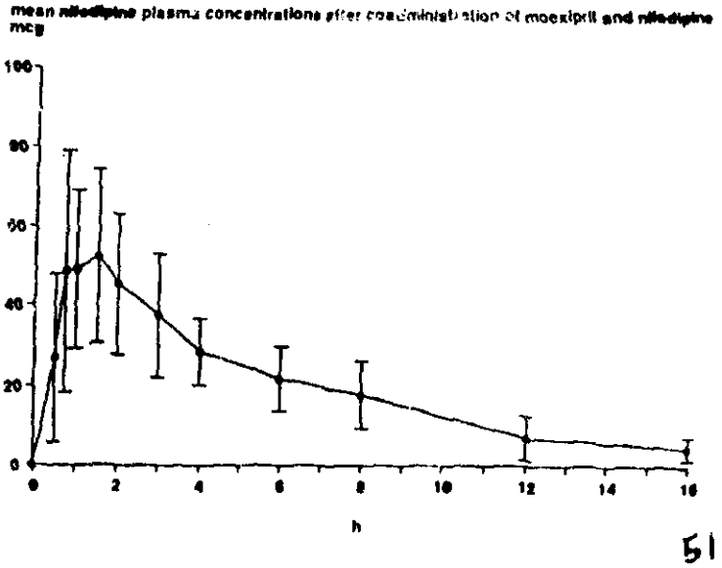


fig. 6.

Evaluation of Drug Interaction of Moexipril with Warfarin

Study No: GHBA-631 Volume: 1.93 to 1.94 Pages: 1 of 1.93 to end of 1.94

Investigator and Site:

Objectives: To determine the effect, in normal male subjects, of moexipril on the anticoagulant activity and peak plasma concentration and pharmacokinetic profile of warfarin (a single oral dose resulting in an anticoagulant response at therapeutic levels).

Formulations: Moexipril 15 mg capsule, batch #905041.
Warfarin 5 mg tablet, batch #WE10195

Study Design: This was an open-label study in which 10 healthy male subjects were randomly assigned to one of two treatment sequences A or B. The study design is summarized in the following table.

SUBJECT NUMBERS	TREATMENT ASSIGNMENTS					
[illegible] A	Day 1	Days 8-12	Day 15	Days 16 - 20	Days 22-26	Day 29
1001, 1004, 1006, 1007, 1009	warfarin 50mg *	FIRST WASHOUT PERIOD	moexipril 1 x 15mg plus warfarin 50mg *	moexipril 1 x 15mg	SECOND WASHOUT PERIOD	FINAL VISIT
[illegible] B	Day 1	Days 2 - 6	Days 8-12	Day 15	Days 22-26	Day 29
1002, 1003, 1005, 1008, 1010	moexipril 15mg plus warfarin 50mg *	moexipril 1 x 15mg daily	FIRST WASHOUT PERIOD	warfarin 50mg *	SECOND WASHOUT PERIOD	FINAL VISIT

* [illegible] x 5mg (taken as a single dose)

Specimens: Blood specimens for measurement of prothrombin time were obtained, prestudy before each administration, daily for five days postdose and at intervals during each washout period. Blood specimens for partial thromboplastin time were obtained prestudy, immediately before each warfarin dose, and at intervals postdose and during each washout period.

Plasma samples for analysis of the R and S enantiomers of warfarin were obtained before each warfarin dose and at 1, 2, 4, 8, 12, 24, 36, 48, 72, 96 and 120 hr postdose.

Assay: HPLC, UV detection at 310 nm.
Linearity: Satisfactory. Calibration curve linear over 0.4 to 5 μg/ml for each enantiomer.
Precision: Interday was 8.1% and 10.3% at 1.25 μg/ml for S(-)-warfarin and R(+)-warfarin respectively and 5.8% and 7% at 2.5 μg/ml for S(-)-warfarin and R(+)-warfarin respectively.
Accuracy: Interday was 3.2% and 6.4% at 1.25 μg/ml for S(-)-warfarin and R(+)-warfarin respectively and 5.0% and 6.8% at 2.5 μg/ml for S(-)-warfarin and R(+)-warfarin respectively.

Data Analysis: For each enantiomer, Cmax, Tmax, $AUC_{(0-t)}$ and $AUC_{(0-120)}$ were determined.

Results: The pharmacokinetic parameters determined for warfarin are shown in the following table. Fig 1 to 4 summarizes plasma concentration time profile for S(-) and R(+) warfarin.

Parameter	Treatment	
	50 mg Warfarin	15 mg Moexipril + 50 mg Warfarin
Warfarin (S configuration)		
C_{max} (μg/mL)	2.85 ± 0.35	2.79 ± 0.37
T_{max} (hr)	1.8 ± 0.9	2.5 ± 3.4
AUC_{0-t} (μg·hr/mL)	94.8 ± 15.7	95.3 ± 18.4
Warfarin (R configuration)		
C_{max} (μg/mL)	2.80 ± 0.42	2.81 ± 0.34
T_{max} (hr)	2.1 ± 1.1	2.5 ± 3.4
AUC_{0-t} (μg·hr/mL)	124 ± 21	125 ± 28

There was no statistically significant difference in Cmax and $AUC_{(0-t)}$ of warfarin when administered alone or with moexipril. The mean Tmax was similar for both administration but the range for concomitant administration was somewhat wider.

The mean coagulation parameters are summarized in table 1. For prothrombin time, warfarin administered alone produced an overall mean elongation of 10.15 seconds. Co-administration of moexipril with warfarin followed by a daily dosing with moexipril for five days produced an overall mean elongation of 9.85 seconds, indicating that co-administration had no significant effect on elongation of prothrombin time. The increase in partial thromboplastin time caused by administration of warfarin was not affected by co-administration of moexipril.

From a total of 12 clinical adverse experiences reported by 5 subjects assigned to sequence A, 6 were following concomitant administration and 3 were following warfarin alone. From a total of 7 clinical adverse experiences reported by 4 subjects assigned to sequence B, 3 were following concomitant administration and 3 were following warfarin alone. Headache and dizziness were more frequently reported following the concomitant administration of warfarin and moexipril.

Comments: The sponsor has drawn a conclusion that concomitant administration of warfarin and moexipril was well tolerated. The medical officer is requested to comment on increased level of adverse effects associated with concomitant administration of warfarin and moexipril.

Conclusion: The concomitant administration of moexipril with a single therapeutic dose of warfarin did not influence warfarin's pharmacodynamic effects or pharmacokinetic parameters.

mean S(-)-warfarin concentrations in plasma after single dose of warfarin

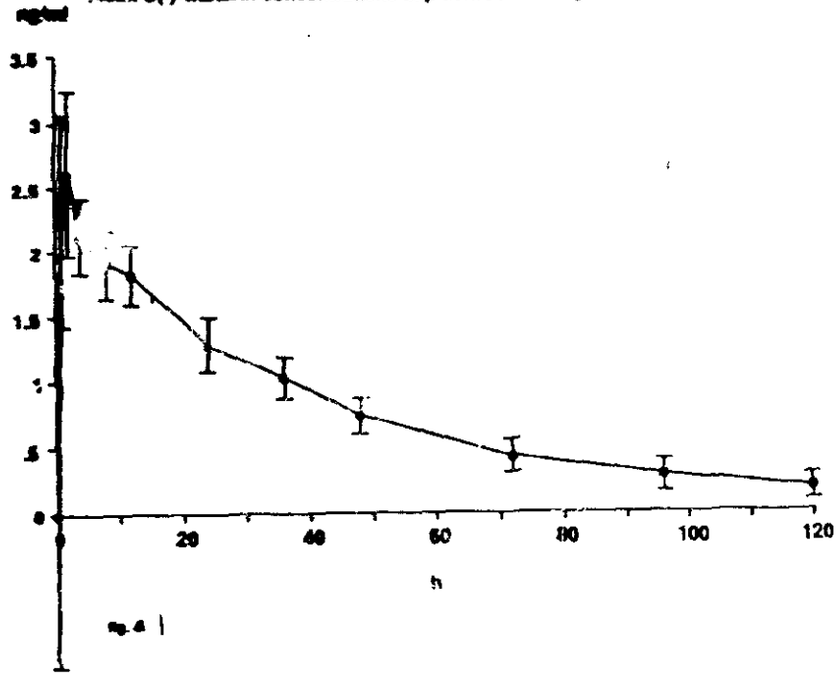


fig. 1

mean R(+)-warfarin concentrations in plasma after single dose of warfarin

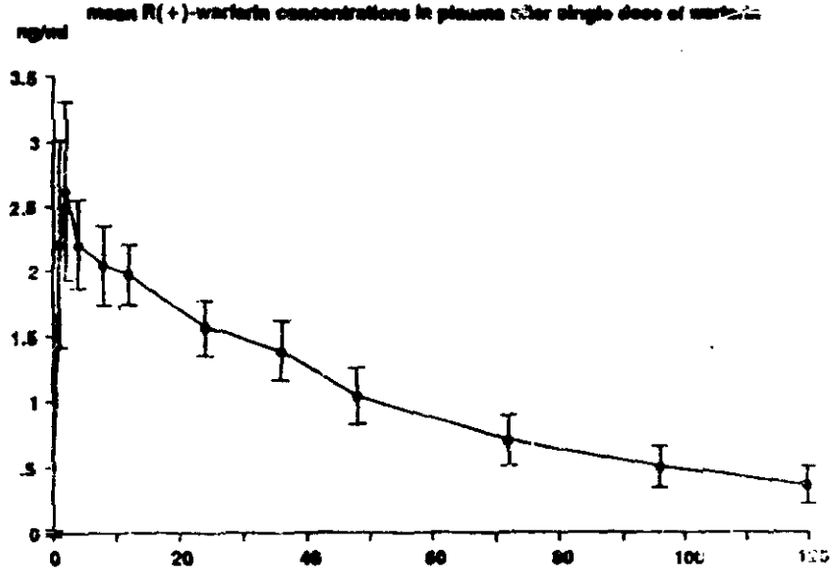


fig. 2

mean S(-)-warfarin concentrations in plasma after coadministration of moexipril and warfarin

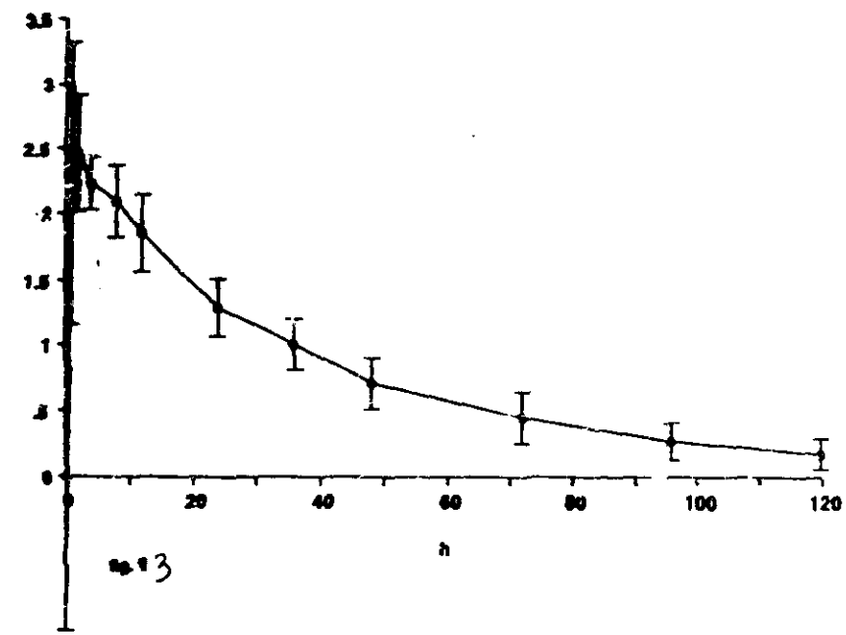


fig. 3

mean R(+)-warfarin concentrations in plasma after coadministration of moexipril and warfarin

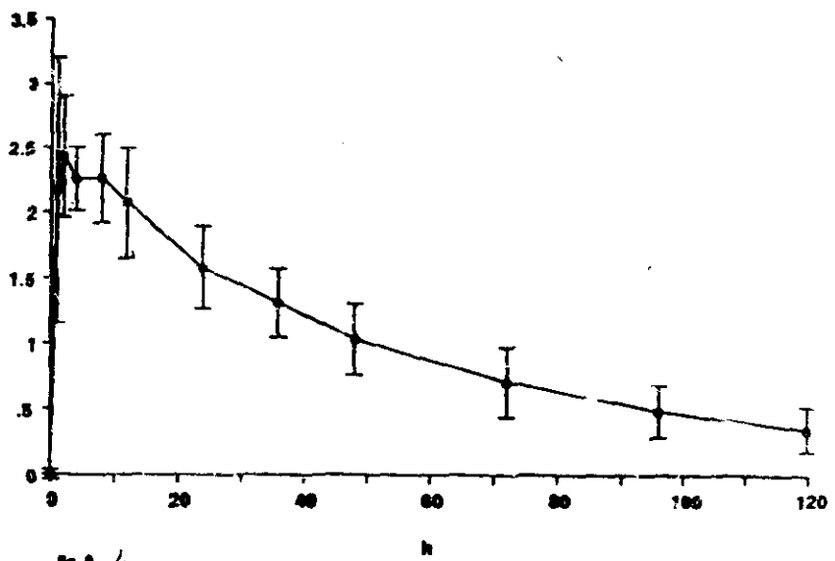


fig. 4

45

SUMMARY OF COAGULATION PARAMETERS
(Mean +/- S.E.)

SEQUENCE A

Study Phase/Day, Timepoint	Prothrombin Time (sec) (N=5)	Partial Thromboplastin Time (sec) (N=5)
Screening*	10.32 +/- 0.02	32.22 +/- 0.89
Warfarin Alone		
Day 1 , Pre-first dose Warfarin	10.08 +/- 0.22	32.66 +/- 0.48
Day 2	14.72 +/- 0.47	
Day 3	21.50 +/- 0.98	42.44 +/- 0.97
Day 4	16.94 +/- 0.94	
Day 5	13.72 +/- 0.63	41.86 +/- 2.04
Day 6	12.15 +/- 0.54 *	
First Washout		
Day 8	10.84 +/- 0.30	34.32 +/- 1.44
Day 10	10.44 +/- 0.24	
Day 12	10.18 +/- 0.21	32.54 +/- 0.92
Warfarin + Moexipril		
Day 15, Pre-dose Warf + Moex	10.18 +/- 0.21	32.62 +/- 0.73
Day 16, Pre-dose Moexipril	14.38 +/- 0.53	
Day 17, Pre-dose Moexipril	18.86 +/- 0.77	41.82 +/- 1.46
Day 18, Pre-dose Moexipril	16.06 +/- 1.24	
Day 19, Pre-dose Moexipril	13.18 +/- 0.78	42.44 +/- 2.58
Day 20, Pre-dose Moexipril	11.10 +/- 0.33	
Second Washout		
Day 22	10.58 +/- 0.21	35.44 +/- 0.78
Day 24	10.35 +/- 0.25	
Day 26	9.84 +/- 0.25	34.24 +/- 0.62
Final Visit		
Day 29	10.00 +/- 0.17	

* N = 4

SEQUENCE B

Study Phase/Day, Timepoint	Prothrombin Time (sec) (N=5)	Partial Thromboplastin Time (sec) (N=5)
Screening*	10.46 +/- 0.12	29.64 +/- 0.84
Warfarin + Moexipril		
Day 1 , Pre-dose Warf + Moex	10.09 +/- 0.18	29.74 +/- 1.19
Day 2 , Pre-dose Moexipril	14.74 +/- 0.24	
Day 3 , Pre-dose Moexipril	21.10 +/- 1.33	38.82 +/- 1.68
Day 4 , Pre-dose Moexipril	16.92 +/- 1.23	
Day 5 , Pre-dose Moexipril	13.60 +/- 0.71	38.36 +/- 2.11
Day 6 , Pre-dose Moexipril	11.80 +/- 0.63	
First Washout		
Day 8	10.38 +/- 0.18	30.64 +/- 0.89
Day 10	10.33 +/- 0.27	
Day 12	10.32 +/- 0.22	30.48 +/- 0.77
Warfarin Alone		
Day 15, Pre-second dose Warfarin	10.18 +/- 0.20	30.08 +/- 0.96
Day 16	14.26 +/- 0.33	
Day 17	19.06 +/- 0.63	38.42 +/- 1.02
Day 18	14.90 +/- 0.73	
Day 19	12.86 +/- 0.27	37.32 +/- 1.56
Day 20	11.30 +/- 0.21	
Second Washout		
Day 22	10.38 +/- 0.21	31.08 +/- 1.13
Day 24	10.15 +/- 0.25	
Day 26	9.80 +/- 0.20	30.82 +/- 0.82
Final Visit		
Day 29	9.97 +/- 0.14	

Single Rising-Dose Efficacy and Pharmacokinetics of Moexipril

Study No: GHBA-621 Volume: 1.72 Pages: 97 to end

Investigator and Site:

Objectives: To investigate pharmacokinetics and pharmacodynamics (ACE inhibition) of moexipril.

Formulations: Moexipril capsule 3.75 mg, Batch #10085-197-4475
7.50 mg, Batch #10085-197-4495N
30.0 mg, Batch #10085-197-4494N

Study Design: This was a double blind placebo controlled trial of parallel design in which each patient received a single dose of moexipril or placebo. Thirty subjects (20 male, 10 female) were sequentially assigned in groups of six to each of 5 dose levels (3.75, 7.5, 15, 30 or 60 mg). Within each group, 4 subjects were randomly assigned to receive a single oral dose of moexipril and two to receive placebo.

Specimens: Blood samples were obtained predose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 and 48 hr postdose.

Assay: The concentrations of moexipril and moexiprilat in plasma samples from the 30 and 60 mg dose groups were assayed GC procedure. The LLQ was 5 ng/ml. The plasma samples obtained from 3.75 mg and 7.5 mg doses were assayed by RIA for moexiprilat only. The samples for 15 mg dose group were assayed for moexiprilat by RIA and GC and for moexipril by GC. The LLQ for RIA for moexiprilat was 0.5 ng/ml.
PIA Precision: Interday at 0.7 ng/ml was 2.5% and at 150 ng/ml was 2.7%, intraday at 0.7 ng/ml was 2.8% and at 150 ng/ml was 3.3%. Precision was not determined at 0.5 ng/ml. Accuracy ranged from 96 to 98% over 0.7 to 150 ng/ml concentration range.

Data Analysis:
Efficacy assessments: Supine blood pressure and heart rate were measured at baseline, at 15, 30 and 45 min after dosing, and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24 and 48 hr after dosing.

Pharmacokinetics: Cmax, AUC, Tmax, plasma terminal elimination half life ($t_{1/2}$) and apparent oral clearance (Cl_o).

Pharmacodynamics: To determine the relationship between plasma concentration of moexiprilat and inhibition of ACE activity, simple sigmoid Emax model was used:
$E = Emax\ C^n / (EC50^n + C^n)$
where E Effect, Emax Maximum possible response,
n Constant, EC50 Concentration that produces half Emax.
Nonlinear regression analysis was used to compare the inhibition of ACE activity with plasma concentrations of moexiprilat.

Results: Fig 1 shows mean supine diastolic blood pressure for each of the treatment groups. The 3.75 and 7.5 mg treatment groups showed effect similar to those for the placebo group. The 15 and 30 mg treatment groups had larger mean drops in blood pressure, compared with baseline values, than did the placebo group. The drop was not as large in the 60 mg group.

Fig 2 shows the mean plasma concentration time profile. The mean (± SEM) for the pharmacokinetic parameters are shown below.

Parameter	Dose of Moexipril		
	15 mg	30 mg	60 mg
Moexipril			
C_{max} (ng/mL)	55 ± 14	87 ± 13	384 ± 216
T_{max} (hr)	1.0 ± 0.2	0.9 ± 0.1	0.9 ± 0.2
$AUC_{0-\infty}$ (ng·hr/mL)	92 ± 24	153 ± 27	665 ± 344
$t_{1/2}$ (hr)	1.0 ± 0.4	0.9 ± 0.3	1.4 ± 0.3
Cl (mL/min/kg)	43 ± 21	51 ± 9	36 ± 13
Moexiprilat			
C_{max} (ng/mL)	19 ± 4	45 ± 8	131 ± 30
T_{max} (hr)	1.6 ± 0.1	1.4 ± 0.1	1.4 ± 0.2
AUC_{0-t} (ng·hr/mL)	138 ± 5.4	160 ± 17	386 ± 55
$t_{1/2}$ (hr)	14.9 ± 4.6	1.7 ± 0.2	2.2 ± 0.5

Parameter	Dose of Moexipril	
	3.75 mg	7.5 mg
Moexiprilat		
C_{max} (ng/mL)	3.2 ± 1.0	5.5 ± 2.0
T_{max} (hr)	2.5 ± 0.5	1.9 ± 0.1
AUC_{0-t} (ng·hr/mL)	37 ± 5	88 ± 15
$t_{1/2}$ (hr)	12.4 ± 3.9	23.4 ± 3.9

Pharmacodynamics: Fig 3 displays a plot of the percentage inhibition of plasma ACE activity compared with plasma concentrations of moexiprilat for all dose levels. The inset graph shows

the plot for 3.75 mg dose group only. The result of nonlinear least square analysis comparing the inhibition of ACE activity with concentrations of moexiprilat in plasma are shown below:

	3.75 mg Group	All Groups
EC50	0.41 ± 0.08	0.40 ± 0.05
N	1.30 ± 0.26	1.31 ± 0.15

Plasma ACE activity was still suppressed by more than 50% even when blood pressure had returned to predose values, implying that in addition to plasma ACE inhibition other factors may contribute to the lowering of blood pressure (fig 4).

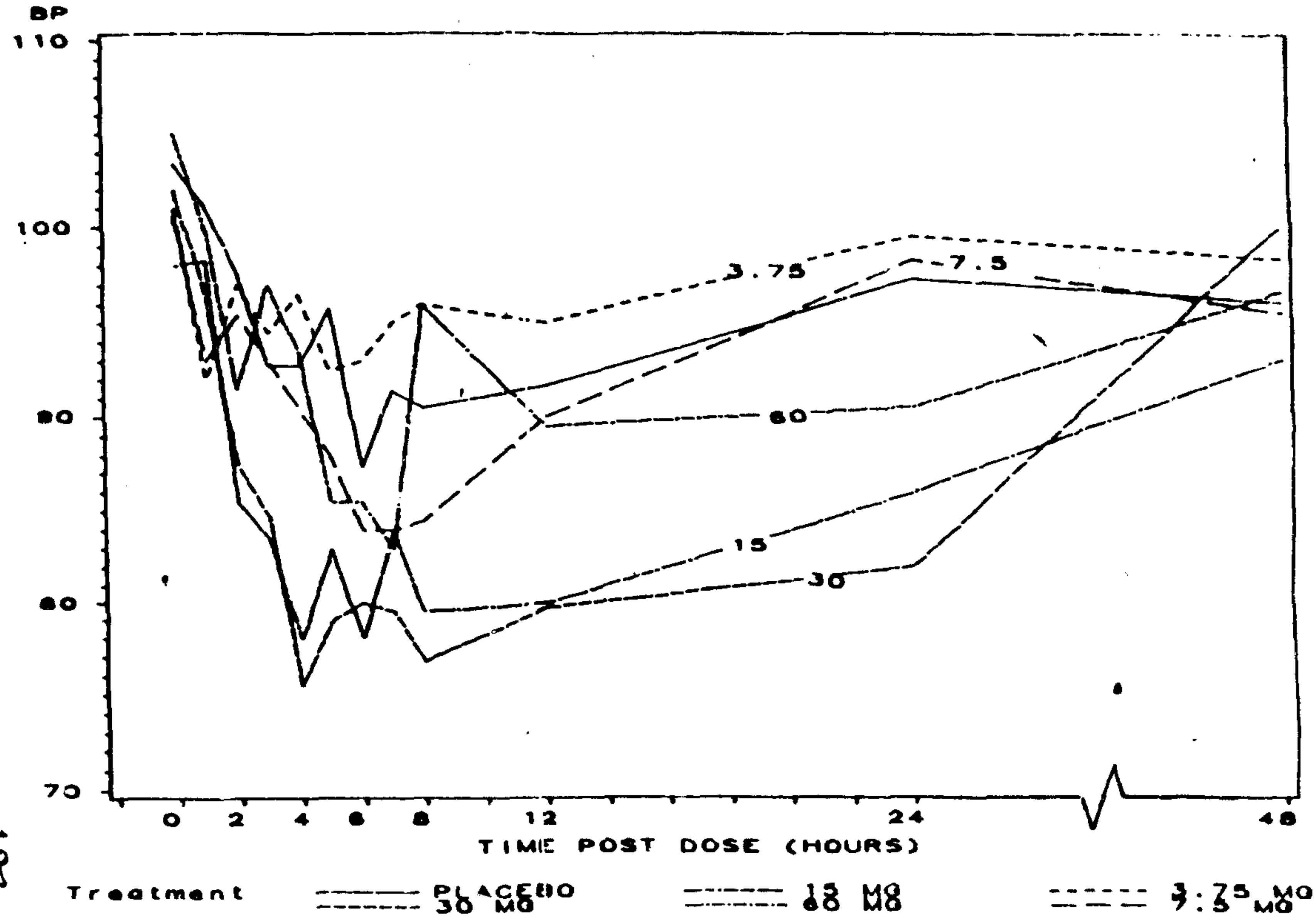
Dose Response: Reduction in blood pressure correlated with increase in dose with the exception of the 60 mg dose. However, there appeared to be no direct correlation between blood pressure changes and plasma concentrations of moexiprilat (fig. 5).

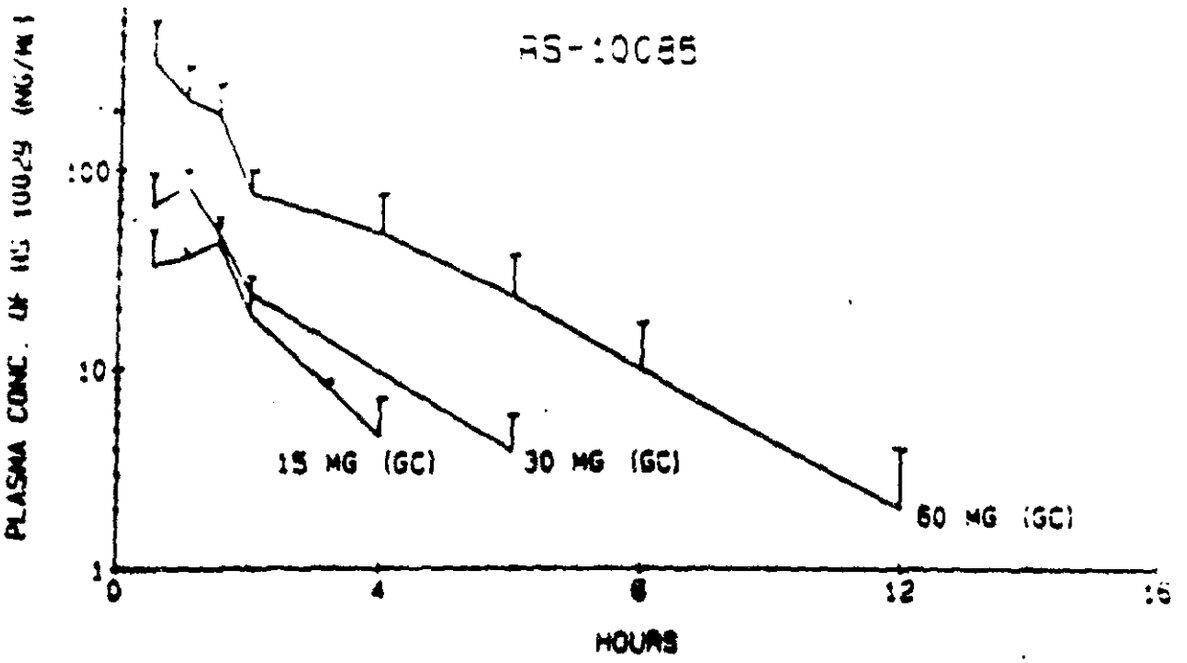
Comments: Oral clearance at doses (15, 30 and 60 mg) showed high variability and no male-female differences were found.

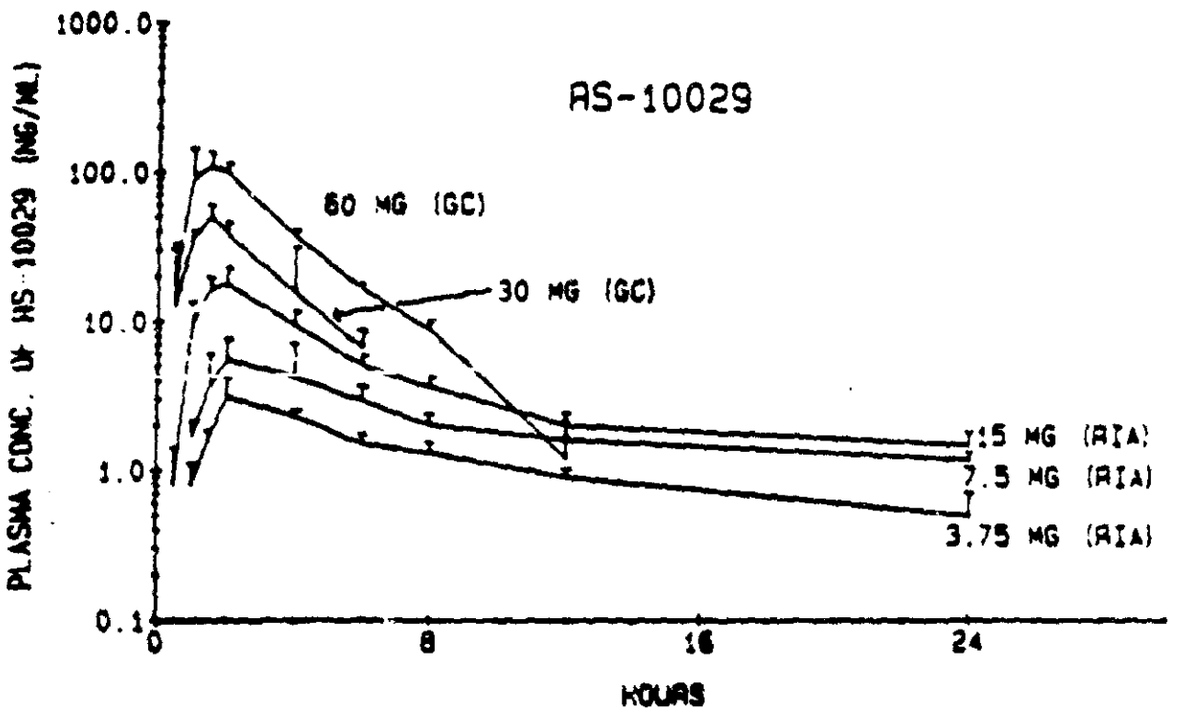
Conclusion: The moexipril and moexiprilat plasma concentrations appeared to increase with increase in dose. Moexipril in single doses of 15, 30 and 60 mg appeared to be more effective than placebo in reducing blood pressure.

FIGURE 1

MEAN SUPINE DIASTOLIC BLOOD PRESSURE – (PLACEBO DOSES COMBINED) – ICM #1394







Mean plasma concentrations of RS-10085 and RS-10029 in hypertensive subjects after a single oral dose of RS-10085. Each value is the mean ± S.E. of data from 4 subjects.

FIGURE # 2

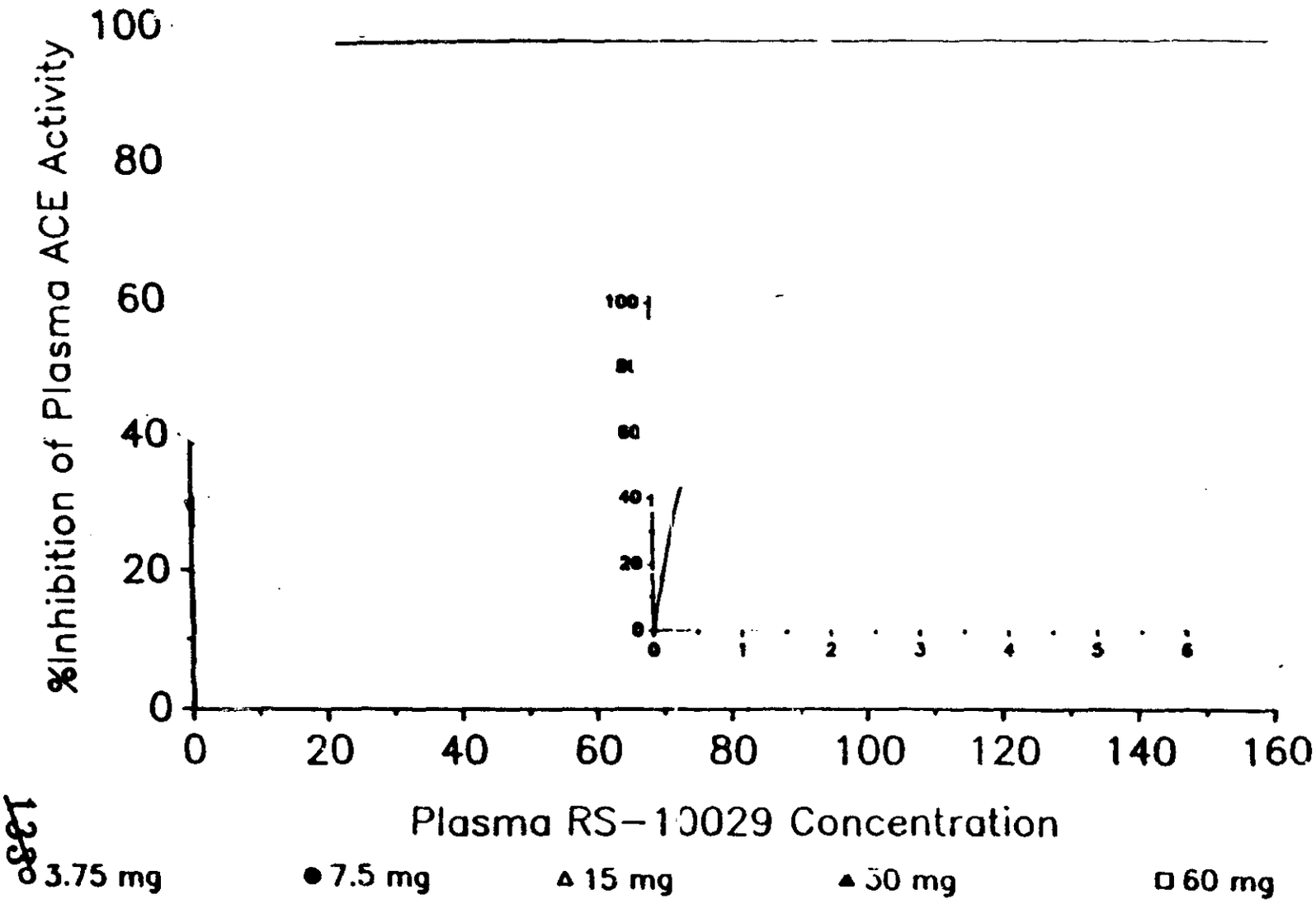
170

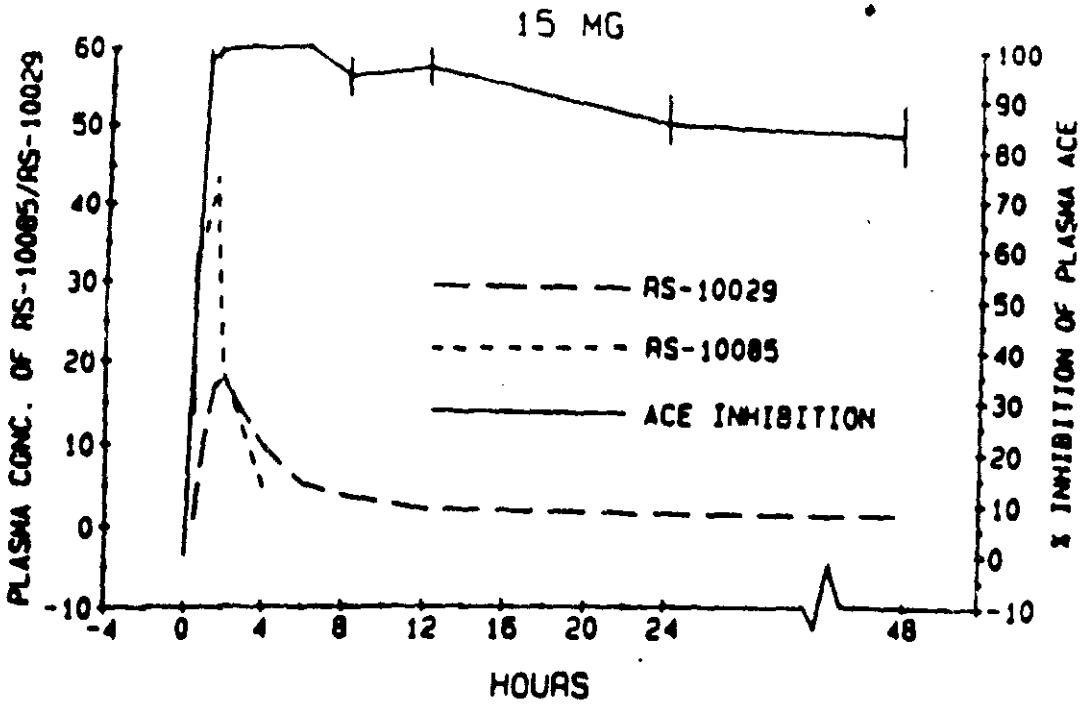
000196

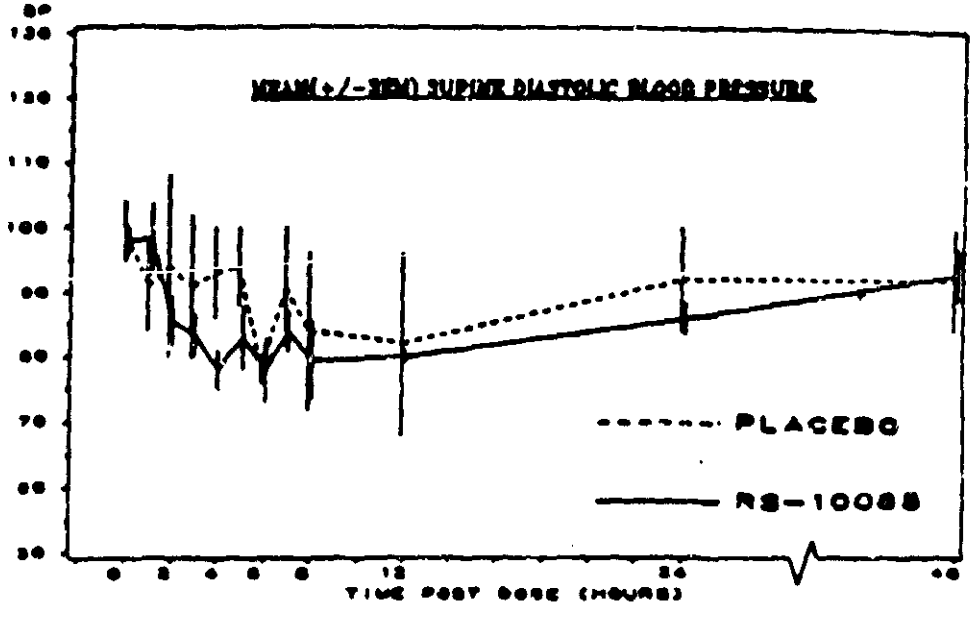
60

FIGURE 3

PERCENT INHIBITION OF PLASMA ACE ACTIVITY
COMPARED WITH RS-10029 CONCENTRATIONS







Plasma concentrations of RS-10029/RS-10085, % inhibition of plasma ACE activity (A) and supine diastolic blood pressures (B) for the 15 mg dose group as a function of time. Values are mean (or mean ± SE) of data from 4 subjects. Blood pressures for the placebo-treated subjects are mean values from 2 subjects.

FIGURE 4

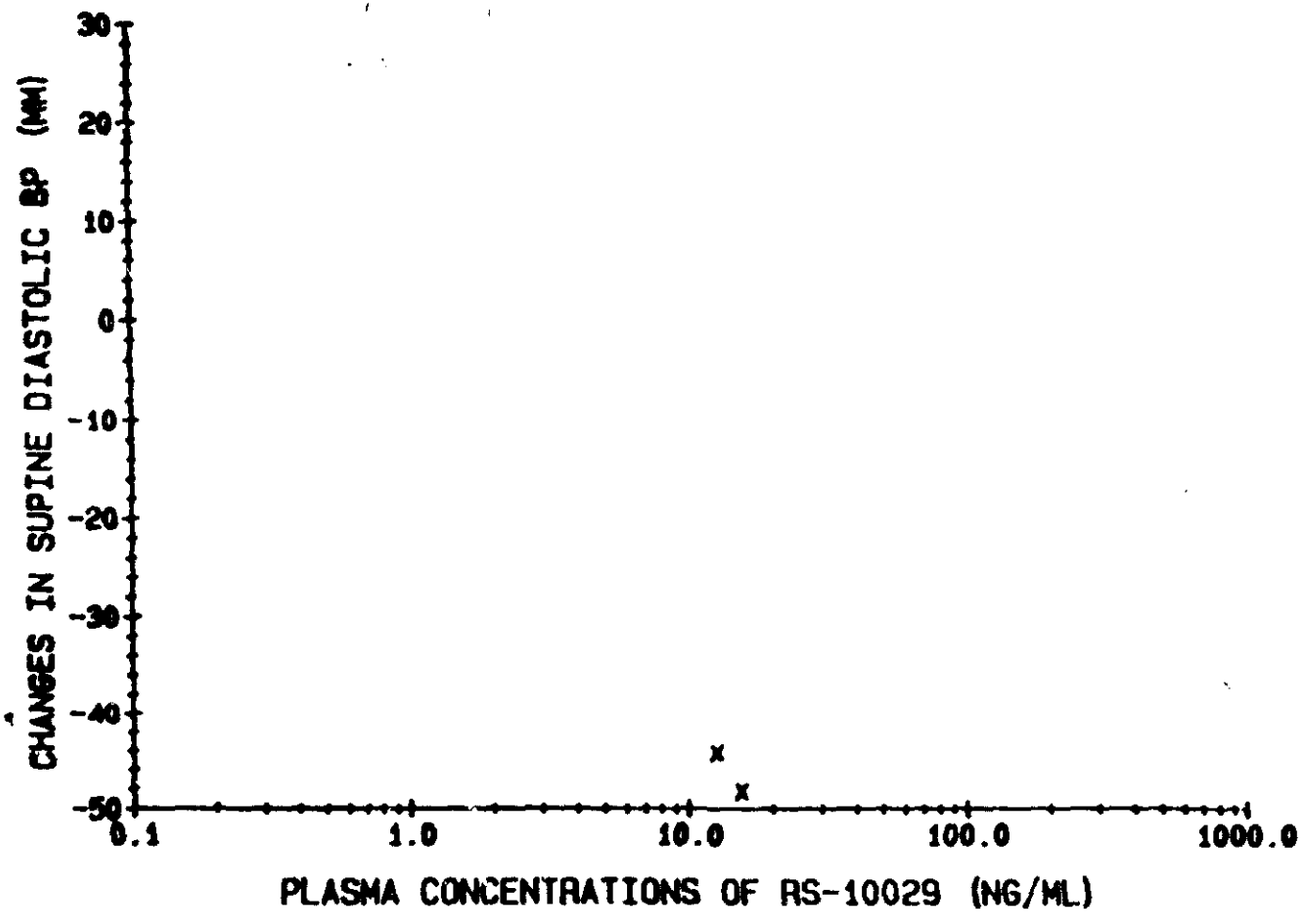


Fig. Correlation between changes in supine diastolic blood pressure with plasma concentrations of RS-10029 in hypertensive subjects treated with 3.75 to 60 mg oral doses of RS-10085.

FIGURE 5

EP 102000

Single Rising Dose Proportionality Study in Patients

Study No. 925-346 (CL4010) Volume: 1.72 Page: 1-96
Investigator and Site:

Outside Investigators:

Objectives: To determine plasma concentration of moexipril and moexiprilat, following single rising doses of moexipril administered in a stepwise fashion in mild to moderate hypertensive subjects.

Study Subjects: 25 mild to moderate hypertensive volunteers (8 females, 17 males). All antihypertensive medications were discontinued two weeks prior to receiving moexipril. None of the volunteer had any significant hepatic, renal or heart disease.

Study Design: Non-blind single rising dose study. The rising doses of moexipril were administered two days apart. All doses were administered with 180 ml of water. Subjects fasted overnight and 2 hr post dose.

Formulations: Capsule batch # 225113 - 1 mg moexipril, batch # 226113 - 2 mg, batch 227113 - 4 mg, batch # 228113 - 7.5 mg, batch # 229113 - 15 mg, batch # CI-164094 - 30 mg, batch # 165094 - 60 mg, batch # 166094 - 120 mg.

Specimens: 10 ml, Blood, at predose, 2, 6, 12, 24 and 48 hr post-dose.

Assay: GC-ECD, method involved solid phase extraction (C18 column) followed by derivatization.
Specificity: Moexipril, moexiprilat and internal standard were resolved with no interference peaks. Standard curves were fitted with a second degree polynomial equation. Precision: Inter-day was 19.1% at 10 ng/ml and 2.6% at 1000 ng/ml for moexipril and 16.5% at 10 ng/ml and 4.6% at 1000 ng/ml for moexiprilat. Intraday precision was not reported.
Accuracy: Inter-day was 6% at 10 ng/ml and 0.001% at 1000 ng/ml for moexipril and 2% at 10 ng/ml and 2.1 % at 1000 ng/ml for moexiprilat. Intraday accuracy was not determined.

Data Analysis: This study combines three protocols viz. 925-3, 925-4 and 925-5. The study doses and individual patient demographic are summarized in appendix II along with the plasma concentrations of moexipril and moexiprilat in patients. The PD data was not provided.

Result and Discussion:

Dose (mg)	N[a]	Mean (%RSD) Plasma Concentrations (ng/ml)			
		2 Hr	6 Hr	2 Hr	6 Hr
1	2	*[b]	*	*	*
2	3	*	*	*	*
4	4	*	*	*	*
7.5	4	*	*	*	*
15	4	*	*	16.3 (49%)	*
30	5	155 (68%)	*	60.2 (94%)	*
60	15	158 (70%)	5.8 (105%)	168 (75%)	25.8 (78%)
120	10	144 (72%)	21.5 (116%)	240 (50%)	34.0 (61%)

[a] N = Number of subjects receiving indicated dose.

[b] * = Mean not calculated since most subject values were below the quantifiable limit of the assay.

Moexipril: Mean concentrations were not determined for doses less than 30 mg since most values were below assay LQL. The mean post dose plasma concentrations for 30, 60 and 120 mg doses did not increase with increase in dose. Most of 12, 24 and 48 hr levels were lower than assay LQL and not considered.

Moexiprilat: Mean 2 hr plasma concentrations in the dose range 15 to 120 mg increased with increasing dose. 12 hr post dose concentrations were measurable in some patients over entire dose range of 1 to 120 mg but were not dose related. The 24 and 48 hr concentrations were lower than assay LQL.

Study showed considerable interpatient variability also it is not clear from this study design, whether lack of conclusive dose proportionality is due to intra-patient variability.

Conclusion: The mean moexiprilat concentrations were variable but generally increased with increasing doses of moexipril.

Multiple dose study

Study No. 925-2 Volume 1.104 Pages 1- 120
INVESTIGATORS AND SITE:

Objectives: To investigate the pharmacokinetics of moexipril and its active metabolite moexiprilat following multiple dose regimens in healthy volunteers.

Study Design: Subjects were randomly assigned in double blind fashion to one of the four treatment groups shown in the following scheme:

Treatment Group	(Subjects)	Moexipril Dose (mg)
1	(4, 8, 9, 16)	30
2	(1, 6, 11, 14)	60
3	(2, 7, 10, 13)	120
4	(3, 5, 12, 15)	Placebo

Single doses were administered on Days 1 and 15. Doses were administered twice daily on Days 2 through 14. All doses were administered with 180 ml of water. Subjects were required to fast ovenight prior to dosing on Days 1, 5, 8, 11 and 15 and remained fasted for two hours postdose on Days 5, 8 and 11 and four hours postdose on Days 1 and 15.

Subject characteristics: Sixteen healthy volunteers (4 females, 12 males) whose mean age and body weight were 37 years and 79.4 kg, respectively, participated in the study conducted at the . All subjects had normal laboratory profiles and physical examinations.

Specimens: Ten ml blood samples were drawn into hepannized tubes, centrifuged and the plasma separated and stored frozen prior to assay of moexipril and moexiprilat. Samples were drawn prior to dosing (pre-Rx) and at 1, 2, 3, 4, 6, 8, 10, 12, 24, 48 and 72 hours following the single doses on Days 1 and 15 and prior to dosing and 2 hours postdose on Days 5, 8 and 11. Twenty-four hour urine samples were collected on Days 1, 2, 3, 15, 16 and 17, the total volume recorded, and a 20 ml aliquot frozen and stored for subsequent assay of moexiprilat and moexiprilat.

Assay: Moexipril and moexiprilat plasma and urine concentrations were measured using a sensitive, specific and validated GC method with electron capture detection.

Analytical Method-Plasma
Specificity: No major interference peaks were observed eluting with moexipril or moexiprilat.
Sensitivity: The lower limit of detection of moexipril and moexiprilat was 10 ng/ml. Concentrations below this limit were not included in parameter calculations.
Linearity: Standard curves of moexipril and moexiprilat were fitted with a second-degree

polynomial equation within the working range of the assay, 10-1000 ng/ml.
Reproducibility: Interday precision of the assay standards ranged from 3.2 to 20.3% with a mean of 10% for moexipril and 2.0 to 20.3% with a mean of 12% for moexiprilat. Accuracy was not determined.

Analytical Method-Urine
Specificity: No major interference peaks were observed eluting with moexipril or moexiprilat.
Sensitivity: The lower limit of detection of moexipril and moexiprilat was 50 ng/ml. Concentrations below this limit were not included in parameter calculations.
Linearity: Standard curves of moexipril and moexiprilat were fitted with a second-degree polynomial equation within the working range of the assay, 50-1000 ng/ml.
Reproducibility: Interday precision of the assay standards ranged from 3.0 to 30.9% with a mean of 14% for moexipril and 1.8 to 20.7% with a mean of 12% for moexiprilat. Accuracy was not determined. Intra day precision was 43% at 300 ng/ml and 3.7% at 6000 ng/ml for moexipril and 40.2% at 300 ng/ml and 4.9% at 6000 ng/ml for moexiprilat.

Data analysis:
Since this study had very small sample size, only Day 1 to Day 15 comparison for Cmax, $AUC_{0-\infty}$ and terminal elimination rate constant was carried out.

Results: Individual and mean moexipril and moexiprilat Cmax, tmax, $AUC_{(0-\infty)}$, λz and $Ae_{(0-24)}$ values along with plasma concentration profiles are attached in appendix II. Mean profiles were not submitted by the sponsor. Comparison of moexipril and moexiprilat parameter values (mean $\pm$ sd) are shown below.

	Moexipril		Moexiprilat	
Cmax (ng/ml)	Day 1	Day 15	Day 1	Day 15
30 mg	122±55.6	84±24.2	80±42.7	75±41.6
60 mg	92.2± 55.6	117±52.7	79.6±29.9	124±73.3
120 mg	197.1±128.4	221.5±142.6	217.2±70.4	221.5±56.9
$AUC_{0-\infty}$				
30 mg	224.3±41.3	156.7±64.8	254.2±153.4	205.5±110.1
60 mg	107.4±26	246.6±18.5	244.5±96.7	418.7±206.3
120 mg	458.7±196.9	375±165	652.5±314.4	755.5±232

Comparison of individual elimination half life on day 1 and 15 did not show any difference. It appears that accumulation of moexiprilat was not significant at dose 120 mg BID. However, less than proportional incxrease in Cmax and $AUC_{0-\infty}$ was seen with increase in the dose in this parallel design study.

Because of the small number of patients in each treatment group and the variability in the

data, definitive assessment of the dose-dependency of moexipril and moexiprilat Cmax and $AUC_{0-\infty}$ was not possible.

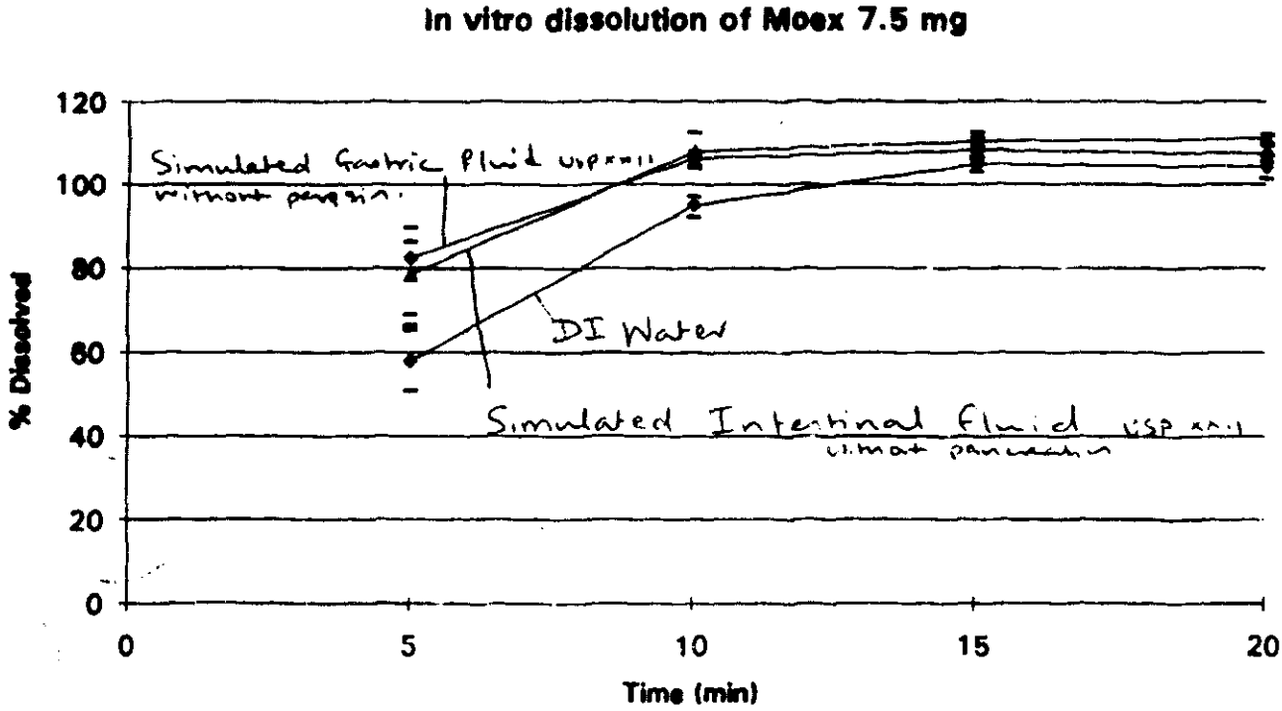
Small amounts of moexipril and moexiprilat relative to dose were excreted in the urine. No dose dependency was observed for either moexipril or moexiprilat values. The mean Ae^{0-24} values were 1.35% for moexipril and 5.9% for moexiprilat.

Conclusion: Accumulation of moexiprilat was not seen in subjects with a high dose of 120 mg moexipril BID.

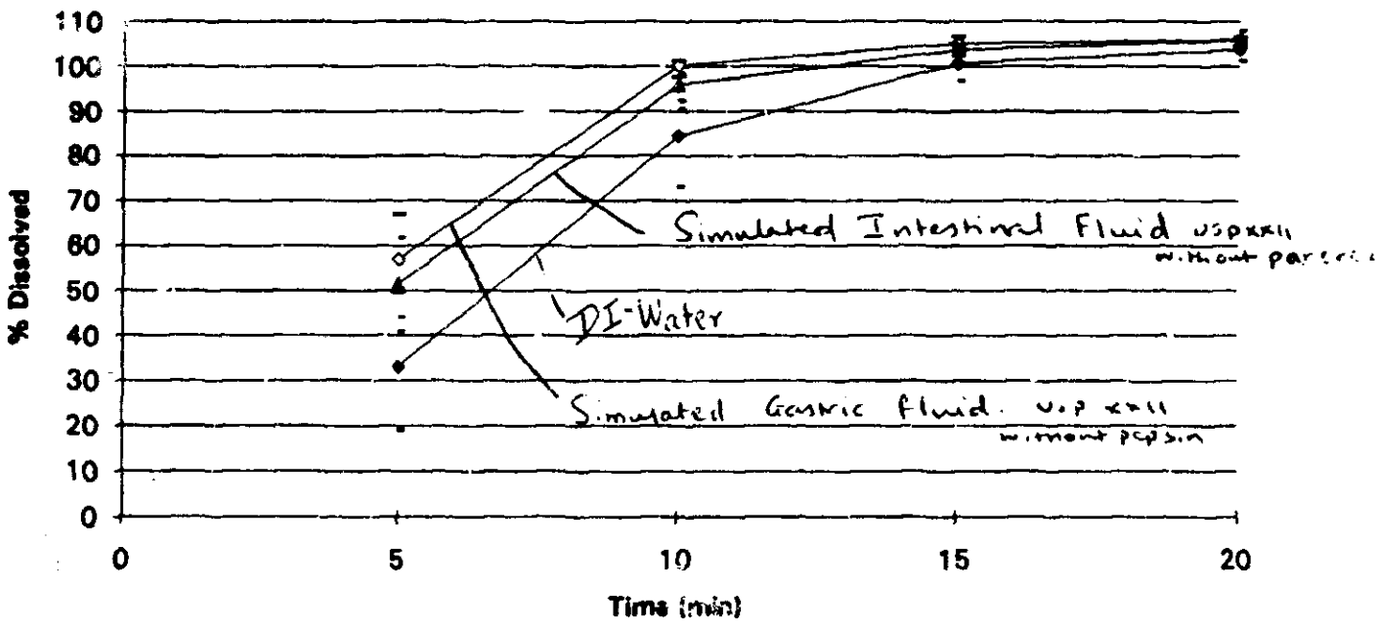
In vitro Dissolution of Moex™ Tablet

Apparatus:	USPXXII, <711>, apparatus II (paddle).
Dissolution Medium:	Deionized and degased water of 37°C and 900 ml.
Paddle speed:	50 rpm
No. of units:	6

The dissolution apparatus was combined with a UV spectrometer with flow through cuvettes. The dissolution medium from the 6 vessels was pumped through the cuvettes in a 5 minutes interval. After recording the absorption at 280 nm, the medium was repumped into the vessels. Thus, the absorption of the samples was recorded over a time period of 5 to 30 min. Similar procedure was also followed for dissolution in simulated gastric and intestinal fluids. These simulated mediums were prepared according to USP XXII specifications, except the enzymes.


In vitro dissolution of Moex 7.5 mg
120
100
80
60
40
20
0
% Dissolved
0
5
10
15
20
Time (min)
Simulated Gastric Fluid USP XXII
without pepsin
DI Water
Simulated Intestinal Fluid USP XXII
without pancreatin

In vitro dissolution of Moex 15 mg



ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-312

UNIVASC™ Tablets

(moexipril hydrochloride)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-312

UNIVASC™

(moexipril hydrochloride)

Tablets

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 **UNIVASC™ Tablets**, **SCHWARZ PHARMA Kremers Urban 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.

Moexipril Hydrochloride is a synthetic drug which is administered as an oral tablet in the treatment of hypertension. The drug substance will be manufactured at SIFA LTD, Shannon Co. Clare, Republic of Ireland or Orgamol SA, Evionnaz, Switzerland. The drug product is manufactured at SCHWARZ PHARMA AG, Monheim, Germany and packaged at SCHWARZ PHARMA Kremers Urban Company, Mequon, Wisconsin or other locations identified in the environmental assessment. The finished drug product will primarily be used by patients in their homes.

Moexipril hydrochloride is rapidly metabolized to the active form, moexiprilat. Moexipril hydrochloride, moexiprilat and other minor unidentified metabolites will be excreted predominantly into publicly owned treatment works (POTW). Chemical and physical test results and information indicate that the structurally related substances will most likely be restricted to the aquatic environment.

As the drug substance and metabolites are expected to persist in the aquatic environment for some time, toxicity studies were conducted. Acute toxicity studies in water fleas (*Daphnia magna)* performed, using both moexipril hydrochloride and moexiprilat, indicate that the compounds are not toxic at concentrations of at least 7 orders of magnitude greater than the maximum expected environmental concentration.

Microbial inhibition studies indicate that there is no adverse effect on microorganisms at concentrations of at least 7 orders of magnitude greater than the maximum expected environmental concentration. No adverse effects on waste water treatment processes are anticipated.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, pharmaceutical processing waste, and user disposal of empty or partly used product and packaging. Waste drug product and pharmaceutical processing waste in the U.S. will be disposed of predominantly at licensed incineration facilities. From patient use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used 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. SCHWARZ PHARMA AG has received authorization from the appropriate authorities to operate their manufacturing facilities and has provided certification that operation is in accordance with applicable German environmental regulations.

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.

3/21/95 Nancy B Sager
DATE Prepared By
Nancy B. Sager
Review Chemist
Center for Drug Evaluation and Research

3/29/95 Phillip G Vincent
DATE Approved
Phillip G. Vincent, Ph.D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

3/30/95 Robert A. Jerussi
DATE Concurred
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments:

I: Environmental Assessment
II: Material Safety Data Sheet (drug substance)
III: Compliance Statements
IV: German Government Certification/SCHWARZ PHARMA AG
V: Swiss Government Statement/Orgamol Ltd.

ATTACHMENT I

NEW DRUG APPLICATION 20-312
ENVIRONMENTAL ASSESSMENT REPORT
MOEXIPRIL HYDROCHLORIDE TABLETS

ITEM 1: DATE

March 2, 1995

ITEM 2: NAME OF APPLICANT

SCHWARZ PHARMA Kremers Urban Company

ITEM 3: ADDRESS

5600 West County Line Road
Mequon, Wisconsin 53092

ITEM 4: DESCRIPTION OF THE PROPOSED ACTION

a. Requested Approval

SCHWARZ PHARMA Kremers Urban Company (SPKU) in this proposed action seeks FDA approval for tablet manufacture, packaging and for the marketed use of drug products designated as UNIVASC™ (moexipril hydrochloride) 7.5 mg and 15 mg tablets as described in this environmental assessment. The drug substance discussed in this proposed action is moexipril hydrochloride (moexipril HCl), with its active metabolite known as moexiprilat.

SCHWARZ PHARMA Kremers Urban Company submits this official public version of this Environmental Assessment as part of the New Drug Application (NDA 20-312) for UNIVASC™ (moexipril HCl) tablets with the format arranged in accordance with 21 CFR 25.31(a). Confidential supporting documents for this environmental assessment (EA) have been organized in appendices 1 to 9 in Item 15. Published literature citations related to the drug substance moexipril hydrochloride and active metabolite, moexiprilat, have been organized in Item 14. Additional nonconfidential supporting documents for items discussed in this EA were organized as appendices 10 and 11 in Item 15.

ITEM 4: DESCRIPTION OF THE PROPOSED ACTION (cont.)

b. Need for Action

The proposed action will provide a new antihypertensive drug product indicated for patient use in the treatment of hypertension, alone or in the combination with thiazide diuretics. The principal pharmacological action of moexipril and its active metabolite, moexiprilat, is an inhibition of angiotensin-converting enzyme (ACE) in humans. The mechanism of action through which moexiprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Inhibition of ACE results in a decrease in plasma angiotensin II, which leads to decreased vasoconstriction, as well as to small decreases in aldosterone secretion and plasma aldosterone concentrations. The latter results in diuresis and natriuresis playing a therapeutic effect in the blood pressure reduction by moexiprilat through the renin-angiotensin-aldosterone system. During chronic therapy, the antihypertensive effect of any dose of moexipril HCl generally had a maximal reduction over 2 to 4 weeks. The antihypertensive effects were further shown in controlled clinical trials to continue during therapy for up to 24 months indicating that moexipril HCl is a highly effective long-term therapy for treatment of hypertension patients

c. Production Locations

As described in the proposed action for this drug product, SPKU proposes to have moexipril HCl drug substance manufactured by SIFA LTD. at their facility in Shannon, Ireland and, Orgamol SA at their facility in Evionnaz, Switzerland (Suisse). The finished bulk drug product, moexipril HCl tablets, will be manufactured by SPKU's parent company, SCHWARZ PHARMA AG (SPAG), at their facility in Monheim, Federal Republic of Germany.

Drug Substance Manufacturer

SIFA LTD.
Shannon Industrial Free Zone
Shannon Co. Clare
Republic of Ireland

Sifa Ltd. is located in the Shannon Industrial Estate adjacent to Shannon town in County Clare, Ireland. Shannon is located on the west central coast of Ireland. The main production plant was built in 198., and it is located within an industrial estate comprising various business enterprises. It is also bordered by an airport runway(s) and farmland. The company is situated in a flat region with temperate climate and urban surroundings consisting

ITEM 4: DESCRIPTION OF THE PROPOSED ACTION (cont.)

c. Production Locations (cont.)

Drug Substance Manufacturer (cont.)

of mixed residential, commercial and industrial area adjacent to the site. Administrative, manufacturing and warehousing operations are conducted on site. One hundred and seventeen (117) employees work at Sifa's Ltd facility.

Orgamol SA
CH-1920 Evionnaz
Switzerland (Suisse)

Orgamol SA is located in Evionnaz near Martigny, in the Canton Valis, Switzerland. The site is situated on the base of the Rhone valley in an industrial zone outside the village of Evionnaz. The surrounding area is designated as industrial area. The plant is close to the highway Lausanne/Simplon (Sion) and the facilities are built on the left and the right side of the Route Cantonal. Orgamol SA consists of two main factories each of which is subdivided into three plants. The company is situated in a mountainous region with temperate climate and rural surroundings. Manufacturing and quality control activities are conducted on this site. Two hundred and thirty (230) employees work at Orgamol SA's Evionnaz facility of whom 100 are involved in manufacturing etc., and 22 in quality control .

Drug Product Manufacturer

SCHWARZ PHARMA AG
D-40789 Monheim
Germany

SPAG is located in Monheim between the cities Dusseldorf and Cologne, State of North Rhine Westfalia. The company is situated in a flat region with temperate climate and urban surroundings. The production and quality control activities are conducted at Monheim Mittelstraße. Mixed residential and commercial areas are adjacent to this facility. About one hundred eighty (180) employees work at this facility. Administrative and warehousing operations are conducted at Monheim Alfred-Nobel-Straße. The surrounding area is designated as industrial area. Mixed residential, commercial and industrial areas are adjacent to the site. Five hundred and twenty-six (526) employees work at this facility.

ITEM 4: DESCRIPTION OF THE PROPOSED ACTION (cont.)

c. Production Locations (cont.)

Drug Product Manufacturer (cont.)

SCHWARZ PHARMA AG (cont.)

After importation of the finished bulk drug tablets into the United States of America (USA), SPKU will package the drug product at their facility in Mequon, Wisconsin, in bottles and have the blister packaging contracted out.

Drug Product Packaging

Packaging in Bottles

SCHWARZ PHARMA
Kremers Urban
5600 W. County Line Rd.
Mequon, WI 53092

SPKU's County Line facility is located in Mequon, Wisconsin approximately five (5) miles from the western shore of Lake Michigan and 10 miles north-northwest of downtown Milwaukee. Mixed residential, farming, commercial and industrial areas surround this facility. Administrative, manufacturing, packaging and warehousing are located on this site. Three hundred and seventy-five (375) employees are employed by SPKU. One-hundred and eighty-three (183) employees work in administrative, manufacturing including quality assurance, packaging and distribution operations at the Mequon facility.

Packaging in Blisters

Anderson Packaging, Inc.
4545 Assembly Drive
Rockford, Illinois 61109

Anderson Packaging's assembly drive facility is located approximately 1 mile north of Rockford Airport and 0.30 miles south of U.S. Route 20 (bypass) and approximately 6.25 mile from the I-90 tollway on 8 acres of land in the Southeast section of the City of Rockford, Rockford Township, Winnebago County, Illinois. Rockford, Illinois is located 65 miles west of Chicago's O'Hare Airport. Mixed residential, commercial and industrial areas surround this facility located in the Greater Rockford Industrial Park.

ITEM 4: DESCRIPTION OF THE PROPOSED ACTION (cont.)

c. Production Locations (cont.)

Drug Product Packaging (cont.)

Packaging in Blisters (cont.)

Anderson Packaging, Inc. (cont.)

Administrative, packaging and warehousing activities are located on this site. Two hundred and eighty-seven (287) employees work at Anderson's Rockford facility.

Sharp Packaging
Ridge Pike and Carland Road
Conshohocken, PA 19428

The Sharp Packaging Corporation plant and offices are located at Ridge Pike and Carland Road, Conshohocken, Pennsylvania. Conshohocken is situated in a suburban area north-northwest of the city of Philadelphia. The facility is located in an area zoned for light industrial and commercial businesses. There are 2 buildings with the original building constructed in 1952. Processing, packaging and warehousing are located on this site in one building with the other building used for production and storage of packaging materials and printed components. Four hundred and forty-eight (448) employees work at Sharp's Conshohocken facility.

Packaging Coordinators, Inc.
"K" Street and Erie Avenue
Philadelphia, PA 19124

The Packaging Coordinators, Inc. plant is located in the City of Philadelphia, Pennsylvania. The site is located ten (10) minutes from downtown Philadelphia and twenty (20) minutes from the Philadelphia National Airport. The site consists of a four story building with the packaging and administrative offices located on the site. The area is surrounded by light industry, commercial establishments and mixed residential communities. The main facility was built in 1930. Four hundred and fifty employees (450) work at the Philadelphia facility.

ITEM 4: DESCRIPTION OF THE PROPOSED ACTION (cont.)

d. Locations of Use

Moexipril HCl will be prescribed as a medication for the treatment of hypertension and will be ingested orally and eliminated at random times and in random locations wherever a patient may spend his/her day. The elimination or excretion of amounts of moexipril HCl is expected to enter local municipal wastewater treatment systems across the USA.

Adherence to CMP regulations, prior to disposal of cleaning fluids used to washdown equipment utilized during packaging operations, is expected before discharge into the drains of the Mequon facility and discharged into the wastewater treatment of the Milwaukee Metropolitan Sewerage District. Materials collected during the cleaning process, bulk manufacturing wastes, and packaging operation wastes will be drummed and labeled in accordance with local statutes and state of Wisconsin Regulations, including transportation laws, and incinerated by the EPA-permitted waste contractor BFI/American Ref-Fuels, Westbury N.Y. Adherence to local laws and regulations is found in the SPKU Compliance Statement in Appendix 7. Any other materials that are nonaqueous, solid including out of specification material or any drug product materials used for laboratory testing will be collected and drummed prior to being shipped to and incinerated by the EPA-permitted waste contractor.

Returned, rejected or expired moexipril HCl will be returned to SPKU where it will be drummed, classified for transportation manifest and transported to the BFI/American Ref-Fuels facility in Westbury, N.Y.(Governmental Permit #2820005643 for air; #30E06 for solid waste).

Materials from contract packagers for the blister packaging of drug product that are considered waste drug product, broken tablets, rejected filled blister cards, residual product dust or floor sweepings that contain drug product will be returned to SPKU where it will be drummed, classified for transportation manifest and transported to the BFI/American Ref-Fuels facility in Westbury, N.Y. Solid wastes that consist of non-hazardous plastic, paperboard, aluminum foil and other waste packaging materials of similar composition will be disposed of or recycled depending on the local and state of Illinois and Commonweath of Pennsylvania Regulations, and availability of recycling facilities located near the facilities. Refer to Appendix 7 for detailed descriptions of waste disposal for the contract packagers, Anderson Packaging, Sharp Packaging and Packaging Coordinators, Inc.

ITEM 4: DESCRIPTION OF THE PROPOSED ACTION (cont.)

e. Disposal Sites

BFI/American Ref-Fuels Facility
as a joint venture between Browning-Ferris, Inc. Houston, TX and
Air Products and Chemicals, Inc., Allentown, PA
600 Ave. C at Stewart Ave.
Westbury, NY 11590

The BFI/American Ref-Fuels Hempstead Resources Recovery facility is located in the northeast corner of Mitchel Field near the Town of Hempstead, New York and is bordered by the Meadowbrook Parkway to the west, Stewart Avenue to the south, a Federal Aviation Administration facility to the east, and Roosevelt Raceway to the north. This area is characterized by high-rise commercial offices, light industrial facilities, educational campuses, transportation corridors, and large-scale recreational facilities including the Nassau Coliseum and a major hotel. Outside the Mitchel Field area proximate land uses include retail commercial development, County park land, and over one-half mile to the east, single-family residences. This facility receives and incinerates approximately 2300 tons per day of residential, commercial and industrial wastes. The waste from the SPKU Mequon facility is subject to waste characterization (returned or rejected drug product) and is handled by Federal and/or state standards or other labeling of special handling. Approved items from the waste characterization manifest are shipped to the Westbury, NY site for destruction by incineration. The incineration process creates electricity which powers nearly 65,000 homes in Hempstead Township, New York. Gases resulting from the mass burn technology and coupled with Best Available Control Technology for air abatement during the incineration process are subject to a series of semi-wet and dry scrubber. The scrubbers are designed to provide for 70% SO_2 removal and 90% + HCl removal. Particulate capture has been shown to be of 0.00206 gr/dscf @ 12% CO_2 in recent testing.

Refer to Appendix 1 for the activities of the different sites involved in the manufacture of Moexipril HCl Tablets.

Refer to Appendices 2 and 3 for letters of authorization and for additional descriptions of the environments surrounding the facilities described in the proposed action.

Refer to Appendix 7 for the EA statements for SIFA LTD., Orgamol SA, SPAG, SPKU, Anderson Packaging, Sharp Packaging and Packaging Coordinators, Inc. for additional information.

Refer to Appendix 7 for the description of the high temperature incinerator used at BFI/American Ref-Fuels facility for the disposal of drug product waste.

ITEM 5: IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

a. Nomenclature - moexipril hydrochloride (moexipril HCl)

i. Established Name (U.S. Adopted Name-USAN)

moexipril hydrochloride

ii. Brand/Proprietary Name:

UNIVASC ™

iii. Chemical Name:

1. Chemical Abstracts (CA) Index Name
3-isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride [3S-[2[R*(R*)],3R*]]-(9CI)

2. USAN (Systematic Chemical Name)
[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy -3-isoquinolinecarboxylic acid, monohydrochloride

3. IUPAC Name
(3S)-2-[(2S)-2-{(1S)-1-Carboxy-3-phenyl-propylamino}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

b. CAS Registry Number 82586-52-5

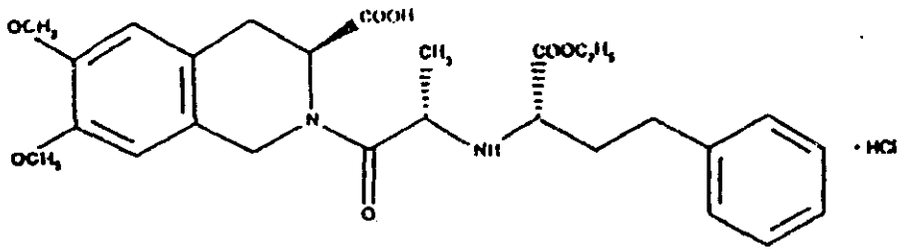
Code Designations RS-10085-197; CI-925; SPM-925; 103775-10-6

c. Molecular Formula $C_{27}H_{34}N_2O_7 \cdot HCl$

d. Molecular Weight 535.04 daltons

ITEM 5: IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION (cont.)

e. Structural Formula



f. Physical Description fine, white to off white powder

g. Nomenclature - moexiprilat (active metabolite of moexipril hydrochloride)

i. Established Name (U.S. Adopted Name-USAN):

moexiprilat

ii. Brand/Proprietary Name:

Not applicable (UNIVASC™, tradename of moexipril HCl)

iii. Chemical Name:

1. Chemical Abstracts (CA) Index Name
   3-Isoquinolinecarboxylic acid, 2-[2-[(1-(carboxy)-3-phenylpropyl])&amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, [3S-[2[R*(R*)], 3R*]-(9CI)

2. USAN (Systematic Chemical Name)
   (3S)-2-((2S)-N-((1S)-1-Carboxy-3-phenylpropyl)alanyl) 1,2,3,4-tetrahydro-6,7, dimethoxy -3-isoquinolinecarboxylic acid

h. CAS Registry Number 103775-14-6

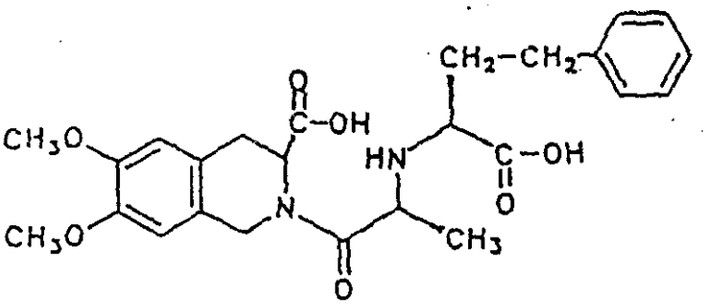
Code Designations RS-10029; SL-No.:202977

ITEM 5: IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION (cont.)

i. **Molecular Formula** $C_{25}H_{30}N_2O_7$

j. **Molecular Weight** 460.53 daltons

k. **Structural Formula**



l. **Physical Description** fine, white to off white powder

m. **Additives**

The excipients of the drug product are the only identified additives. Refer to Appendix 4 for list of excipients.

n. **Impurities**

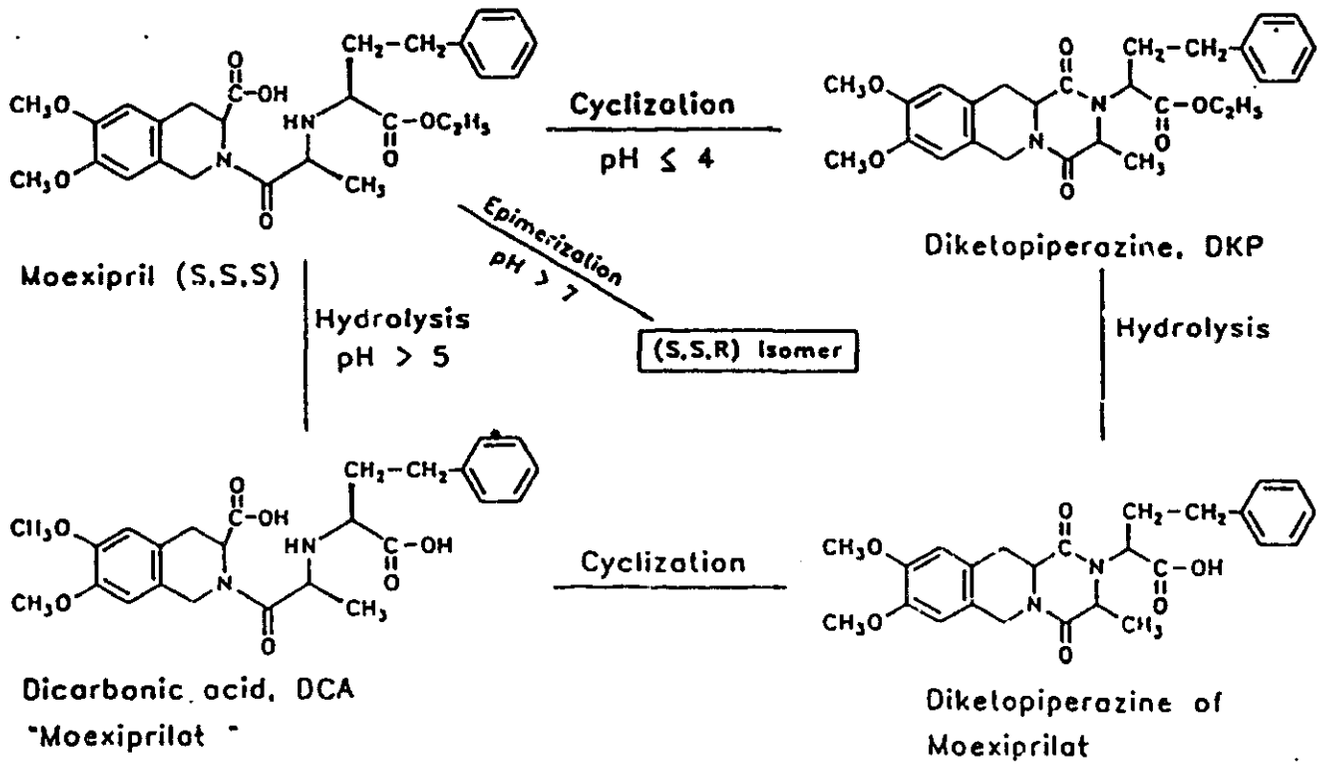
Figure 1, shows the structure of moexipril and the two chemicals, moexiprilat and diketopiperazine (DKP) which are degradation products that are formed when the drug substance is influenced by oxygen, humidity, temperature, light or altered pH.

The degradation product moexiprilat results from hydrolysis of the ethyl ester group in moexipril and is the major excretory moiety of this drug. The third chemical, DKP, has been detected as a minor metabolite in human urine. Diketopiperazine is additionally known as an impurity in the cyclization product from the synthesis of moexipril HCl.

The total quantity of detected impurities in any acceptable batch of bulk drug substance is less than 1 percent. The total quantity of any single impurity, moreover, does not exceed 0.5%.

Figure 1.

MECHANISM OF DIKETOPIPERAZINE (DKP) FORMATION FROM MOEXIPRIL



ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

a. Substances Expected to be Emitted

i. Introduction Due to the Manufacture of the Drug Substance, Moexipril HCl

A list of substances expected to be emitted during the drug substance manufacture is provided. Letters of authorization for moexipril HCl from SIFA LTD. and Orgamol SA are located in Appendix 2. Additional supportive documents are listed below:

1) Residual Substances Expected to be Entering the Environment During Drug Substance Manufacture Appendix 8

2) Environmental Impact Analysis prepared by SIFA, LTD. Appendix 7

3) Government certification for Orgamol SA Appendix 7

4) General Compliance Statement SIFA LTD. Appendix 7

5) General Compliance Statement Orgamol SA Appendix 7

During the production of the drug substance, pollution of air and water is controlled according to environmental protection laws in Ireland and Switzerland. Their respective governments attest to the compliance with the applicable regulations.

ii. Introduction Due to the Manufacture of the Drug Product, Moexipril HCl Tablets

The manufacture of the drug product will take place in SPAG facility in Monheim, Germany. The estimated fifth-year (1999) production for moexipril tablets is located in Appendix 8.

Enclosed in Appendix 7 are the following documents to support the control of substances released to the environment and compliance statements in the manufacture of the drug product in accordance with applicable Federal Republic of Germany, State and Local Regulations:

ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT (cont.)

a. Substances Expected to be Emitted (cont.)

ii. Introduction Due to the Manufacture of the Drug Product, Moexipril HCl Tablets (cont.)

1) SCHWARZ PHARMA AG Environmental Assessment covering Introduction of Substances into the Environment.

2) SCHWARZ PHARMA AG Statement of Compliance assuring compliance with applicable laws and regulations.

3) Letter regarding the SCHWARZ PHARMA AG facility and operations from the German agencies with translation and certification of signature of translation.

Particulate control devices for the collection of dust during the tablet manufacture process assure dust is absorbed into filters. Based on the high efficiency (99%) of these filters, in accordance with German regulations, emissions expected during the fifth year of production which represent only traces of the drug product are located in Appendix 8.

iii. Introduction Due to the Packaging Operations of Moexipril HCl

Normal packaging operations at SPKU facility in Wisconsin generate a minimal amount of tablet "dust" which is collected by the local dust extraction and collection system in the packaging areas. The normal tablet "dust" will be substantially minimized for moexipril hydrochloride, because the product is film coated.

Upon approval of the proposed action, SPKU anticipates packaging 7.5 mg and 15 mg moexipril HCl tablets (refer to Appendix 8 for fifth year sales figures). This sales figure represents the year of highest projected sales. Given this estimate of volume, and the friability of the product, an estimation of "tablet dust" generated per year by packaging operations would range from _ of moexipril hydrochloride (see calculations in Appendix 8). Because this product is film coated, it is anticipated that the dust shed in packaging would be minimal. The _ . ar figure reflects the maximum potential environmental introduction due to normal patient use and/or normal disposal of the products, of product handling, and the possibility of breakage during processing. This tablet dust will be collected and sent to BFI/American Ref-Fuels for disposal by incineration.

ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT (cont.)

a. Substances Expected to be Emitted (cont.)

iii. Introduction Due to the Packaging Operations of Moexipril HCl (cont.)

In addition to the collection of tablet dust, air emitted from these packaging operations will be cleaned with filters before being vented into the atmosphere. The particulate matter from this dust collection system will also be collected and sent to BFI/American Ref-Fuels for disposal. Finally, residual amounts of moexipril HCl would be expected to remain on the packaging equipment prior to cleaning. Cleaning processes would be expected to remove these residual amounts, and be flushed down the Mequon facility drains. This would then enter the greater Milwaukee Metropolitan Sewerage District sewer system for disposal through wastewater collection system in any of the wastewater treatment plants, and be diluted to so low a concentration as to have a negligible impact on the ecosystem.

iv. Introduction of Moexipril HCl and its Metabolites from Biological Systems into the Environment:

Moexipril is relatively rapidly converted to its active metabolite moexiprilat. Following oral administration of moexipril, peak plasma concentrations of moexipril are reached between 0.75 hours and 1.5 hours. The elimination half-life of moexipril is a little over 1 hour, while that of moexiprilat is estimated to be 2 to 9 hours. Moexiprilat is about 50% protein bound. The bioavailability of moexipril is greater than 20%. After IV administration of moexipril, about 40% of the dose appears in the urine as moexiprilat, about 18 % as moexipril, and small amounts of the corresponding diketopiperazine derivatives and other unknown metabolites (3%, 1%; respectively). About 26% of the IV dose appears in feces, principally as moexiprilat. After oral administration, only about 7% of the dose appears in urine as moexiprilat, about 1% as moexipril, with about 5 % as other metabolites. More than 70% of the dose is recovered in feces as moexiprilat and 1% as moexipril (see Appendix 6, Powles and Ward, 1992; and Appendix 11). These residual amounts would be flushed down the toilet facility drains of patients across the USA. The fecal and urine byproducts would then enter the metropolitan sewer systems for disposal through wastewater collection system in any of the wastewater treatment plants, and to undergo degradation to so low a concentration as to have a negligible impact on the ecosystem.

ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT (cont.)

b. Controls Exercised

i. Controls Exercised in the Manufacture of the Drug Substance, Moexipril HCl

Trace air emissions of products used to manufacture the drug substance are removed by a local exhaust ventilation system and discharged via a scrubber stack under the local, state and federal regulations in Ireland and Switzerland. Additionally, trace emissions into the air are due to incineration of waste byproducts during chemical synthesis and monitored to ensure compliance or treated to meet compliance of emission limits

Any small to negligible volumes of wastewater discharge are monitored during the synthesis of the drug substance and neutralized and treated by a biological wastewater treatment plant.

Spent catalyst from the synthesis of the last steps of the drug substance may be returned to the supplier for precious metal recovery. Additionally, appropriate disposal of other synthesis wastes such as solvents, filters or residues are incinerated at approved incineration sites and listed in Appendix 3.

ii. Controls Exercised in the Manufacture of the Drug Product, Moexipril HCl Tablets

All drug product tablet manufacture waste, including powdered filter material, is collected through a series of local vacuum system pickups. The sources are connected for the collection of the tableting and granulation dust by high efficiency filters where a minimum of 99% of the product dust is collected and destroyed off-site by incineration as pharmaceutical waste in compliance with local, state and federal regulations in Germany.

In general, all drug product residuals are collected in a dry state and do not enter the wastewater treatment sewer system. Compliance with GMP procedure does require system washings from the manufacturing process equipment and cleaning, which collects negligible amounts of drug product which is discharged to the sewer system for treatment at a biologic wastewater facility as referenced in Appendix 7.

ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT (cont.)

b. Controls Exercised (cont.)

iii. Control Exercised in the Packaging Operations of the Drug Product

Air emissions both at the SPKU plant and at the contract packaging operations may include trace particles as a result of equipment handling of the drug product and bottle filling or blister packaging. Air filters and vacuum dust collection systems are installed to provide for a minimum of 90% to 99% control efficiency for these particulates. The filters are in general removed and incinerated at EPA permitted facilities.

Wastewater from the packaging operations generally consists of washouts of equipment and cleaning materials as collected during GMP standard operating procedures. Loose product residue may be removed by washings. If the washings contain spent tablets prior to disposal, the spent tablets are collected into solid waste containers to be drummed and incinerated. Municipal wastewater treatment facilities, included in the proposed action are Milwaukee Metropolitan Sewerage District in Milwaukee, Wisconsin; the Rock River Water Reclamation District's Treatment System in Rockford, Illinois; disposal via on-site septic system with removal by a licensed contractor in Conshohocken, Pennsylvania or into the Philadelphia Water Treatment Authority Facility in Philadelphia, Pennsylvania (refer to Appendix 7).

Solid nonhazardous wastes (cardboard, plastic, paper, etc) from packaging operations are hauled by a licensed hauler to an EPA-permitted recycler or land-fills. Chemically contaminated materials, including broken tablets, rejected goods and residual product dust are returned to SPKU for disposal by incineration by BFI/American Ref-Fuels at Westbury, N.Y and documented in Appendix 7.

iv. Occupational Safety of Workers

For the production of the drug product and packaging, all employees are advised about the handling of hazardous substances. In production protocol sheets (HP-Scheine) and Standard Operating Procedures (according to Hazardous Goods Guidelines), the handling of specific substances is described including warning signs and instructions to protect the worker from exposure to hazardous substances and accidental injury. Building environmental protective measures are in place to protect the worker and external environment from hazardous substances and include such mechanical devices as exhaust systems to protect the worker from product dust. Also, protective clothing (dust masks, gloves, shoe protectors and if

ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT (cont.)

b. Controls Exercised (cont.)

iv. Occupational Safety of Workers (cont.)

necessary respirators) are to be worn according to the product's hazardous substance Standard Operating Procedures (see Appendix 7 and MSDS in Appendix 10).

c. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

In the proposed action, drug substance synthesis and drug product manufacturing of moexipril HCl will not require expansion of existing facilities nor any installation of new equipment or relocation of existing equipment. All operations will be scheduled to fit into existing framework of production activities to be in compliance with emission requirements as applicable for both foreign and domestic operations. Statements of compliance with applicable federal, state and local safety and environmental regulations pertinent to the production of moexipril HCl drug substance or drug product tablets including the packaging of the drug product for distribution for patient use are provided in Appendix 7.

d. Citation of and Statement of Compliance with Applicable Emission Requirements

Occupational Health and Safety Administration (29 CFR §1901)

Occupational exposure to and regulations for worker safety and handling of chemicals are regulated by the Occupational Safety and Health Administration to ensure 1) safety of exposure limits to the drug product, 2) safe handling of the drug product, 3) safe handling of waste byproducts during clean-up operations and 4) hazardous waste material communication.

FEDERAL

COUNTRY	SUBJECT	REGULATION IN EFFECT FOR COMPLIANCE
Ireland	Drug Substance	Clean Air Act
		Statutes and Regulations for Emissions Requirements, Country of Ireland
		Regulations of Pharmaceutical Inspection Convention
		World Health Organization
Switzerland	Drug Substance	Clean Air Act
		Regulation of Pharmaceutical Inspection Convention
		World Health Organization
		Interkantonale Kontrollstelle Für Heilmettel - Bern
Federal Republic of Germany	Drug Product	Federal Emission Protection Act
		Administrative regulations concerning the Federal Emission Protection Act (BImSchV)
		First general administrative regulation concerning the Federal Emission Protection Act (Clean Air Directive) of 27 February 1986.
		State Trade Inspection Authority, Düsseldorf
		Waste Management Act
		Administrative regulations concerning Waste Management Act
		Water Management Act

FEDERAL

COUNTRY	SUBJECT	REGULATION IN EFFECT FOR COMPLIANCE
United States	Packaging and Waste Disposal	Clean Air Act (40 CFR § 50-69): National Primary Ambient Air Quality Standards (NPAAQS) National Emission Standards for Hazardous Air Pollutants (NESHAP)
		Federal Water Pollution Control Act (40 CFR § 100-149, 400-469) The Clean Water Act (33 U.S.C. 1251; 40 CFR § 403, 40 CFR § 439) National Pollution Discharge Elimination System (NPDES, 40 CFR § 122) Safe Drinking Water Act (42 U.S.C. 300g-1)
		Toxic Substance Control Act 40 CFR § 372
		Hazardous Material Transportation Act 49 CFR § 171-177

STATE

STATE	COUNTRY	SUBJECT	REGULATION IN EFFECT FOR COMPLIANCE
	Ireland	Drug Substance	Draft Air License, County Clare
	Switzerland	Drug Substance	Statutes and Regulation Central Authority Intercantonal Office - Bern
			Construction Supervision Department of the Canton Valais for Air Scrubbers
			Department of Air Pollution Control - Canton Valais
			Water Protection Agency - Canton Valais
	Federal Republic of Germany	Drug Substance	State Waste Management Act
			Disposal / Recycling certificate no. 10352 of AGR Abfall-Entsorgungs-Gesellschaft Ruhrgebiet mbH of 3 May 1991
			District of Mettmann Water and Waste Management Department
			North Rhine Westphalia State Water Management Act
			District of Mettmann, Water and Waste Management Department
			Bergisch-Rheinischer Water Utility, Haan
Wisconsin	USA	Packaging and Waste Disposal	Clean Air Act (40 CFR § 50-69)
			Department of Natural Resources (DRN) Wisconsin Statutes § 144.30 - 144.426 Implementation Regulations: Wisconsin Administrative Code NR 400 NR 494
			Air Emissions Chapter NR 410

STATE

STATE	COUNTRY	SUBJECT	REGULATION IN EFFECT FOR COMPLIANCE
Wisconsin (cont'd)	USA	Packaging and Waste Disposal	Waste Water NR 101
			Hazardous Waste NR 600-685
			Hazardous Waste Generator s. 144.442(1s)
			Solid Waste Transportation Services NR 500-520
Illinois	USA	Packaging and Waste Disposal	Clean Air Act (40 CFR § 50-69)
			Illinois Environmental Protection Agency (IEPA)
			Water Pollution Contract Act - Illinois Statues Title 35 subtitle C, Chapter 1
Pennsylvania	USA	Packaging and Waste Disposal	Clean Air Act - Commonwealth of Pennsylvania Department of Environmental Resources (PADER)
New York	USA	Packaging and Waste Disposal	Resource Conservation and recovery Act (40 CFR § 240-300): BFI / American Ref-Fuel Hempstead Resource Recovery Facility Permit No.: 2820005643 Combustion gas temperature is maintained above 1500° F after the last point of overfire air injection.
			New York State Department of Environmental Conservation Emissions Incinerator

LOCAL

LOCAL	COUNTRY	SUBJECT	REGULATION IN EFFECT FOR COMPLIANCE
Shannon	Ireland	Packaging and Waste Disposal	Draft Air License - City of Shannon, County Clare
Evionnaz	Switzerland	Packaging and Waste Disposal	Statutes and Regulations Cantonal Authority
Monheim	Federal Republic of Germany	Drug Product	Statutes concerning water disposal for properties and connection to the public wastewater system of the city of Monheim (Property Water Disposal Statues) of 22 December 1989. City of Monheim
Mequon, WI	USA	Packaging and Waste Disposal	Brown Deer Water Public Utility
			Milwaukee Metropolitan Sewerage District
Rockford, IL	USA	Packaging and Waste Disposal	Rock River Water Reclamation District
Philadelphia, PA	USA	Packaging and Wast Disposal	Philadelphia Water Authority
			Philadelphia Municipal Sewage Treatment and Water Treatment Authority
Conshohocken, PA	USA	Packaging and Water Disposal	Philadelphia Water Authority
			Philadelphia Municipal Sewage Treatment and Water Treatment Authority

ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT (cont.)

e. Predicted Environmental Concentrations

The pharmacokinetic profile of moexipril hydrochloride has been described in Item 14, reference number 2, and in Volumes 1.52 to 1.107 of NDA 20-312. Based on fifth year sales estimates of 7.5 mg and 15.0 mg tablets, the calculations of MEEC (Maximum Expected Emitted Concentration) for moexipril HCl, moexiprilat, DKP derivatives, and unknowns are as follows (and in Appendices 6 and 8):

Maximum Expected Environmental Concentrations (MEEC) - Use, Production and/or Disposal

Based on sales estimates, the Maximum Expected Emitted Concentrations (MEEC) for moexipril and its metabolites are expected to be in the range of 10^{-5} to 10^{-7} ppm. Calculations and results for the Maximum Expected Emitted Concentrations (MEEC) can be found in Appendices 6 and 8.

ITEM 7: FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

a. Identification of Chemical Compounds of Interest

Moexipril HCl is a non-sulfhydryl containing precursor (pro-drug) of the active angiotensin- converting enzyme (ACE) inhibitor moexiprilat, of the enalapril type and dipeptide structure. The molecular structure of moexipril is closely related to quinapril. Moexipril HCl, its decomposition products and its metabolites are anticipated to be, in a large part, disposed of through sewer systems, after administration to man, from subsequent urine excretion and feces elimination. Data has been developed for both moexipril HCl and moexiprilat.

b. Physical/Chemical Characterization

i. Water Solubility

Strickley, Visor, Lin, and Gu (1989) measured and reported the water solubility of moexipril hydrochloride. Solubility was determined as a function of pH, with the lowest solubility observed at pH 4, approximately 15 mg/mL.

Solubilities at pH 6 or higher are greater than 100 mg/mL. This high solubility is typical for hydrochloride salts of amines. The water solubility of moexiprilat is slightly less and varies with pH. Gu and Strickley (1988) measured and reported the water solubility of moexiprilat. A full solubility curve was determined spanning the pH range from 0 to 6. Above pH 5.5, the

ITEM 7: FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT (cont.)

b. Physical/Chemical Characterization (cont.)

i. Water Solubility (cont.)

solubility exceeds 150 mg/mL, and the data could not be reliably determined. The solubility curve is at a minimum at pH 3 with a measured solubility of 1 mg/mL (1,000 mg/L). Refer to Table 1 for the Chemical and Physical Properties of Moexipril HCl and Moexiprilat.

ii. Dissociation Constants

The dissociation constants for moexipril hydrochloride were determined by Gu and Strickley (1987). At 25°C, two pKas were determined, pKa_1 at 3.03 and pKa_2 at 5.40. This means the compound can be found in three forms, depending upon pH. At pHs below 3.03, the compound is principally a cation, at pHs between 3.03 and 5.40 it is mainly a zwitterion, and above 5.40 an anion. This data is consistent with the extremely high water solubility observed. The pKas for moexiprilat were reported by Gu and Strickley (1988) to be 2.4, 3.1 and 8.0. These are consistent with the solubility profile determined for moexiprilat, in which the solubility is lowest near pH 3.

iii. Octanol/Water Partition Coefficient

The octanol/water partition coefficients for moexipril hydrochloride were determined by SPAG at three pHs. The log(Kow) at pH 1.0 is 0.37, at pH 4.2 the log(Kow) is 0.92 and at pH 7.5 the log (Kow) is -0.60. All three values are consistent with the ionic nature of moexipril hydrochloride and the high water solubility. These low partition coefficients indicate that moexipril hydrochloride will not bioconcentrate in tissue (log(Kow) less than 3). The octanol/water partition coefficient for moexiprilat was determined using QSAR (quantitative structure activity relationships) modeling. Based on the molecular structure, moexiprilat has a calculated log(Kow) of 2.65. As for moexipril hydrochloride, moexiprilat will not bioconcentrate in tissue.

iv. Vapor Pressure

The vapor pressures for moexipril hydrochloride and moexiprilat were determined using QSAR modeling. The vapor pressures for both compounds were calculated to be less than 1×10^{-7} torr at 25°C. Neither moexipril hydrochloride and moexiprilat would be expected to volatilize from water. This is consistent with the ionic nature of both compounds in water, preventing movement into the atmosphere.

TABLE I

Chemical and Physical Properties of Moexipril Hydrochloride and Moexiprilat [a]

Parameter	Moexipril HCl	Moexiprilat
Molecular formula	$C_{27}H_{34}N_2O_7 \cdot HCl$	$C_{25}H_{30}N_2O_7$
Molecular weight	535.04	460.53
Melting point	155-160° C (decomposition)	139-146° C
Solubility in water (20° C)	>100 mg/ml (distilled water)	1 mg/ml (distilled water) >100 mg/ml (pH>5.4)
Density [b]	N D	N D
Vapor Pressure [c]	1 x 10^{-7} @ 25° C	1 x 10^{-7} @ 25° C
Log octanol-water partition coefficient (37° C)[d]	0.37 (pH 1.0) 0.92 (pH 4.2) -0.60 (pH 7.5)	2.65 [QSAR]
Log soil sorption coefficient	Koc < 7.76	Koc < 6.2
Log bioconcentration factor	-0.03	1.10
Dissociation constants (25° C) pK_a 1 pK_a 2 pK_a 3	 3.0 5.4 -	 2.4 3.1 8.0
Electromagnetic absorption maximum (>300 nm)	none Small maximum at 280 nm	same behavior expected

a Values are taken from the CMC Section (confidential), unless otherwise indicated.

b Not determined because density a colligative property rather than a molecular property. Thus, the density of Moexipril HCl and Moexiprilat (as a separate solid phase) is not relevant to the behavior of the dissolved molecules. In environmental release of Moexipril HCl and Moexiprilat or its metabolite occur, they will always be in the dissolved state at concentrations well below the maximum solubility. This justification for not measuring density is substantiated by 21 CFR 25.1(b)(3).

c Not determined for Moexipril HCl and Moexiprilat because it will be an ionic substance under ambient environmental conditions and, therefore, will not volatilize from water or soil. This justification for not measuring the vapor pressure is substantiated by 21 CFR 25.1(b)(3).

d Calculated from the distribution between the two-phase mixture octanol-water at different pH-values.

ITEM 7: FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT (cont.)

b. Physical/Chemical Characterization (cont.)

v. Melting Points

The melting points for moexipril hydrochloride and moexiprilat were determined by SPAG. Moexipril hydrochloride had a melting range of 155 - 160°C (with decomposition evident) and moexiprilat had a melting range of 139 - 146°C (for the dihydrate form). The decomposition evident for moexipril hydrochloride is consistent with the salt of an organic base and corroborates the lack of vapor pressure.

vi. Sorption

The log soil sorption coefficient, log(Koc), of moexipril hydrochloride and moexiprilat were calculated from the following equation (Kenaga, 1980, "Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals" *Ecotoxicology and Environmental Safety*, Vol. 4, p. 26, referenced in the FDA Technical Assistance Handbook, Section 3.01, Water Solubility):

$$\log(Koc) = 3.64 - 0.55\ (\log(S))$$

(correlation coefficient = 0.84, n = 106)

S = water solubility in mg/L

Using >100 mg/mL (>100,000 mg/L) for the solubility of moexipril hydrochloride, the calculated log(Koc) is <0.89. This translates to a Koc of <7.76. Using >150 mg/mL for moexiprilat (150,000 mg/L), the calculated log(Koc) is <0.79. This translates to a Koc of <6.2. These sorption coefficients indicate that moexipril hydrochloride and moexiprilat are not significantly bound to organic carbon and are likely to be located in the aqueous environmental compartment. Binding to soil and sediment is extremely low.

c. Depletion Mechanism

The hydrolysis of moexipril hydrochloride has been extensively studied and is found in several literature articles located in Item 14. These are Gu and Strickley (1987), and Strickley, Visor, Lin, and Gu (1989), and Gu and Strickley (1990). At a variety of pHs and using several different buffer systems, the hydrolysis half-lives of moexipril hydrochloride were determined. At 100 mg/L, under acidic conditions, at pH 2 (0.01 M HCl) the half-life is 5.5 days. At 100 mg/L, in unbuffered water (final pH 3.9) the

ITEM 7: FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT (cont.)

c. Depletion Mechanism (cont.)

half-life is 51 days. At 100 mg/L, in acetate buffer (pH 4.3) the half-life is 60 days. At a relatively neutral solution (pH 6.8) in phosphate buffer, the half-life is 38 days. At the lower pHs, the principal hydrolysis product is diketopiperazine, the cyclization product. At pH greater than 5, the hydrolysis product is moexiprilat.

d. Summary

Based on a projected fifth-year sales, the estimated worst case environmental concentration of moexipril and its metabolites is 1.66×10^{-5} mg/L. This concentration does not take into consideration the patient metabolism expected, but nonetheless is several orders of magnitude lower than the water solubility. The high water solubility, the low vapor pressure, and the low sorption coefficients suggest that moexipril hydrochloride entering the environment will remain in the aqueous phase, and not move into the soil or atmospheric compartments. Degradation by hydrolysis occurs at all pHs of environmental relevance indicating that moexipril hydrochloride will not persist in the environment.

ITEM 8: ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

In man, rat and dog the parent compound, moexipril HCl is quickly converted in a first metabolic step to the active metabolite, moexiprilat, through enzymatic hydrolysis of the ethylester function. The urinary metabolic profile of moexipril HCl includes moexipril, moexiprilat, small amounts of corresponding diketopiperazines and other unknown metabolites. Due to the short half-life of moexipril, no expected accumulation of the parent compound is expected. However, similar to other ACE inhibitors, moexiprilat has a prolonged terminal elimination rate. This is presumably due to slow release of the active moiety from the human ACE receptor. In ADME-studies with different species (rat, dog, man) no indication of an accumulation of the parent compound or metabolites was observed (see Appendix 5).

In the environmental compartment after exposure to the parent compound, moexipril HCl or active metabolite, moexiprilat, would be expected to undergo some degradation through similar mechanisms in other species. Therefore, it is important to understand the relative indicators of potential acute hazards to the ecosystem and to determine other mediated transformations that may occur in the environment.

ITEM 8: ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES (cont.)

a. Environmental Effects

A variety of environmental organisms were tested to evaluate the potential ecotoxicity of moexipril HCl and moexiprilat. Following the FDA Technical Assistance Handbook (USFDA, 1987) procedures, both the Microbial Growth Inhibition (4.02) and *Daphnia magna* Static Acute Toxicity (4.08) studies were conducted for both compounds.

The results of microbial growth inhibition studies conducted with moexipril HCl and moexiprilat indicate that both compounds are non-toxic. The following Table 2 summarizes the testing completed with five species of microorganisms and lists each inhibitory concentration.

TABLE 2
Toxicity Testing of Moexipril HCL and Moexiprilat in Representative Environmental Organisms

Moexipril Hydrochloride

Test Organism	Conditions	Results	Study Report
Daphnia magna 24-hour EC50	Static acute toxicity (TAD 4.08) (USFDA, 1987)	800 mg/L[a]	Study #95-2-5696 [d] entitled "Moexipril Hydrochloride - Acute Toxicity to Daphnids *(Daphnia Magna)* Under Static Conditions".
Daphnia magna 48-hour EC50		800 mg/L[a]	
Daphnia magna 24-hour NOEC		620 mg/L[a]	
Daphnia magna 48-hour NOEC		620 mg/L[a]	

Moexiprilat

Test Organism	Conditions	Results	Study Report
Daphnia magna 24-hour EC50	Static acute toxicity (TAD 4.08) (USFDA, 1987)	>1,000 mg/L[a]	Study #95-1-5690 [d] entitled "Moexipril Hydrochloride - Acute Toxicity to Daphnids *(Daphnia magna)* Under Static Conditions".
Daphnia magna 48-hour EC50		>1,000 mg/L[a]	
Daphnia magna 24-hour NOEC		>1,000 mg/L[a]	
Daphnia magna 48-hour NOEC		600 mg/L[a]	

a The EC50 is the concentration where 50% of the organisms are affected by the test substance, NOEC is the no observed effect concentration where none of the organisms are affected.

b The above table summarizes the testing completed with five species of microorganisms and lists each minimum inhibitory concentration (MIC). The results of microbial growth inhibition studies conducted with moexipril hydrochloride and moexiprilat indicate that both compounds are not-toxic.

c The lowest MIC value for all species tested is 400 mg/L, which is more than seven orders of magnitude greater than the predicted worse case environmental concentration ($1.66 \times 10\ 10^{-5}$ mg/L).

d Full study reports located in Appendix 9.

TABLE 2 (cont.)
Toxicity Testing of Moexipril HCL and Moexiprilat in Representative Environmental Organisms (cont.)

Moexipril Hydrochloride

Test Organism	Conditions	Results (MIC)	Study Report
Aspergillus niger	Microbial Growth[c] Inhibition (TAD 4.02) (USFDA, 1987)	>1,000 mg/L[b]	Study #95-2-5697 [d] entitled "Moexipril Hydrochloride - Determination of Microbial Growth Inhibition".
Trichoderma viride		>1,000 mg/L[b]	
Clostridium perfringens		>1,000 mg/L[b]	
Bacillus subtilis		>1,000 mg/L[b]	
Nostoc		400 mg/L[b]	

Moexiprilat

Test Organism	Conditions	Results	Study Report
Aspergillus niger	Microbial Growth[c] Inhibition (TAD 4.02) (USFDA, 1987)	>1,000 mg/L[b]	Study #95-2-5698 [d] entitled "Moexiprilat - Determination of Microbial Growth Inhibition" .
Trichoderma viride		>1,000 mg/L[b]	
Clostridium perfringens		>1,000 mg/L[b]	
Bacillus subtilis		>1,000 mg/L[b]	
Nostoc		400 mg/L[b]	

a The EC50 is the concentration where 50% of the organisms are affected by the test substance, NOEC is the no observed effect concentration where none of the organisms are affected.

b The above table summarizes the testing completed with five species of microorganisms and lists each minimum inhibitory concentration (MIC). The results of microbial growth inhibition studies conducted with moexipril hydrochloride and moexiprilat indicate that both compounds are not-toxic.

c The lowest MIC value for all species tested is 400 mg/L, which is more than seven orders of magnitude greater than the predicted worse case environmental concentration ($1.66 \times 10\ 10^{-5}$ mg/L).

d Full study reports located in Appendix 9.

ITEM 8: ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES (cont.)

b. Summary

The full reports from these four studies are presented in Appendix 9. As is evident from this information, both moexipril HCl and moexiprilat are largely non-toxic to a variety of environmental organisms. The lowest (MIC) value for all species tested is 400 mg/L, which is more than seven orders of magnitude greater than the predicted worst case environmental concentration (1.66×10^{-5} mg/L). Therefore, the concentration of moexipril HCl and its active metabolites in the environment that could potentially result from approval of the proposed action will not have an adverse effect on living organisms.

ITEM 9: USE OF RESOURCES AND ENERGY

a. Natural Resources and Energy

i. Drug Substance

The raw materials utilized to manufacture the drug substance moexipril HCl, are common compounds, which are in ample commercial supply. Energy consumption for bulk drug production of moexipril HCl is marginal. Only very small increases in the resource utilization are anticipated, since production occurs at existing production facilities. This fact is based on estimates that the production of moexipril HCl will constitute less than 3 - 5% of SIFA's and 1% of Orgamol's total production operations at the indicated sites.

ii. Drug Product

It is anticipated that use of resources and energy for the production of 7.5 mg and 15 mg tablets, based on projected sales volume for the fifth year at the Schwarz Pharma AG facility in Germany, is minimal compared to the total production operations at this site. Production of moexipril HCl tablets will constitute less than 12% of this site's operations.

U.S. activities for the drug product, moexipril HCl, involves packaging, warehousing, distribution and disposal.

ITEM 9: USE OF RESOURCES AND ENERGY (cont.)

a. Natural Resources and Energy (cont.)

iii. Disposal in the United States

Amount of returned goods for the fifth year of sales can be found in Appendix 8. Returned goods from the SPKU facility will be collected, drummed and forwarded for disposal to BFI/American Ref-Fuels (governmental permit #2820005543). The incineration process creates electricity which powers nearly 65,000 homes in Hempstead Township, New York.

iv. Transportation of Drug Substance and Drug Product

The transportation of the drug substance to production facilities for bulk drug product production is by sea and land. Drug product is shipped worldwide by air, sea, road and rail services as available to the appropriate destination. The environmental consequences of transporting the drug substance and/or drug product is not considered to have adverse effects on the environment.

b. Effect on Endangered or Threatened Species

No endangered or threatened species are required to be used in the bulk drug substance or tablet manufacture process. Because controls are exercised to release minimal effects on the environment during manufacture, and ecotoxicity and microbial growth inhibition concentration test results indicated no adverse effects of the drug substance to aquatic life, negligible environmental effects would be expected in general. This drug product's marketed use is intended for human consumption, therefore, endangered and threatened species are not included in the marketed application of this drug product and should not be impacted. No effects are expected in the physical environment or upon endangered or threatened species as a result of the disposal of and incineration of moexipril HCl.

c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places

The proposed action will not adversely affect any physical environment or any historical, architectural, archeological, or cultural sites and values at drug substance or bulk drug products manufacture at production locations in Ireland, Switzerland and the Federal Republic of Germany. The locations of these facilities are not in the vicinity of historical, architectural, archeological, or cultural sites and values as identified in Item 4 c.

ITEM 9: USE OF RESOURCES AND ENERGY (cont.)

c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places (cont.)

The proposed action will not adversely affect any physical environment or affect a property listed in or eligible for listing in the National Register of Historic Places or any additional historical, architectural, archeological, or cultural sites and values at drug product packaging, distribution or disposal sites in the States of Wisconsin, Illinois, New York (USA), and Commonwealth of Pennsylvania as identified in Item 4c. This determination is important in the event the projected sales volume for the fifth year, as produced at the SPAG facility, were destroyed in total would cause no adverse effect.

ITEM 10: MITIGATION MEASURES

No potential adverse environmental impact of the proposed action as estimated by the calculation of the expected emitted substances as described in Item 6 a, e for tablet manufacture, packaging, patient use and disposal are foreseen. Compliance of the proposed action with applicable emission standards in Ireland, Switzerland, Federal Republic of Germany and the United States was discussed in Item 6 b, c, d , as well, including the citation of and certifications of emission requirements. The safe handling and use, including emergency procedures and first aid procedures, of the drug substance is provided in the Material Safety Data Sheet (MSDS) located in nonconfidential Appendix 10.

The manufacture and disposal of the drug substance takes place under highly regulated and controlled conditions designed to further mitigate against negative environmental consequences and careless hazardous contamination. Any release of particulate dust from tablet manufacture will be effectively mitigated via use of high efficiency dust collection system. Adherence to Good Manufacturing Practices (GMP) regulations prior to disposal of cleaning fluids used to washdown equipment before discharge into municipal wastewater treatment facilities will cause minimal exposure to the environment. Waste materials collected during the cleaning process, dust collection, and drug product packaging operation will be drummed and labeled in accordance with local laws and state regulations, for the States of Wiscor , Illinois and Pennsylvania. These regulations, including transportation laws of the solid waste products to be incinerated by EPA- permitted waste contractors, have been discussed and are located in detail in Appendix 7.

Returned, rejected or outdated drug product that contains moexipril HCl will be collected by SPKU, drummed and destroyed in the EPA-permitted incinerator at Hempstead, N.Y.

ITEM 11: ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental impacts are foreseen with the tablet manufacture, packaging or for the marketed use of drug products designated as UNIVASC™ (moexipril hydrochloride) 7.5 mg and 15 mg tablets as described in this environmental assessment. The drug substance discussed in this proposed action known as moexipril hydrochloride (moexipril HCl), and its active metabolite, moexiprilat, have been shown to have acceptable levels of emitted substances into the environment during tablet manufacture, packaging and projected marketed use. Also, no deleterious ecotoxicity or microbial growth inhibition to a variety of environmental organisms were demonstrated during environmental testing with the lowest value concentration being more than seven orders of magnitude greater than the predicted worst case environmental concentration (1.66×10^{-5} mg/L). Therefore, the concentrations of moexipril HCl and its metabolites in the environment that could potentially result from approval of the proposed action will not have an adverse effect on living organisms. Furthermore, a clear degradation path for moexipril HCl was demonstrated proving that the drug will not persist in the environment.

The proposed action will provide a new antihypertensive drug product indicated for patient use in the treatment of hypertension, alone or in the combination with thiazide diuretics. The use of moexipril HCl will directly benefit patients with hypertension. During chronic therapy, the antihypertensive effect of any dose of moexipril HCl generally had a maximal reduction over 2 to 4 weeks. The antihypertensive effects were further shown in controlled clinical trials to continue during therapy for up to 24 months indicating that moexipril HCl is a highly effective long-term therapy for treatment of hypertensive patients

Approval of moexipril hydrochloride is justified from an environmental perspective and is preferable to non-approval.

An alternative to the proposed action would be non-approval of UNIVASC™ tablets. The non-approval of the proposed action could be perceived as denying the opportunity of patients with hypertension the potential benefits of UNIVASC™ (moexipril HCl).

ITEM 12: LIST OF PREPARERS

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OVERALL ACCOMPLISHMENTS: Graduated first in Ph.D. class with an A average. I have worked 9 years in the pharmaceutical industry in a clinical research capacity in new drug or biotechnology applications. I have also worked 2 years as a consultant to biotech companies. The strength of my industry accomplishments are clinical trials research in cardiovascular, oncologic, neurologic, orthopedic and inflammatory/ antiinfective areas. I have 7 years additional experience in hospital clinical trials research, pre-clinical animal, study budgets, study management with physicians in the development of drugs and devices for industry in similar clinical areas.

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M.S. Nursing
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Ph.D. Major: Statistics and Experimental Research Design
Texas Woman's University
Houston, Texas, 1991

FELLOWSHIP:

Statistics, Research Design and Research Administration
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EMPLOYMENT:

1993 - 1994	Senior Statistician II G.D. Searle Skokie, Illinois
1991 - 1993	Research Associate & Database Administrator Cardiac Surgery Associates Milwaukee, Wisconsin
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1985 - 1987	Clinical Associate 3M Orthopedics Division
1982 - 1985	Clinical Service Specialist Clinical Product Research and Development Baxter Travenol Laboratories
1981 - 1982	Statistician and Research Associate University of Texas Medical School Houston, Texas Departments: Cardiology, Cardiovascular Surgery
1981	Assistant Director of Cardiac Electrophysiology Baylor College of Medicine Houston, Texas
1979 - 1981	Clinical Research Associate Mead Johnson Pharmaceutical Company
1978	Visiting Professor University of Nottingham College of Medicine Nottingham, England

1977 - 1978	Research Associate R.A. Marrese, M.D. - Orthopedic Surgeon Evansville, Indiana
1974 - 1979	Instructor, College of Nursing Medical-Surgical Nursing, Research, Statistics University of Evansville Evansville, Indiana
AWARDS:	American Association for Women in Science Outstanding Scholar, 1990
	Outstanding Clinical Service Specialist Baxter Travenol Laboratories, 1984
	Outstanding Hoosier Scholar Indiana University, 1974
DISSERTATION:	Perceived Control and Health-Promoting Behaviors of Predictors of Life Satisfaction and Well-Being Outcomes in Women with Long-term Spinal Cord Injury. Funding by the National Institute for Disabilities Research and Rehabilitation (NIDRR).
CONSULTING:	Society for Thoracic Surgery Statistician and Database Manager National Database Registry, 1992 - 1994
	Synthes Corporation - Consultant FDA Product Development with Baylor College of Medicine, 1988 - 1991
	Gortex Corporation - Consultant FDA Product Development with Baylor College of Medicine, 1988 - 1990
LICENSURE:	Wisconsin Board of Nursing # 107427
FOREIGN LANGUAGES:	Fluent in Spanish Read French & Italian

COMMUNITY VOLUNTEER:

Junior League of Houston and Chicago
Milwaukee Friends of Ballet
Florentine Opera Company Guild
Wisconsin Lipid Club

ABSTRACTS:

1. Auer, JE, Hazelrigg, SR, Seifert, PH, Nunchuck, SK. Alternative Arterial Conduits in Reoperative Myocardial Revascularization. Submitted European Cardio-Thoracic Society Meeting, September, 1992.

2. Nunchuck, SK, Auer JE, HAzelrigg, SR, Seifert PH. Risk Factor Score Prediction for Patients Requiring Intraaortic Balloon Pumps. Submitted American Association of Thoracic Surgery Meeting, April, 1992.

3. Hazelrigg, SR, Landrenau, RJ, Mack, M, Nunchuck, SK, Ritter, P. Quality of Life: Thorascopy versus Thoracotomy. Submitted Society Thoracic Surgery Meeting, January, 1993.

4. Hazelrigg, S, Nunchuck, S. LoCicero, J. Video Assisted Thoracic Surgery Study Group Data. Presented Society of Thoracic Surgery Meeting, Jan. 1993.

5. Landreneau, R, Mack, M, Hazelrigg, S, Naunheim, K, Dowling, R, Ritter, P, Nunchuck, S, Magee, M, Keenan, R, Ferson, R. Prevalence of Chronic Pain Following Pulmonary Resection by Thoracotomy or Video Assisted Thoracic Surgery. Presented Society of Thoracic Surgery Meeting, Jan. 1993.

6. Landreneau, R, Mack, M, Hazelrigg, S, Naunheim, K, Dowling, R, Ritter, P, Nunchuck, S, Magee, M, Keenan, R, Ferson, R. Acute Pain Comparisons Thoracoscopic Surgery Compared to Thoracotomy. Presented Western Thoracic Surgical Association, June, 1993.

7. Hazelrigg, S, Nunchuck, S, LoCicero J. Video Assisted Thoracic Surgery in the Elderly. Presented Chest Physician's Meeting. September, 1993.

8. Landreneau, R, Mack, M, Mazelrigg, S, Naunheim, K, Dowling, R, Ritter, P, Nunchuck, S, Magee, M, Keenan, R, Ferson, R. Chronic Thoracic Pain. Presented to American Society of Thoracic Surgery. April, 1993.

9. LoCicero, J, Nunchuck, S. The Thoracoscopic Surgery Study Group. Thoracoscopic Surgery in AIDS Patients. Submitted to International AIDS meeting.

STATISTICAL PUBLICATIONS:

1. Browner, B, Cole, J, Nunchuck, S, Cotler, H. (1987). Delayed Posterior Internal Fixation of Unstable Pelvic Fracture. Journal of Trauma, 27:9-15.

2. Lindsay, R, Dick, W, Nunchuck, S, Zach, G. (1991). Long-term Effects of the Fixateur Interne. SPINE, 16:140-145.

3. Moseley, R, Shields, C, Nunchuck, S. (1991). Long-term Patient Outcome of the Gortex ACL Graft, Journal of Bone and Joint Surgery (In Press).

4. Hazelrigg, SR, Landrenau, RJ, Mack, M, Acuff, T, Nunchuck, SK, Auer, JE, Seifert, PH. (1992). Cost Analysis for Thoracoscopy: Thorascopic Wedge Resection. Annals of Thoracic Surgery 56: 633-5.

5. Hazelrigg, S. Nunchuck, S, LoCicero, J. (1993). Video Assisted Thoracic Surgery Study Group Data. Annuals of Thoracic Surgery 56: 1039-48.

6. Landreneau, R., Mack, M, Hazelrigg, S, Naunheim, K, Dowling, R, Ritter, P, Nunchuck, S, Magee, M, Keenan, R, Ferson, R. (1994). Prevalence of Chronic Pain Following Pulmonary Resection by Thoracotomy or Video Assisted Thoracic Surgery. Journal of Thoracic and Cardiovascular Surgery 107:1079-86.

7. Hazelrigg, S, Nunchuck, S, LoCicero, J. (1993). Video Assisted Thoracic Surgery in the Elderly. Submitted to Chest. (In Press)

OTHER PUBLICATIONS:

1. Nunchuck, SK. (1974). You and Your Head and Neck Surgery. Indiana University Hospitals, Patient Brochure.

2. Nunchuck, SK. (1978). The Effect of Operant Conditioning in Patients with Chronic Low Back Pain. Master Thesis.

3. Conway, B. (1982). Neurological and Neurosurgical Nursing, C.V. Mosby, 8th ed. St. Louis. Contributed 8 of 12 chapters.

4. Nunchuck, SK. (1981). Cardiac Catheterization. Hermann Hospital. Patient Education Brochure.

5. Nunchuck, SK. (1982). Cardiac Electrophysiology. Hermann Hospital. Patient Education Brochure.

OTHER PUBLICATIONS (cont.)

6. Weeks, L. (1986). Advanced Concepts in Critical Care Nursing. Blackwell Scientific Publications. London, England. Contributed 3 chapters.

7. Naccarelli, GV and Nunchuck, SK. (1982). Update on Newer Antiarrhythmic Drugs. Therapeutics Update. Texas Medical Center News.

8. Naccarelli, GV and Nunchuck, SK. (1981). Antiarrhythmic Drugs. Therapeutics Update. Texas Medical Center News.

9. Naccarelli, GV and Nunchuck, SK. (1981). Antiarrhythmic Agents in Electrophysiologic Research. Therapeutics Update. Texas Medical Center News.

10. Naccarelli, GV and Nunchuck, SK. (1982). Encainide and Wolff-parkinson-White Syndrome. Therapeutics Update. Texas Medical Center News.

11. Nunchuck, SK. (1987). Cast Care. Hermann Hospital. Patient Education Brochure.

November 11, 1992

CURRICULUM VITAE

Dr. rer. nat. Klaus Sandrock, Dipl. Chem.

PRESENT POSITION: Director Safety and Environmental Department

Business Address:
SCHWARZ PHARMA AG
Alfred-Nobel-S tr. 10
4019 Monheim
(02173) 48-0

BIOGRAPHICAL:

Date of Birth:	July 23, 1946
Place of Birth:	Bonn
Marital Status:	
Home Address:	

EDUCATION:

University of Bonn	1966 - 1974
Diplom-Chemist	1972
Doctorate	1974

EMPLOYMENT EXPERIENCE:

GSF, Munich: 1974 - 1976

Group Leader of Isotopic Lab., Institut for ecological Chem.

SCHWARZ PHARMA AG, Monheim: - 1976

since 1976	Group Leader of Isotopic Lab.
since 1978	Director Chemistry Department incl. chemical synthesis, scale up and Isotopic Lab.
since 1986	Responsible for Industrial Safety and Environmental Protection incl. hazardous transports

LANGUAGE/ABILITY:
English / read, speak

/contd.

PROFESSIONAL ACTIVITIES AND MEMBERSHIPS:

Member of the German Chemical Society and team of specialists for Medicinal Chemistry and Analytics

Leader of the Regional Group Bergisch-Land of the Association of Company's Representatives for Environmental Protection

Member of the Environmental Committee of the District Council Langenfeld

Member of the Environmental Committee of the Industrial Chamber of Commerce, Düsseldorf

SPECIAL PROFESSIONAL EXPERIENCES:

Metabolism investigations incl. structure elucidations

Microsynthesis of labelled compounds

R & D synthesis

Knowledge of and representative for environmental protection

Specialized knowledge in the field of air and water protection as well as chemical waste disposal

Monheim, November 10, 1992

Dr. Klaus Sandhock

PAUL H. FACKLER

BIRTHPLACE AND DATE: Wheaton, Illinois; September 18, 1956

EDUCATION:

Ph.D. Analytical/Inorganic Chemistry, Boston College, Chestnut Hill, MA, 1984

B.S. Chemistry, Harvey Mudd College, Claremont, CA, 1978

PROFESSIONAL EXPERIENCE:

1991-Present - Director, Environmental Chemistry, Springborn Laboratories, Inc., Wareham, Massachusetts. The principal contact for FDA registration programs with respect to Environmental Assessments for NDA and NADA submission. Responsible for providing technical and managerial expertise to the analytical and technical sections of the Environmental Fate Department. Duties include design and management of research programs, preparation of proposals, supervision of scientific personnel and instrumentation, GC, HPLC, GC/MS, LC/MS, AA, UV-vis, and other analytical equipment. Testing overseen includes physical properties determination, environmental fate studies and microbiological effect tests. Also presently Radiation Safety Officer.

1987-1991 - Director, Chemistry Department, Springborn Laboratories, Inc., Wareham, Massachusetts. Responsible for providing technical and managerial expertise to the Analytical and Environmental Fate Sections of the Chemistry Department. Duties include design and management of research programs, preparation of proposals, supervision of scientific personnel and instrumentation, GC, HPLC, GC-MS, AA, UV/VIS, TOC analyzer, and other analytical equipment. Also presently Radiation Safety Officer, and manager of hazardous waste disposal for facility.

1986-1987 - Group Leader, Analytical Chemistry, Johnson Matthey, Inc., West Chester, Pennsylvania. Duties included supervision of analytical research in support of drug research program consisting of four primary projects. These programs included developing analogs of the anti-cancer drug Cis-Platin, gold based anti-cancer drugs and organic anti-arthritis compounds. Responsibilities included supervision of personnel, compiling annual reports and program summaries, interfacing with outside collaborators and sponsors, and maintenance of analytical instrumentation.

1985-1986 - Senior Research Chemist, Johnson Matthey, Inc., West Chester, Pennsylvania. Job description similar to above.

1984-1985 - Postdoctoral Assistant, University of Cincinnati. Worked on projects that dealt mainly with identification of nanogram quantities of technetium containing radiopharmaceuticals. Instrumental techniques included HPLC, gamma counting, liquid scintillation counting, TLC, NMR, and mass spectroscopy.

1981-1982 - Laboratory Technician, Poly-Drug, Inc., Boston, Massachusetts. Routinely analyzed serum and urine from hospitals in the Boston area for therapeutic and toxic drugs. Methods used include HPLC, GC, GC/MS, TLC, AA, radioimmunoassay, and enzyme related assays.

PUBLICATIONS AND PRESENTATIONS:

Erstfeld, K.M., O'Grodnick, J.S., Mao, J., Fackler, P.H. 1992. Tralomethrin and Deltamethrin - Fate During an Aquatic Microcosm Study. Presented at the 13th Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 1992, Paper #294.

Fackler, P.H., Dionne, E., Hamelink, J., Hobson, J. 1992. Bioconcentration of Octamethylcyclotetrasiloxane (OMCTS) in Fathead Minnows. Presented at the 13th Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 1992, Paper #277.

Mao, J., Erstfeld, K.M., Fackler, P.H. Simultaneous Determination of Tralomethrin, Deltamethrin and Related Compounds by HPLC with Radiometric Detection. 1992. Submitted to the Journal of Agricultural and Food Chemistry.

Mao, J., Fackler, P.H. 1992. Use of HPLC with Flow-through Radiometric Detection for Low-level Environmental Analysis. Presented at the 204th National Meeting of the American Chemical Society. Washington, D.C.. August 1992. Analytical Paper #15.

Fackler, P.H. 1991. Environmental Fate Studies Targeted for FDA Submission. Presented at the 7th Annual Meeting of the Society for Quality Assurance. Kansas City, Missouri. October 1991. Session C - Environmental Fate.

Hanley, D.A., Fackler, P.H. 1990. Biodegradation Testing - An Overview. Presented at the Annual Meeting of the American Nuclear Society. Nashville, Tennessee. June 1990. Biology and Medicine Division. Section 1.2.

Abrams, M.J., Fackler, P.H., Picker, D.H., Lock, C.J.L., Howard-Lock, H.E., Faggiani, R., Teicher, B.A., and Richmond, R.C. 1986. The Synthesis and Structure of $[Rhodamine\ 123]_2PtCl_4 \cdot H_2O$. The First Tetrachloroplatinate(II) Salt with Anti-cancer Activity, Inorganic Chemistry, 25: 3980

Kastner, M.E., Fackler, P.H., Podbielski, L., Charkoudian, J., and Clarke, M.J. 1986. A Dissymmetric μ-Oxo Technetium Complex. Inorganica Chimica Acta, 114(1): L11-L15

Lindsay, M.J., Fackler, P.H., Clarke, M.J., and Kastner, M.E. 1985. Synthesis and Structure of $trans\text{-}[O_2(Im)_4Tc]Cl\cdot 2H_2O$, $trans\text{-}[O_2(1\text{-}Me\text{-}Im)_4Tc]Cl\cdot 3H_2O$ and Related Compounds. Inorganica Chimica Acta, 109(1): 39

PAUL H. FACKLER

Fackler, P.H., Czerwinska, A., Deutsch, E., Yelton, R., Schumaker, R. and Lieberman, M.L. 1985. Synthesis, Characterization, and Thermal Decomposition of tr[Co($^{15}NH_2$)(N_4CCN)(NH_3)$_4$](ClO_4)$_2$. Presented at the 190th National Meeting of the American Chemical Society; Chicago, Illinois; September 1985; Inorganic Paper #175

Fackler, P.H., Kastner, M.E., Clarke, M.J., and Deutsch, E. 1984. Synthesis and Structure of trans-$[O_2(TBP)_4Tc]^+$ (TBP = 4-tert-butylpyridine) and Related Complexes. Inorganic Chemistry, 23: 46836

Fackler, P.H., Kastner, M.E., and Clarke, M.J. 1984. Synthesis, Spectra, and Structure of af-dibromo-b-ethoxo-d-oxo-ce-bis(4-nitropyridine)technetium(V) and Related Complexes. Inorganic Chemistry, 23: 3968

Fackler, P.H., Kastner, M.E., and Clarke, M.J. 1982. Synthesis and Structure of Oxo Technetium Complexes with Pyridine Ligands. Presented at the 186th Meeting of the American Chemical Society; Washington, D.C.; August 1983; Inorganic Paper #106

Clarke, M.J. and Fackler, P.H. 1982. The Chemistry of Technetium: Toward Improved Diagnostic Agents. Structure and Bonding, 50: 55

CURRICULUM VITAE

Steven R. Pollock, R.Ph., M.B.A.

PROFESSIONAL EXPERIENCE

November, 1991 - Present

Associate Director, Regulatory Affairs/Department Manager, Regulatory Affairs
SCHWARZ PHARMA/Kremers Urban Company
Milwaukee, Wisconsin

This position is accountable for overseeing all operational and registrational regulatory affairs activities for this smaller sized ($65 million) PMA company. Department manager responsibility includes supervision of five regulatory professionals, three technicians and two clerical personnel. Registrational activity includes primary responsibility for all interactions with the following FDA Divisions: the Center for Biologic Evaluation and Research (CBER), the Division of Cardio-Renal, Division of Gastrointestinal and Coagulation, Division of Metabolism and Endocrine and the Office of Generic Drugs. Operational responsibilities includes oversight of label and promotional material review and interacting with the FDA on a local and district level. In addition, this position is responsible for the overseeing of the development of good clinical practices standard operating procedures (GCP-SOP's) and assuring company compliance with GCP's.

April, 1990 - November, 1991

FDA Regulatory Affairs Manager/FDA Regulatory Liaison Specialist
U. S. Pharmaceutical Regulatory Affairs
The Upjohn Company, Kalamazoo, MI

The position was accountable for the effective management of U.S. registration of human pharmaceutical products to expedite market introduction. This accountability included new product development, licensed acquisitions and existing marketed products within assigned therapeutic areas. Position acted as primary liaison with the FDA and interacted with the following FDA divisions: Pilot Drug Evaluation, Division of Anti-Viral, Division of Oncology and Pulmonary, Division of Medical Imaging, Surgical and Dental Drug Products, and the Center for Biologic Evaluation and Research.

November, 1984 - April, 1990

Senior Medical Research Associate/Medical Research Associate
Clinical Pharmacokinetics
The Upjohn Company, Kalamazoo, MI

This position was accountable for the design, implementation and evaluation of data for biopharmaceutic and pharmacokinetic clinical studies of assigned corporate projects. The studies were conducted to support development and registration of new products, facilitate formulation or manufacturing changes for existing products and generate bioavailability data to protect the market position of existing products. Experience included assisting in the preparation of biopharmaceutic and pharmacokinetic components of NDAs for submission to Food and Drug Administration and international dossiers for submission to international regulatory agencies. In addition, this position was responsible for tracking of both the unit clinical grant and unit operational budgets.

March, 1982 - November, 1984

Developmental Pharmacist, III/Developmental Pharmacist II/Developmental Pharmacist
Formulation and Pharmacy (Ag. Research and Development)
The Upjohn Company, Kalamazoo, MI

Responsibilities included the research and development of new formulations of assigned corporate projects in the area of veterinary pharmaceuticals. Experience included work in the lyophilization, sterile powders and compressed tablet areas. Experience included work in formulation development, stability protocols, raw material evaluations, and product support.

June, 1979 - March, 1982

Retail/Consultant Pharmacist
Lange's Pharmacy, Racine, Wisconsin

January 1987 - May 1987

Associate Professor of Finance
Western Michigan University
Kalamazoo, MI.

PERSONAL INFORMATION

Business Address:

SCHWARZ PHARMA Kremers Urban
P. O. Box 2038
Milwaukee, WI 53201
(414) 362-4335

Home Address:

5829 N. Bay Ridge Avenue
Whitefish Bay, WI 53217
(414) 332-5803

EDUCATION

M.B.A.

Masters in Business Administration - Corporate Finance)
Western Michigan University
Kalamazoo, Michigan
Degree awarded December, 1986

B.S. in Pharmacy

School of Pharmacy
University of Wisconsin
Madison, Wisconsin
Degree awarded May, 1979

PROFESSIONAL ORGANIZATIONS

Regulatory Affairs Professional Society
Drug Information Association

PUBLICATIONS

1. "Bioavailability of Flurbiprofen Following Buccal Administration," D. J. Stalker and S. R. Pollock, Pharmaceutical Research, 8, 5, (1991), pp 605 -607.

2. "Extent and Variability of the First-Pass Elimination of Adinazolam Mesylate In Healthy Male Volunteers," J. C. Fleishaker, H. Friedman, S. R. Pollock, Pharmaceutical Research, 8, 2, (1991), pp 162 - 167.

3. "Clinical Pharmacology of Adinazolam and N-desmethyladinazolam Mesylate Following Single Oral Doses of Each Compound in Healthy Volunteers," J. C. Fleishaker, H. Friedman, S. R. Pollock, T.C. Smith, Clin. Pharmacol. Ther., 48:652-664 (Dec 1991).

4. "Clinical Pharmacology Approaches to the Assessment of Novel Drug Delivery Concepts", S. R. Pollock and L. S. Olanoff, J. Controlled Release, 11, (1990) 331-341.

5. "Pharmacokinetic Interaction Between Flurbiprofen and Maalox in Healthy Volunteers," G. Caille, P. duSouich, M. Vezina, S. R. Pollock and D. J. Stalker, Biopharm. Drug Dispos., Vol. 10, 6078-615 (1989).

ABSTRACTS

1. In Vitro/In Vivo Correlations for Prototype SR Formulations of NSAIDs I. Formulation Specificity, S. R. Cox, D. J. Stalker, S. R. Pollock, M. V. Mikelsons, J. A. Sytsma, Pharm. Res., 7(9) (Supplement): S-306 (1990).

2. Kinetics/Dynamics of Adinazolam and its Metabolite N-Desmethyladinazolam After oral Administration of Each Compound in Man, J. C. Fleishaker, H. L. Friedman, S. R. Pollock, T. C. Smith, Pharm. Res., 6(9) (Supplement): S-241 (1989).

3. The Influence of Food and Milk on the Bioavailability of Flurbiprofen, D. J. Stalker, S. R. Pollock, Pharm. Res., 6(9) (Supplement): S-230 (1989)

4. The Pharmacokinetics of Minoxidil in Normal Volunteers After the Administration of 2.5 and 20 mg as Loniten Tablets and as Oral Solution, S. R. Pollock, D. J. Stalker, Pharm. Res., 5(10) (Supplement):S-179 (1988).

5. The Effects of Antacid on the Bioavailability of Flurbiprofen in Elderly Subjects, D. J. Stalker and S. R. Pollock, Pharm. Res., 4 (Supplement): S-92 (1987).

6. The In-Vivo Assessment of Buccal Absorption of Flurbiprofen, D. J. Stalker, S. R. Pollock and K. S. Albert, Pharm. Res., 3 (Supplement): 113S (1986).

7. The Bioavailability of Ibuprofen Rectal Suppositories, D. J. Stalker, S. R. Pollock and K. S. Albert, Pharm. Res., 3 (Supplement): 112S (1986).

ITEM 13: CERTIFICATION

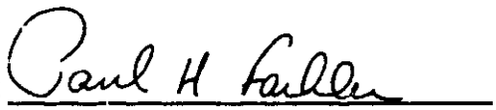
The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for preparation of the environmental assessment.

DATE: March 2, 1995

SIGNATURE OF RESPONSIBLE OFFICIAL: 

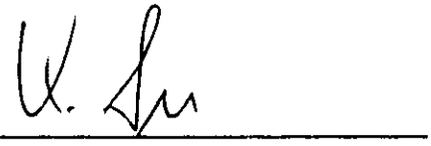
TITLE: Associate Director, Regulatory Affairs
SCHWARZ PHARMA Kremers Urban Company

DATE. March 2, 1995

SIGNATURE OF RESPONSIBLE OFFICIAL: 

TITLE: Manager, Analytical Chemistry
Springborn Laboratories

DATE: March 2, 1995

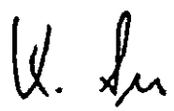
SIGNATURE OF RESPONSIBLE OFFICIAL: 

TITLE: Dr. rer.nat. Klaus Sandrock, Dipl. Chem.
Director Safety and Environmental Department
SCHWARZ PHARMA AG

Moxidectin NDA 20-312 Environmental Assessment

Confirmation of complete signature

Herewith I confirm that the signature below is complete and is my full signature.



Dr. Klaus Sandrock
Director Environmental Protection
and Safety
2 December 1996\mosid\sandsig

ITEM 14: REFERENCES

1. NDA #20-312 for Moexipril HCl Tablets submitted to FDA on December 18, 1992 (Confidential)

2. USAN and the USP dictionary of drug names. 1995. The United States Pharmacopeial Convention Inc. 12601 T brook Parkway, Rockville, MD 20852

3. Code of Federal Regulations. (1994). Part 25 - Environmental impact considerations. U.S. Food and Drug Administration. Department of Health and Human Services. 21 CFR Part 25.31 (a).

4. Ericksen C, Harrass M, Osborne C, et al. (1987). Environmental assessment technical assistance handbook. U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition and Center for Veterinary Medicine. NTIS PB87-175345.

5. Gu L. and Strickley R. Diketopiperazine formation, hydrolysis, and epimerization of the new dipeptide angiotensin-converting enzyme inhibitor RS-10085. Pharmaceutical Research, 4 (1987): 392-397. (Non-confidential)

6. Gu L. and Strickley R. Preformulation stability studies of the new dipeptide angiotensin-converting enzyme inhibitor RS-10029. Pharmaceutical Research, 5 (1988): 765-771. (Non-confidential)

7. Gu L. and Strickley R. A profound solvent effect on the diketopiperazine formation of the new dipeptide angiotensin-converting enzyme inhibitor, moexipril. International Journal of Pharmaceutics, 60 (1990): 99-107. (Non-confidential)

8. Gu L., Strickley R., Chi L., and Chowhan Z. Drug-excipient incompatibility studies of the dipeptide angiotensin-converting enzyme inhibitor, moexipril hydrochloride: Dry powder vs wet granulation. Pharmaceutical Research, 7 (1990): 379-383. (Non-confidential)

9. Strickley R., Visor G., Lin L., and Gu L. An unexpected pH effect on the stability of moexipril lyophilized powder. Pharmaceutical Research, 6 (1989): 971-975. (Non-confidential)

ITEM 15: APPENDICES

1. Sites involved in the Manufacture of Moexipril HCl Tablets (Confidential)

2. Letters of Authorization (Confidential)

3. Descriptions of environments for manufacturing, packaging and disposal facilities (Confidential)

4. Statement of Commitment Excipients of moexipril HCl for film-coated 7.5 mg and 15 mg tablets (Confidential)

   Composition of Moexipril HCl 7.5 mg and 15 mg Tablets

   Stability specification 3707.SPC.07, 7.5 mg tablets (Confidential)

   Stability specification 3715.SPC.08, 15 mg tablets (Confidential)

5. In vitro inhibition of purified angiotensin-converting enzyme from rabbit lung (Study GIHBP-001-92) (Confidential)

   LPT acute toxicity study of DKP of moexipril by oral administration to NMRI mice (Study 6902/91) (Confidential)

   LPT acute toxicity study of DKP of moexipril by oral administration to Sprague-Dawley Rats (Study 6901/91) (Confidential)

6. A phase I, open-label drug disposition study to determine the absorption, metabolism and excretion of (^{14}C)-labelled moexipril following oral and intravenous administration to healthy male volunteers (GHBA-628) (Confidential)

7. **SIFA Ltd.** Environmental Impact Analysis on the Manufacture of Moexipril HCl (Confidential)

   - General Compliance Statement (Non-confidential)

   Orgamol Ltd. Environmental Assessment (Moexipril HCl) (Confidential)

   - General compliance statement (Orgamol) (Non-confidential)

   Schwarz Pharma AG Environmental Assessment - Moexipril (Confidential)

   - General Compliance Statement (Non-confidential)

   - Letter from German Ministry and English Translation (Non-confidential)

ITEM 15: APPENDICES (cont.)

Schwarz Pharma Kremers Urban Company General Compliance Statement (Non-confidential)

- Standard Operating Procedure "General Cleaning and Housekeeping of Packaging Facilities" (Confidential)

Anderson Packaging EA covering introduction of substances into the environment (Confidential)

Sharp Packaging EA covering introduction of substances into the environment (Confidential)

Packaging Coordinators, Inc. EA covering introduction of substances into the environment (Confidential)

BFI-American Ref-Fuels letter and **Hempstead Resource Recovery Facility** history and initial operating results (Confidential)

8. Residual substances expected to be entering the environment during drug substance manufacture (Confidential)

SPAG EA covering introduction of substances into the environment (Confidential)

Estimation of Moexipril HCl Particulate Matter (dust) generated by Packaging Operations (Confidential)

Estimation of Exposure of Moexipril HCl and its Metabolites to the Aquatic Environment (Confidential)

Certificate of Analysis (SPAG) Moexipril hydrochloride (Confidential)

Certificate of Analysis (Orgamol) Moexipril hydrochloride (Confidential)

Certificate of Analysis (SPAG) Moexiprilat (Confidential)

9. Final protocol and results for moexipril HCl - Acute toxicity to daphnids (*daphnia magna*) under static conditions (Confidential)

Final protocol and results for moexiprilat - Acute toxicity to daphnids (*daphnia magna*) under static conditions (Confidential)

Final protocol and results for moexipril HCl - Determination of microbial growth inhibition (Confidential)

ITEM 15: APPENDICES (cont.)

Final protocol and results for moexiprilat - Determination of microbial growth inhibition (Confidential)

10. Material Safety Data Sheet (MSDS) for Moexipril HCl (Nonconfidential)

11. Moexipril HCl Package insert (Nonconfidential)

ATTACHMENT II

Material Safety Data Sheet
May be used to comply with OSHA's Hazard Communication Standard, 29 CFR 1910.1200. Standard must be consulted for specific requirements.

U.S. Department of Labor
Occupational Safety and Health Administration
(Non-Mandatory Form)
Form Approved
OMB No. 1218-0072

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IDENTITY (As Used on Label and List) | Note: Blank spaces are not permitted. If any item is not applicable, or no information is available, the space must be marked to indicate that.

Section I

Manufacturer's Name: SCHWARZ PHARMA AG	Emergency Telephone Number: 00353 61 62 199 (SIFA Ltd.)
Address (Number, Street, City, State, and ZIP Code): Alfred-Nobel-Str. 10	Telephone Number for Information: 0040 61 901 54-50 (SELOC AG)
D-W-4019 Monheim	Date Prepared: 11-05-1992
	Signature of Preparer (optional): Dr. K. Sandrock

Section II — Hazardous Ingredients/Identity Information

Hazardous Components (Specific Chemical Identity; Common Name(s))	OSHA PEL	ACGIH TLV	Other Limits Recommended	% (optional)
2-(2-((1-Ethoxycarbonyl)-3-phenylpropyl)-amino-oxopropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, hydrochloride (S,S,S)				
C27 H35 N2 O7 Cl MW: 535.04				
CAS-No.: 82856-52-5				

Information on toxicity: LD50 mice oral: 2360 mg/kg
LD50 rat oral: 4150 mg/kg

ACE inhibitors may be fetotoxic when administered during the second and third trimesters of pregnancy. There are no adequate and well controlled studies in pregnant women. Appropriate protective equipment should be worn by wome during pregnancy.

Section III — Physical/Chemical Characteristics

Boiling Point		Specific Gravity (H_2O = 1)	
Vapor Pressure (mm Hg.)		Melting Point: 155 - 160 ° C	
Vapor Density (AIR = 1)		Evaporation Rate (Butyl Acetate = 1)	

Solubility in Water: > 100 g / 1 (20 ° C)

Appearance and Odor: fine white to off-white powder without odour

Section IV — Fire and Explosion Hazard Data

Flash Point (Method Used): ./.	Flammable Limits: ./.	LEL	UEL

Extinguishing Media: CO_2, water, foam or powder

Special Fire Fighting Procedures: ./.

Unusual Fire and Explosion Hazards: ./.

Section V — Reactivity Data

Stability	Unstable		Conditions to Avoid ./.
	Stable	X	

Incompatibility (Materials to Avoid)

Hazardous Decomposition or Byproducts

Hazardous Polymerization	May Occur		Conditions to Avoid ./.
	Will Not Occur	X	

Section VI — Health Hazard Data

Route(s) of Entry: Inhalation? harmful Skin? Ingestion? harmful

Health Hazards (Acute and Chronic)

Carcinogenicity: NTP? IARC Monographs? OSHA Regulated?

Signs and Symptoms of Exposure: Exposure can cause: hypotensive effects

Medical Conditions Generally Aggravated by Exposure

Emergency and First Aid Procedures: Body: Remove contaminated clothes. Wash skin with water and soap. Eyes: Flush with copious amounts of water for at least 15 minutes. Inhalation: Remove to fresh air. Call a physician. Ingestion: Call a physician.

Section VII — Precautions for Safe Handling and Use

Steps to Be Taken in Case Material Is Released or Spilled

Sweep up and place in closed containers for disposal.

Waste Disposal Method: Dispose of in accordance with all local, state and federal regulations.

Precautions to Be Taken in Handling and Storing: Store in well closed containers. Avoid inhalation of dust.

Minimize direct contact with skin and eyes.

Other Precautions

Section VIII — Control Measures

Respiratory Protection (Specify Type): dust mask

Ventilation	Local Exhaust	Special
	Mechanical (General)	Other

Protective Gloves: Latex gloves | Eye Protection: should be worn

Other Protective Clothing or Equipment

Work/Hygienic Practices: Observe working regulations for pharmaceuticals.

MATERIAL SAFETY DATA SHEET

	Product name	: MOXIPRIL-(SPM-925)
	Status	: 29.04.94
1.1	Chem.characterization	: (2-(2-((1-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-oxopropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, hydrochloride (S,S,S) C27 H35 N2 O7 Cl MW: 535,04 CAS-No.: 82586-52-5
1.2	Form	: fine powder
1.3	Colour	: white to off-white
1.4	Odour	: without odor
1.5	Hazardous constituents	:

	Physical data and safety data		
2.1	Change in physical state		Tested according to:
	Melting point	: 155-160 °C	Dec.
2.2	Density	: (°C)	g/cm3
		(bar)	
2.3	Vapour pressure	: (°C)	mbar
		(°C)	mbar
2.4	Viscosity dynam.	: (°C)	
2.5	Solubility in water	: (20 °C)	> 100g/l
	other solvents	: Ethanol 166 g/l	
2.6	pH value	: (20 °C)	1,8
		at g/l H_2O = 100	
2.7	Flash point	: °C	
2.8	Ignition temperature	: °C	
2.9	Explosion limits -top:		
	-bottom:		
2.10	Thermal decomposition	:	
2.11	Hazardous decomposition products	:	
.12	Hazardous reactions	:	
2.13	Further information	:	

3.	Transport		Packaging group
	GGVSee/IMDG-Code	:	
	GGVS/GGVE	:	
	RID/ADR	:	
	ICAO/IATA-DRG	:	
	MFAG	:	
	EMS	:	
	UN-Nummer	:	
	Other information	:	

not applicable

4. Regulations

Danger	:	
Danger symbols	:	
R-phrases	:	
S-phrases	:	07/09-20/21-24/25 Keep container tightly closed and in a well-ventilated place. When using do not eat, drink or smoke. Avoid contact with skin and eyes.
VbF	:	
Other points	:	

5. Protective measures, storage and handling

5.1	Technical protective measure	:	Avoid inhalation of dust. Minimize direct contact with skin and eyes.
5.2	Personal protective equipment		
	- Respiration	:	In case of dust
	- Eye protective	:	Eye protection should be worn.
	- Hand protective	:	latex gloves
	- Other	:	
5.3	Industrial hygiene	:	Don't eat, drink or smoke during work; wash thoroughly after handling.
5.4	Protection against fire and explosion	:	
5.5	Disposal	:	Dispose of in accordance with all local, state and federal regulations.
	Waste code (D)	:	53502

6. Measures in case of accidents and fires

6.1	After spillage/leakage/gas leakage	:	Sweep up and place in closed containers for disposal. Dispose of in accordance with all local, state and federal regulations.
6.2	Extinguishing media Suitable	:	Water, foam, carbon dioxide.
6.3	Firstaid		
	Body	:	Remove and wash contaminated clothing promptly. Wash skin with water and soap.
	Eyes	:	In case of contact, immediately flush eyes with copious amounts of water for at least 15 minutes.
	Respiratory	:	Remove to fresh air. Call a physician.
	Devour	:	Call a physician.
6.4	Further information for the doctor	:	
6.5	Other information	:	

7. Information on toxicity

Results from animal experiments

LD50 oral	:	(Mouse) 2360 mg/kg
LC50 inhal	:	( )
Risk for health	:	Exposure can cause: hypotensive effects.
Other characteristics	:	

ACE inhibitors may be fetotoxic when administered during the second and third trimesters of pregnancy. There are no adequate and well controlled studies in pregnant woman. Appropriate protective equipment should be worn by women during pregnancy.

LD 50 rat oral 4150 mg/kg.

8. Information on ecological effects

8.1 Acute toxicity

8.2 Other information : Moexipril is a pharmaceutical substance with applications to humans, so any ecological problems appear unlikely. So we have no information about any problems in a sewage plant.

Water endangering class

9. For further information and for emergency contact:

Schwarz Pharma AG
Environmental Protection and Safety Dept.
Alfred-Nobel-Str. 10
40789 Monheim
Tel. 02173 - 481185

All the above-mentioned details correspond to our current level of knowledge. These details describe the product with regard to safety data; they do not guarantee the product properties in the sense of the technical specifications.

ATTACHMENT III

SIFA LTD.
FINE CHEMICAL MANUFACTURERS

GENERAL COMPLIANCE STATEMENT

SHANNON
CO. CLARE
IRELAND
TELEPHONE 061-472199
TELEX 72094 SIFA EI
TELEFAX 061-472484

SIFA Ltd. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of ***Moexipril Hydrochloride*** at its facilities in Shannon, Co. Clare as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of ***Moexipril Hydrochloride*** at its facilities in Shannon, Co. Clare.

Signed:

J. O'Donoghue

John O'Donoghue
Safety & Environmental Manager
20th February, 1995

Orgamol SA
CH-1902 EVIONNAZ (VS) SUISSE

FABRICATION DE
PRODUITS CHIMIQUES

GENERAL COMPLIANCE STATEMENT

Orgamol SA states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Moexipril Hydrochloride at its facilities in Evionnaz (CH) as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Moexipril Hydrochloride at its facilities in Evionnaz (CH).

Signed :

J.-P. Surbeck

Title: Managing Director

Date : 24.02.1995

SCHWARZ PHARMA AG, D-W 4019 Monheim, West Germany

GENERAL STATEMENT OF COMPLIANCE

SCHWARZ PHARMA AG states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of MOEXIPRIL HYDROCHLORIDE tablets at its facilities in MONHEIM, GERMANY, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of MOEXIPRIL HYDROCHLORIDE tablets at its facilities in MONHEIM, GERMANY.

Signed:

Dr Klaus Sandrock
Director
Safety and Environmental Department
November 10, 1992

SCHWARZ
PHARMA

KREMERS URBAN COMPANY

GENERAL COMPLIANCE STATEMENT

SCHWARZ PHARMA Kremers Urban Company states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the packaging of moexipril hydrochloride (HCl) 7.5 mg and 15 mg tablets at its facilities in Mequon, Wisconsin as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the packaging of moexipril hydrochloride (HCl) 7.5 mg and 15 mg tablets at its facilities in Mequon, Wisconsin.

Federal regulations and guidelines include:

1) **Clean Air Act (40 CFR § 50-69):**

A) Federal standards established under:

National Primary Ambient Air Quality Standards (NPAAQS)
and
National Emission Standards for Hazardous Air Pollutants (NESHAP)

B) State standards established under:

Department of Natural Resources (DNR)
Wisconsin Statutes § 144.30 - 144.426
Implementation Regulations:
Wisconsin Administrative Code
NR 400- NR 494

2) **Federal Water Pollution Control Act (40 CFR § 100-149, 400-469):**

A) Federal standards established under:

The Clean Water Act
and
National Pollution Discharge Elimination System
(NPDES, 40 CFR § 122)

Mail P.O. Box 2038 · Milwaukee, WI 53201 · 5600 W. County Line Road · Mequon, WI 53092
Phone 414-354-4300 · Telex 4311043 · Fax 414-354-4309

3) Resource Conservation and Recovery Act (40 CFR § 240-300):

A) Product incinerated at:

BFI/American Ref-Fuels Hempstead Resource Recovery Facility
Permit No.: 2820005643
Combustion gas temperature is maintained above 1500° F after the last point of overfire air injection.

B) Hazardous Waste Management

Wisconsin Statutes § 144.60 - 144.77

C) Solid Waste and Recycling

Wisconsin Statutes § 144.43 - 144.52

4) Occupational Health and Safety Administration (29 CFR § 1901):

The following information should serve to assure that all applicable OSHA guidelines are currently being met:

SCHWARZ PHARMA Kremers Urban Company (SPKU) processes and procedures are engineered to preclude personal and environmental contamination. The air in the manufacturing and packaging areas is filtered through dust collection devices, and the resulting solids are disposed of through an approved waste management group (BFI/American Ref-Fuels Hempstead Resource Recovery Facility, Westbury, N.Y.). SPKU's production and packaging operators are provided adequate personal protection through approved procedures and personal protection equipment -- i.e., clothing, glasses, and respiratory system protectors.

SIGNED:

Gunter E. Pawlowski
Senior Vice President of Operations
SCHWARZ PHARMA
Kremers Urban Company
March 2, 1995

Steven R. Pollock
Associate Director of Regulatory Affairs
SCHWARZ PHARMA
Kremers Urban Company
March 2, 1995

ATTACHMENT IV

Ministerium für Umwelt, Raumordnung und Landwirtschaft
des Landes Nordrhein-Westfalen

Ministerium für Umwelt, Raumordnung und Landwirtschaft · Postfach 300632 · 4000 Düsseldorf 30

Schwannstraße 3, 4000 Düsseldorf 30
Telefon (02 11) 45 66 - 0
Durchwahl (02 11) 45 66 - 521
Telefax (02 11) 45 66 - 3 88
Teletex 211709=UMNW

An
Schwarz Pharma AG
Postfach 10 06 92

4019 Monheim

EINGANG
- 9. Okt. 1992
Abt. Umweltschutz / Arbeitssicherheit / Synthese

Datum
6. Oktober 1992
Aktenzeichen (bei Antwort bitte angeben)
IV C 4- 31.8.1

Betr.: Umweltschutzerklärung

Bezug: Ihre Schreiben vom 1.6. und 9.7.1992 - UAW/Dr. Sa-If -

Anhand der mir vorliegenden Bescheinigungen

- des Regierungspräsidenten Düsseldorf - GMP-Zertifikat für pharmazeutische Produkte,
- des Stadtdirektors der Stadt Monheim - Genehmigung der Einleitung von Abwässern mit Anteilen an Äthanol und Aceton in das städtische Kanalnetz,
- des Oberkreisdirektors des Kreises Mettmann - Bestätigung über die Einhaltung der Einleitungsgrenzwerte von Abwässern des Werkes Monheim, Mittelstraße,
- des Staatlichen Gewerbeaufsichtsamtes Düsseldorf - baurechtliche oder spezielle Genehmigungen zur Errichtung und Betrieb der Anlagen, Luftreinhaltung,
- des Regierungspräsidenten Münster - Entsorgungs-/ und Verwertungsnachweis für pharmazeutische Produktionsrückstände und Altarzneimittel,

bestätige ich, daß eine gesetzes- und genehmigungskonforme Betriebsweise Ihrer Anlagen vorliegt.

Im Auftrag

(Huber)

Ministerium für Umwelt, Raumordnung und Landwirtschaft
des Landes Nordrhein-Westfalen
(Ministry for the Environment, Regional Planning and Agriculture
of the Land of North Rhine-Westphalia)
Schwannstr. 3
D-W-4000 Düsseldorf 30

Schwarz Pharma AG
Postfach 100692

4019 Monheim

Date: 6 October, 1992
Reference: IV C 4- 31.8.1

Re: Declaration of compliance with environment regulations
Ref.: Your letters of 1 June and 9 July, 1992 - UAW/Dr. Sa-If -

On the basis of the certificates on file, issued by

- the Regierungspräsident [chief official in the administrative district] of Düsseldorf: GMP certificate for pharmaceutical products,
- the Stadtdirektor [administrative head] of the city of Monheim: permission to drain waste water containing ethanol and acetone into the municipal sewage system,
- the Oberkreisdirektor [administrative head] of the district of Mettmann: confirmation of the compliance with the drainage limit values of the waste water emitted by the plant located in Monheim, Mittelstraße,
- the Staatliches Gewerbeaufsichtsamt [Trade Inspection Office], Düsseldorf: licences pursuant to the building law or special licences to build and operate those plants, air pollution control,
- the Regierungspräsident of Münster: certificate on the disposal and utilization of the waste of pharmaceutical production and of old pharmaceuticals,

I confirm that your plants are operated in agreement with the law and the necessary licences.

By order
Huber

Swora Translation

Übersetzungsbüro
Lic.-Phil. R. Kaufmann
Hamburgerstr. 25 51381 Leverkusen
Tel. (02171) 84530 Fax: (02171) 51283

Nov 28, 1994

Richard Cornelius Kaufmann 3152-753

ATTACHMENT V

INTERKANTONALE KONTROLLSTELLE FÜR HEILMITTEL - BERN
OFFICE INTERCANTONAL DE CONTRÔLE DES MÉDICAMENTS - BERNE
UFFICIO INTERCANTONALE DI CONTROLLO DEI MEDICAMENTI - BERNA

Certificate

We certify herewith

that Orgamol SA, CH-1902 Evionnaz, Switzerland , have been duly authorized to manufacture and sell bulk pharmaceutical chemicals in Switzerland;

that Orgamol SA, CH-1902 Evionnaz, are keeping the required level for good practices in the manufacture of bulk pharmaceutical chemicals according to the Swiss regulations in force. These regulations are in accordance with the requirements for good practices in the manufacture and quality control as recommended by the Pharmaceutical Inspection Convention (PIC) and the World Health Organization;

that the manufacturing plant of Orgamol SA, CH-1902 Evionnaz, is subject to official periodic inspections;

that the requirements regarding manufacture and quality control for bulk pharmaceutical chemicals for export are identical to those applicable to products sold in Switzerland.

This certificate is valid until 30 September 1996 and can be renewed if the firm continues to fulfil the specified requirements.

Berne, 16 September 1994
No HK94-325

INTERCANTONAL OFFICE
for the Director
M. Zobrist
Dr. M. Zobrist

94-325.DOC/Lr

END

J.H.M. RESEARCH &DEVELOPMENT, INC. 5776 SECOND STREET,N.E. WASH. DC 20011