studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in Table 1.

Table 1: Osteoporosis Treatment Studies in Postmenopausal Women Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX* % (n=196)	Placebo % (n=397)	FOSAMAX† % (n=3236)	Placebo % (n=3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

* 10 mg/day for three years

† 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

Gastrointestinal Adverse Reactions: One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin, developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered. In the Study 1 and Study 2 populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. *[See Warnings and Precautions (5.1).]*

Laboratory Test Findings: In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Weekly Dosing

The safety of FOSAMAX 70 mg once weekly for the treatment of postmenopausal osteoporosis was assessed in a one-year, double-blind, multicenter study comparing FOSAMAX 70 mg once weekly and FOSAMAX 10 mg daily. The overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse reactions considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in Table 2.

Table 2: Osteoporosis Treatment Studies in Postmenopausal Women Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Once Weekly FOSAMAX 70 mg % (n=519)	FOSAMAX 10 mg/day % (n=370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Prevention of Osteoporosis in Postmenopausal Women

Daily Dosing

The safety of FOSAMAX 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse event occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

Weekly Dosing

The safety of FOSAMAX 35 mg once weekly compared to FOSAMAX 5 mg daily was evaluated in a one-year, double-blind, multicenter study of 723 patients. The overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse reactions from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in Table 3.

Table 3: Osteoporosis Prevention Studies in Postmenopausal Women Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant Use with Estrogen/Hormone Replacement Therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Osteoporosis in Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse event were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse reactions considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in Table 4.

Table 4: Osteoporosis Studies in Men Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients

	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Glucocorticoid-Induced Osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse reactions considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in Table 5.

Table 5: One-Year Studies in Glucocorticoid-Treated Patients Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's Disease of Bone

In clinical studies (osteoporosis and Paget's disease), adverse events reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal

adverse reactions in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse events occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of FOSAMAX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications, have also been reported *[see Dosage and Administration (2); Warnings and Precautions (5.1)]*.

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with delayed healing, has been reported rarely *[see Warnings and Precautions (5.4)]*.

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating *[see Warnings and Precautions (5.3)]*; joint swelling; low-energy femoral shaft and subtrochanteric fractures *[see Warnings and Precautions (5.5)]*.

Nervous System: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

7 DRUG INTERACTIONS

7.1 Calcium Supplements/Antacids

Co-administration of FOSAMAX and calcium, antacids, or oral medications containing multivalent cations will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

7.2 Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

7.3 Nonsteroidal Anti-Inflammatory Drugs

FOSAMAX may be administered to patients taking nonsteroidal anti-inflammatory drugs (NSAIDs). In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of

fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

Reproduction studies in rats showed decreased postimplantation survival and decreased body weight gain in normal pups at doses less than half of the recommended clinical dose. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at approximately 3 times the clinical dose in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. No similar fetal effects were seen when pregnant rabbits were treated with doses approximately 10 times the clinical dose.

Both total and ionized calcium decreased in pregnant rats at approximately 4 times the clinical dose resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as one tenth the clinical dose when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) also occurred in the female rats treated at approximately 4 times the clinical dose for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; intravenous calcium supplementation prevented maternal, but not fetal deaths.

Exposure multiples based on surface area, mg/m^2, were calculated using a 40-mg human daily dose. Animal dose ranged between 1 and 15 mg/kg/day in rats and up to 40 mg/kg/day in rabbits.

8.3 Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

8.4 Pediatric Use

FOSAMAX is not indicated for use in pediatric patients.

The safety and efficacy of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta (OI). One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain. The oral bioavailability in children was similar to that observed in adults.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including FOSAMAX. *[See Adverse Reactions (6.2).]*

8.5 Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies *[see Clinical Studies (14.1), (14.3), (14.4), (14.5)]*, 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall

differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

FOSAMAX is not recommended for patients with creatinine clearance <35 mL/min. No dosage adjustment is necessary in patients with creatinine clearance values between 35-60 mL/min *[see Dosage and Administration (2.8) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic impairment. No dosage adjustment is necessary *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

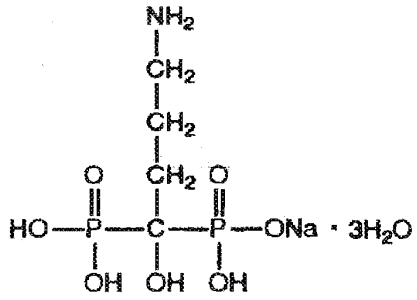
Dialysis would not be beneficial.

11 DESCRIPTION

FOSAMAX (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

FOSAMAX tablets for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. FOSAMAX 10 mg tablets also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial

raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

12.2 Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in Postmenopausal Women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis and once weekly FOSAMAX 35 mg for the

prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with FOSAMAX 5 mg/day. In one-year studies with once weekly FOSAMAX 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men

Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg.

Glucocorticoid-Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, FOSAMAX 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, FOSAMAX 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

FOSAMAX decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

12.3 Pharmacokinetics

Absorption

Relative to an intravenous reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single intravenous dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg intravenous dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following intravenous administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Specific Populations

Gender: Bioavailability and the fraction of an intravenous dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary in elderly patients.

Race: Pharmacokinetic differences due to race have not been studied.

Renal Impairment: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative intravenous doses of 35 mg/kg in young male rats. Although no formal renal impairment pharmacokinetic study has been conducted in patients, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with creatinine clearance 35 to 60 mL/min. FOSAMAX is not recommended for patients with creatinine clearance <35 mL/min due to lack of experience with alendronate in renal failure.

Hepatic Impairment: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic impairment. No dosage adjustment is necessary.

Drug Interactions

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to approximately 0.1 to 1 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to

approximately 0.3 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (approximately 1 times a 40 mg human daily dose based on surface area, mg/m^2).

13.2 Animal Toxicology and/or Pharmacology

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

Daily Dosing

The efficacy of FOSAMAX 10 mg daily was assessed in four clinical trials. Study 1, a three-year, multicenter double-blind, placebo-controlled, US clinical study enrolled 478 patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture; Study 2, a three-year, multicenter double blind placebo controlled Multinational clinical study enrolled 516 patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture; Study 3, the Three-Year Study of the Fracture Intervention Trial (FIT) a study which enrolled 2027 postmenopausal patients with at least one baseline vertebral fracture; and Study 4, the Four-Year Study of FIT: a study which enrolled 4432 postmenopausal patients with low bone mass but without a baseline vertebral fracture.

Effect on Fracture Incidence

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in Table 6.

Table 6: Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT (patients with vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)*				
≥1 new vertebral fracture	7.9	15.0	7.1	47[†]
≥2 new vertebral fractures	0.5	4.9	4.4	90[†]
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26[‡]
≥1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54[§]
Hip fracture	1.1	2.2	1.1	51[¶]
Wrist (forearm) fracture	2.2	4.1	1.9	48[¶]

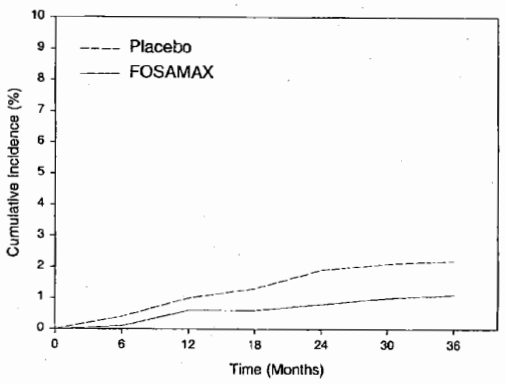
*Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
[†]p<0.001, [‡]p=0.007, [§]p<0.01, [¶]p<0.05

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. Figure 1 displays the cumulative incidence of hip fractures in this study.

Figure 1:

Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT (patients with radiographic vertebral fracture at baseline)



Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in Table 7 for the patients with osteoporosis.

Table 7: Effect of FOSAMAX on Fracture Incidence in Osteoporotic* Patients in the Four-Year Study of FIT (patients without vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)†				
≥1 new vertebral fracture	2.5	4.8	2.3	48‡
≥2 new vertebral fractures	0.1	0.6	0.5	78§
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22¶
≥1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)#
Hip fracture	1.0	1.4	0.4	29 (NS)#
Wrist (forearm) fracture	3.9	3.8	-0.1	NS#

*Baseline femoral neck BMD at least 2 SD below the mean for young adult women
†Number evaluable for vertebral fractures: FOSAMAX, n=1426; placebo, n=1428
‡p<0.001, §p=0.035, ¶p=0.01
#Not significant. This study was not powered to detect differences at these sites.

Fracture Results Across Studies

In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p=0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p=0.034).

FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p<0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p<0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p=0.035).

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

Effect on Bone Mineral Density

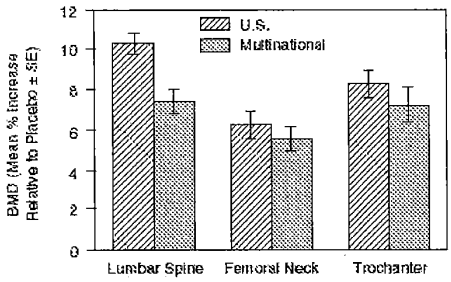
The bone mineral density efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration.

Figure 2 shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.

Figure 2:

Osteoporosis Treatment Studies in Postmenopausal Women

Increase in BMD
FOSAMAX 10 mg/day at Three Years

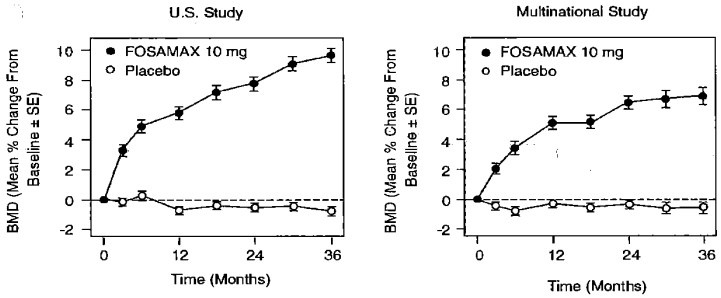


At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See Figure 3 for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean).

Figure 3:

Osteoporosis Treatment Studies in Postmenopausal Women

Time Course of Effect of FOSAMAX 10 mg/day Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



In patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups.

Bone Histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Effect on Height

FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Weekly Dosing

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Concomitant Use with Estrogen/Hormone Replacement Therapy (HRT)

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

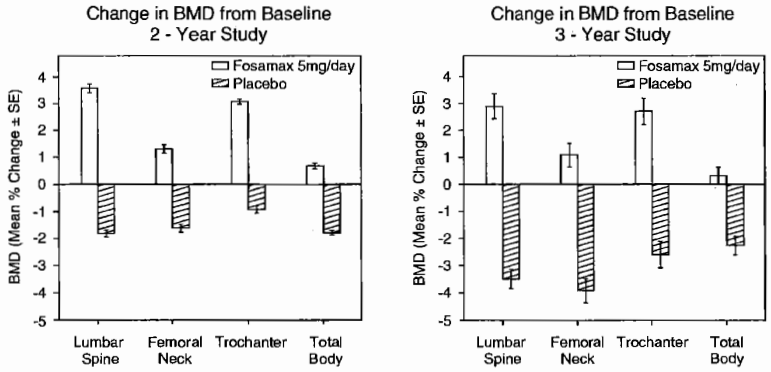
14.2 Prevention of Osteoporosis in Postmenopausal Women

Daily Dosing

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40-60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n=498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day; n=88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see Figure 4). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Figure 4:

Osteoporosis Prevention Studies in Postmenopausal Women



Bone Histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received FOSAMAX at doses of up to 10 mg/day.

Weekly Dosing

The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%; 95% CI) in the 5-mg daily group (n=298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

14.3 Treatment to Increase Bone Mass in Men with Osteoporosis

The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

Daily Dosing

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

Weekly Dosing

A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

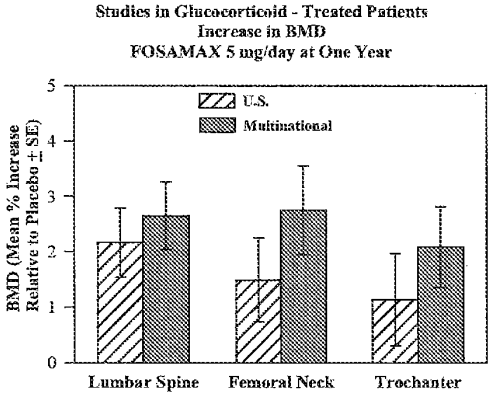
In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL vs. ≥9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >-2.5).

14.4 Treatment of Glucocorticoid-Induced Osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX

2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. Figure 5 shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.

Figure 5:



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received FOSAMAX 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with FOSAMAX 5 mg/day. The increases in BMD with FOSAMAX 10 mg/day were similar to those with FOSAMAX 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with FOSAMAX 10 mg/day were greater than those with FOSAMAX 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. FOSAMAX was effective regardless of dose or duration of glucocorticoid use. In addition, FOSAMAX was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received FOSAMAX at doses of up to 10 mg/day.

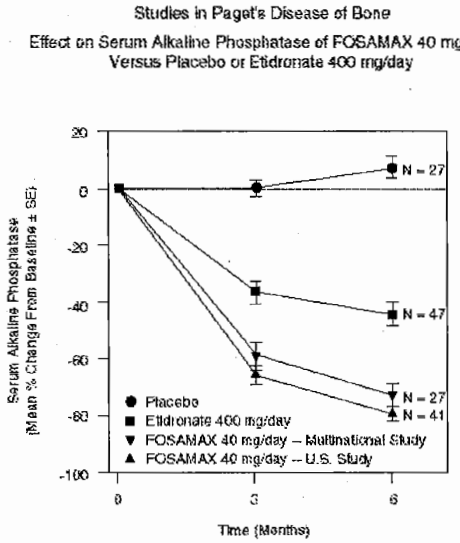
Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with FOSAMAX 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (FOSAMAX 0.7% vs. placebo 6.8%).

14.5 Treatment of Paget's Disease of Bone

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. Figure 6 shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.

Figure 6:



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for 6 months. As in patients treated for osteoporosis *[see Clinical Studies (14.1)]*, FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other:

- **NDC** 0006-0925-31 unit-of-use bottles of 30
- **NDC** 0006-0925-58 unit-of-use bottles of 100.

No. 3797 — Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other:

- **NDC** 0006-0936-31 unit-of-use bottles of 30
- **NDC** 0006-0936-58 unit-of-use bottles of 100
- **NDC** 0006-0936-28 unit dose packages of 100
- **NDC** 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets FOSAMAX, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other:

- **NDC** 0006-0077-44 unit-of-use blister package of 4
- **NDC** 0006-0077-21 unit dose packages of 20.

No. 8457 — Tablets FOSAMAX, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other:

- **NDC** 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets FOSAMAX, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other:

- **NDC** 0006-0031-44 unit-of-use blister package of 4
- **NDC** 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor:

- **NDC** 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15-30°C (59-86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Do not freeze.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Physicians should instruct their patients to read the Medication Guide before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

17.1 Osteoporosis Recommendations, Including Calcium and Vitamin D Supplementation

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

17.2 Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX *[see Clinical Pharmacology (12.3)]*.

Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6-8 oz). To facilitate gastric emptying, patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution.

Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day.

Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems.

Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Revised: 02/2012

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7. Bonefos Product Monograph, Part III: Consumer Information Bonefos® clodronate disodium, pages 25-28, revised September 22, 2011, *available at* http://www.bayer.ca/files/BONEFOS-PM-ENG-PT3-22SEP2011-147998.pdf ("Bonefos monograph")

PART III: CONSUMER INFORMATION

BONEFOS®
clodronate disodium

This leaflet is part III of a three-part "Product Monograph" published when BONEFOS was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about BONEFOS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

BONEFOS is used:

- for the management of hypercalcemia due to malignancy (high blood calcium in adult patients who have cancer), and
- as an adjunct in the management of osteolytic bone metastases (bone destruction when cancer cells have spread to the bone)

What it does:

BONEFOS belongs to a group of medicines called bisphosphonates. BONEFOS binds tightly to bone and blocks the function of cells which re-absorb bone. This strengthens the bones, and thus helps to relieve bone pain and prevent future problems with your bones (such as fractures). It also prevents the release of too much calcium into the blood (hypercalcemia).

When it should not be used:

You should not take BONEFOS if any of the following conditions apply to you.

- You have severe kidney disease.
- You have severe stomach or bowel problems.
- You are pregnant or breastfeeding.
- You are being treated with another bisphosphonate.
- You have an allergy to bisphosphonates, clodronate disodium, or to any ingredient in the formulation or component of the container of BONEFOS.

What the medicinal ingredient is:

Clodronate disodium

What the important nonmedicinal ingredients are:

Capsules: calcium stearate, colloidal anhydrous silica, gelatin, iron oxide (red and yellow), lactose, talc, titanium dioxide.

Solution for injection: sodium hydroxide, water for injection.

What dosage forms it comes in:

Capsules: Each yellow BONEFOS capsule contains 400 mg of clodronate disodium. BONEFOS capsules are provided in plastic bottles containing 120 capsules.

Solution for Injection: BONEFOS solution for injection is available in 5 mL glass ampoules containing anhydrous clodronate disodium 60 mg/mL. The solution must be diluted prior to infusion.

WARNINGS AND PRECAUTIONS

BEFORE starting treatment with BONEFOS talk to your doctor if:

- you suffer from kidney problems, as your dose may need to be reduced.
- you have stomach or bowel problems.
- you are pregnant or planning to become pregnant. BONEFOS should not be given during pregnancy.
- you are breast-feeding. Mothers being treated with BONEFOS should not breast-feed their children.
- you have ever had an allergic reaction to BONEFOS (or similar medicines called bisphosphonates) or any other ingredients of the drug or components of the container.
- you are presently taking another bisphosphonate.
- you have any dental problems or any dental procedures planned in the future.

Osteonecrosis (pronounced OSS-tee-oh-ne-KRO-sis) of the jaw, a rare condition that involves the loss or breakdown of the jaw bone, has been reported in patients with cancer receiving bisphosphonates. It is not known what role, if any, these medications played in its development. The majority of the cases were associated with dental procedures. Other possible factors that may increase the risk of osteonecrosis of the jaw include:

- chemotherapy;
- radiation therapy;
- steroid therapy (eg, cortisone);
- underlying cancer;
- anemia (low red blood cell count);
- infection; and
- poor dental health or poor oral hygiene.

If any of these risk factors applies to you, you should have a dental exam prior to starting treatment with BONEFOS. Be sure to tell your dentist about your cancer diagnosis and treatments.

Unusual fractures of the thigh bone have been reported with the use of bisphosphonates.

Contact your doctor if you feel any pain, weakness or discomfort in your thigh, hip or groin as this may be an early sign of a possible fracture of the thigh bone.

Visual (ocular) disturbances have been reported with bisphosphonate therapy. These include inflammation, infection, and/or irritation of the eye. Patients with visual disturbances other than uncomplicated conjunctivitis should be referred to an ophtalmologist for evaluation. Contact your doctor if you experience inflammation, infection and/or irritation of the eye.

The effect of BONEFOS on the ability to drive or use machines is not known.

Since there is no clinical experience in children, BONEFOS is only recommended for use in adult patients.

INTERACTIONS WITH THIS MEDICATION

Before you start treatment with BONEFOS, be sure to tell your doctor about any other prescription or over-the-counter medicines that you are using or intend to use.

Medicines that may interact with BONEFOS include:

- nonsteroidal anti-inflammatory drugs (NSAIDs), especially diclofenac;
- other bisphosphonates;
- other calcium-reducing agents, including corticosteroids, phosphate, calcitonin, mithramycin or loop diuretics (eg, furosemide);
- aminoglycoside antibiotics;
- estramustine phosphate;
- antacids; and
- dietary supplements containing calcium, iron, magnesium or aluminum.

BONEFOS capsules should be taken on an empty stomach, with a glass of plain water, at least 2 hours before or after food, because food may decrease the amount of BONEFOS absorbed by the body.

BONEFOS capsules should never be taken with milk or food containing calcium or other divalent cations because they interfere with the absorption of BONEFOS.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will determine the appropriate dose for you. Follow the dosing instructions exactly and ask your doctor or pharmacist if you are not sure.

BONEFOS for Injection:

- 300 mg/day is given as a slow infusion into a vein.

BONEFOS Capsules:

- Hypercalcemia due to malignancy: 1600 mg to 2400 mg (four to six capsules) daily. Maximum daily dose is 3200 mg (eight capsules). The daily dose can be taken once, or in two divided doses.
- Osteolytic bone metastasis due to malignancy: starting dose of 1600 mg (four capsules) daily. Maximum daily dose is 3200 mg (eight capsules).

BONEFOS capsules are to be taken on an empty stomach, with a glass of plain water, at least two hours before or after food or any other oral drugs.

BONEFOS capsules should be swallowed whole.

You will need to drink enough fluid or be hydrated during treatment with BONEFOS.

Overdose:

If you think you have taken or given more BONEFOS than you should, contact your doctor or a poison control centre immediately.

Missed Dose:

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule.

Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, BONEFOS may have, in addition to its beneficial effects, some unwanted effects.

The following side effect has been reported very commonly:

- increased transaminases (a group of liver enzymes) within normal range

The following side effects have been reported commonly:

- nausea;
- vomiting;
- stomach pain;
- diarrhea; and
- increased liver enzyme levels more than twice the normal range without impaired liver function

The following side effects have been reported rarely:

- low blood calcium levels with symptoms (eg, muscle cramps or spasms);
- increased serum parathyroid hormone (a hormone of the small glands adjacent to the thyroid gland) associated with decreased serum calcium;

- increased blood alkaline phosphatase levels (in patients with metastatic disease, this may also be due to liver and bone disease); and
- skin rash due to drug-related allergy.

The following side effects were reported during postmarket experience:

- severe kidney damage (especially after rapid intravenous infusion of high doses of clodronate);
- airway constriction (due to a hypersensitivity reaction or in patients with acetylsalicylic acid-sensitive asthma);
- allergic skin reactions and overactivity of the parathyroid glands which control the amount of calcium in the blood;
- isolated cases of kidney failure, in rare cases with fatal outcome, have been reported, especially when NSAIDs, most commonly diclofenac, were used at the same time;
- severe bone, joint, and/or muscle pain (the onset of symptoms varied from days to several months after starting BONEFOS).

Osteonecrosis of the jaw has also been reported during post-market experience in some cancer patients receiving bisphosphonates. However, it is not known what role, if any, these medications play in its development (see **WARNINGS AND PRECAUTIONS**). Symptoms of osteonecrosis of the jaw may include:

- pain, swelling or infection of the gums;
- loosening of teeth;
- poor healing of the gums; and
- numbness or the feeling of heaviness in the jaw.

If you experience any of these or other dental symptoms, tell both your oncologist and your dentist immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor	
		Only if severe	In all cases
	Abnormal thigh bone fractures		✓
	Inflammation, infection and/or irritation of the eye		✓

This is not a complete list of side effects. For any unexpected effects while taking BONEFOS, contact your doctor or pharmacist.

HOW TO STORE IT

BONEFOS should be stored at room temperature (between 15°C and 30°C). Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance or Bayer Inc.:

Canada Vigilance Program:

You can report any suspected adverse reactions associated with the use of heath products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

Bayer Inc.

You can report any suspected adverse reactions associated with the use of health products to Bayer Inc. by:

- Toll-free telephone: 1-800-265-7382
- E-mail: canada.medinfo@bayer.com
- Regular Mail: Bayer Inc.
  77 Belfield Road
  Toronto, Ontario
  M9W 1G6
  Canada

NOTE: Should you require information related to the management of the side effect, please contact your healthcare professional. Bayer Inc. does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or Canada.medinfo@bayer.com.

This document plus the full Product Monograph, prepared for health professionals, can be found at http://www.bayer.ca or by contacting the Sponsor at the above mentioned phone number and email address.

This leaflet was prepared by:

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8. Leonard et al., Safety Profile of Zoledronic acid in a novel oral formulation, Poster presentation at AACR-NCI-EORTC Molecular Targets & Cancer Therapeutics Conference, Background section (November 2009) ("Leonard 2009").

SAFETY PROFILE OF ZOLEDRONIC ACID IN A NOVEL ORAL FORMULATION

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Background

Orazol™ (MER-101) tablets utilize GIPET® to formulate an oral alternative to intravenous zoledronic acid (ZA) IV (Zometa®). Orazol's enteric coating and high bioavailability decreases GI exposure and provides a tablet with an excellent safety profile. Three clinical trials on doses from 10 to 20 mg demonstrated that a weekly 20 mg tablet delivers systemic ZA doses equivalent to 4 mg infusions given every 4 weeks. Therapeutic equivalence of 20 mg tablets and the 4 mg infusion has been demonstrated in prostate cancer patients with bone metastatic disease based on change from baseline values for biomarkers of bone metabolism, including uNTX and sCTX.

Methods

Safety information from three open label studies is presented here.

MER-101-01 was a pilot single weekly dose, 3-way crossover study in 13 osteoporotic women. Orazol tablets 10 mg and 20 mg were administered versus a 1 mg IV infusion after an overnight fast (and 4 hours fast post-dose). Absorption was determined by LCMS urine assay over 48 hours post-dose.

MER-101-02 was a single-dose, 5-way crossover study in 30 postmenopausal women and examined Orazol 15 mg and 20 mg tablets versus 1 mg IV infusion. Absorption was determined by serum LCMS assay over 36 hours post-dose.

Treatments:

(a) Orazol 15 mg, overnight fast, breakfast 30 minutes later.

(b) Orazol 20 mg, overnight fast, breakfast 30 minutes later.

(c) Orazol 20 mg, FDA standardized breakfast.

(d) Orazol 20 mg, bedtime, following a 4-hour fast.

(e) ZA 1 mg IV infusion.

MER-101-03 was a multi-center, 8 week, Phase II study comparing 2 regimens of Orazol tablets 20 mg to the standard dose of ZA 4 mg infusion in male bisphosphonate-naive hormone-refractory prostate cancer patients with bone metastases. The cohorts were:

Cohort A: ZA 4 mg infusion, Day 0 & 28.

Cohort B: Orazol Tablets 20 mg, Days 0, 7, 14, 21, 28, 35, 42 & 49.

Cohort C: Orazol Tablets 20 mg, Days 0, 1, 2, 3, 28, 35, 42 & 49.

Safety assessments included AE monitoring, PE, hematology, urinalysis, and blood chemistry panels.

Results

Orazol tablets yielded a very acceptable safety profile. In MER-101-03, which evaluated Orazol tablets directly against the 4 mg infusion, the greatest incidence of AEs occurred in patients on the ZA infusion (75%). Half of the patients in this cohort experienced fever following administration, which lasted up to 72 hours post-dose. The incidence of bone pain was twice that in patients on oral Orazol therapy. There was a consistent decrease in mean diastolic blood pressure, and a greater number of abnormal hematology laboratory results for patients on IV than for Orazol. In analyzing MER-101-01 and MER-101-02 together, which compared Orazol tablets to a 1 mg Zometa infusion, AEs were evenly distributed across groups. GI related AEs were similar with the Orazol treatments compared to the ZA infusions.

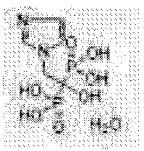
Conclusions

Based on data collected thus far, Orazol tablets offer a substantial improvement over IV infusion in bisphosphonate therapy for oncological uses. The results of these studies combined with the excellent safety profile of Orazol tablets 20 mg administered weekly support further development as a preferred route of ZA administration. Results to date indicate Orazol is an effective and potentially safer alternative to IV ZA, which may substantially improve patients' quality of life. Orazol offers a new treatment paradigm for patients with metastatic bone cancer.

BACKGROUND

Zoledronic acid is a bisphosphonate used in the treatment of bone metastases. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone, decreasing bone resorption by reducing osteoclastic activity. Studies have demonstrated that zoledronic acid reduces the incidence of skeletal-related events (SREs) in metastatic bone cancer. A reduction in levels of markers of bone metabolism, particularly urinary NTX, has been shown to be predictive of a reduction in SREs.[1] Orazol Tablets 20 mg (MER-101, zoledronic acid) dosed once-a-week have been shown to deliver doses systemically equal to zoledronic infusions 4 mg dosed every 4 weeks. Once-a-week therapy with the 20 mg tablet has also been shown to reduce urinary NTX and serum CTX levels to an extent greater than or equal to the reduction achieved with Zometa IV infusion 4 mg administered every 4 weeks.[2]

Zoledronic acid has a molecular weight of 290.1 with an empirical formula $C_5H_{10}N_2O_7P_2.H_2O$. The structural formula is:



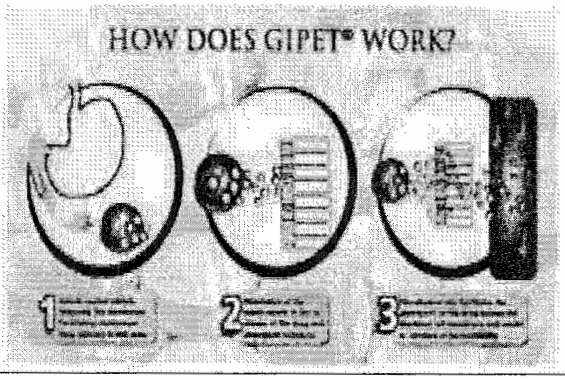
All bisphosphonates, including zoledronic acid, have poor oral bioavailability. This has limited their use in oncological therapies to intravenous infusion to achieve the doses required for efficacy. The local gastric irritation that occurs with existing oral bisphosphonates is also an important consideration in oncological indications, as it can result in adverse reactions in the GI tract, including esophageal erosions and ulceration.

Orazol (MER-101, Zoledronic Acid)

- A weekly tablet providing an equivalent systemic dose to a regimen of 4 mg IV infusion every 4 weeks
- Provides an improvement in administration profile:
  - Lower systemic dose taken more frequently
    - Less potential for renal damage due to the reduced C_{max}
    - Ability to easily modify frequency and dose
    - More frequent exposure of metastatic cells to plasma levels of drug
  - Enteric coating eliminates potential for stomach and esophageal complications associated with other bisphosphonates
  - Enhanced absorption in the intestines:
    - Decreases overall GI drug load (which has further potential to decrease GI side effects)
    - Enables delivery of an oncological dose

Gastrointestinal Permeation Enhancement Technology (GIPET® I)

- Oral platform technology for poorly absorbed compounds based on food grade excipients
- Physical mixtures of enhancer system and drug in a tablet form
- Facilitates safe absorption:
  - Very little effect on the GIT
  - Primary mechanism of mixed micelles to improve transcellular absorption
- Classified as food substance:
  - Reviewed by EU Scientific Committee for Food and determined 'safe in use', and the FAO/WHO Joint Expert Committee of Food Additives, with no limit on intake
  - Listed in the US CFR as a direct food additive with no limit on intake
- Successfully applied to poorly absorbed compounds across several physical/chemical categories



Three studies have been conducted on GIPET-enhanced Orazol tablets, two clinical pharmacology (CP) studies and a Phase 2 study in patients with metastatic prostate cancer. Two doses of Orazol were administered in the first CP trial, and four doses in the second trial. The reference in both CP trials was a 1 mg infusion of zoledronic acid injection. The Phase 2 study lasted for 8 weeks, and used 4 mg of zoledronic acid infusion as the control.

[1] Robert E. Coleman *et al.* Predictive Value of Bone Resorption and Formation Markers in Cancer Patients with Bone Metastases Receiving the Bisphosphonate Zoledronic Acid. J Clin Oncol 23:4925-4935 © 2005 ASCO.

[2] Thomas W. Leonard *et al.* MER-101-03, A Multi Center, Phase II Study to Compare MER-101 20mg Tablets to Intravenous Zometa 4mg in Prostate Cancer Patients. ASCO © 2009.

MER-101-01 STUDY

- ❑ Phase 1, single dose, randomized, open label, 3-way crossover study
  - ❖ The study population was 13 postmenopausal women with osteoporosis

Objective

- ❑ To compare absorption of 2 investigational oral dosage forms of zoledronic acid to the market product IV infusion

Treatments and Method

- ❑ Three treatment arms:
  - ❖ MER-101 Tablet 10 mg
  - ❖ MER-101 Tablet 20 mg
  - ❖ Zometa IV Infusion 1 mg
- ❑ Fasting 10.5 hours prior to dosing until 4 hours post-dose
- ❑ 7 Day interval between doses
- ❑ Bioavailability was determined from urinary excretion of zoledronic acid over 48 hours; assayed via LC/MS/MS
- ❑ Medical history and physical examinations were conducted
- ❑ Chemistry, hematology, and urinalysis labs were obtained at screening, at check-in, and post study
- ❑ Vital signs were obtained prior to dosing in each period

Safety Results

- ❑ A total of 13 subjects were enrolled; 12 subjects completed all 3 treatment periods
- ❑ No SAEs were reported during the study
- ❑ There were 50 AEs reported by 12 subjects, as follows:

MER-101-01 Incidence of Adverse Events Reported by Treatment Groups: MER-101 Oral Dosage vs Market Product Injection

Body System / AE	Test A (N=12) MER-101 10 mg	Test B (N=13) MER-101 20 mg	Ref. C (N=12) Zometa Infusion 4 mg
Body as a Whole			
Chills		2	
Body aches			1
Fever		1	
Weakness	1	1	
Near syncope		1	
Respiratory			
Sinusitis		2	
Runny nose		1	
Sneezing		1	
Neurologic/Psychiatric			
Headache	3	7	5
Lightheadedness		2	1
Dizziness		1	
Musculoskeletal			
Back pain	2	1	1
Arthralgias		2	
Gastrointestinal			
Nausea		3	
Emesis		2	1
Diarrhea	1		
Gas pain	1		1
Constipation		1	1
Other Organ Systems			
Right eye pain	1		
IV site sore			2
Total	9	28	13

N = Number of subjects

MER-101-02 STUDY

- Single dose, randomized, 5-way crossover study, fasted and fed conditions
  - The study enrolled 30 postmenopausal women
    - 28 subjects had evaluable data
    - 23 subjects completed all treatment arms

Objective

- To determine the effect of food on absorption of zoledronic acid
- To evaluate a nighttime dosing regimen
- To compare the relative bioavailability of two strengths of MER-101 Tablets 15 mg and 20 mg to Zometa IV 1 mg infusion

Treatments and Method

- Five treatment arms:
  - MER-101 Tablets 15 mg orally after an overnight fast, FDA standardized breakfast 30 minutes post-dosing
  - MER-101 Tablets 20 mg orally after an overnight fast, FDA standardized breakfast 30 minutes post-dosing
  - MER-101 Tablets 20 mg orally immediately following FDA standardized breakfast
  - MER-101 Tablets 20 mg orally at bedtime after a 4-hour fast following supper. Breakfast 10.5 hours post dosing
  - Zometa IV infused intravenously (1 mg in 100 mL sterile 0.9% Sodium Chloride, USP) over 15 minutes after an overnight fast, FDA standardized breakfast 30 minutes post-dosing
- 7 Day washout interval between treatment arms
- Medical history and physical examinations were conducted prior to enrollment
- Chemistry, hematology, and urinalysis labs were obtained prior to enrollment and post study
- Vital signs were obtained prior to dosing each period
- Subjects were confined to the facility from evening before dosing until after 36-hour blood collection
- Blood samples were collected pre-dose and at intervals over 36 hours after dosing in each period
- Bioavailability was assessed by the appearance of unchanged drug in serum collected at intervals over a 36-hour period after administration of drug

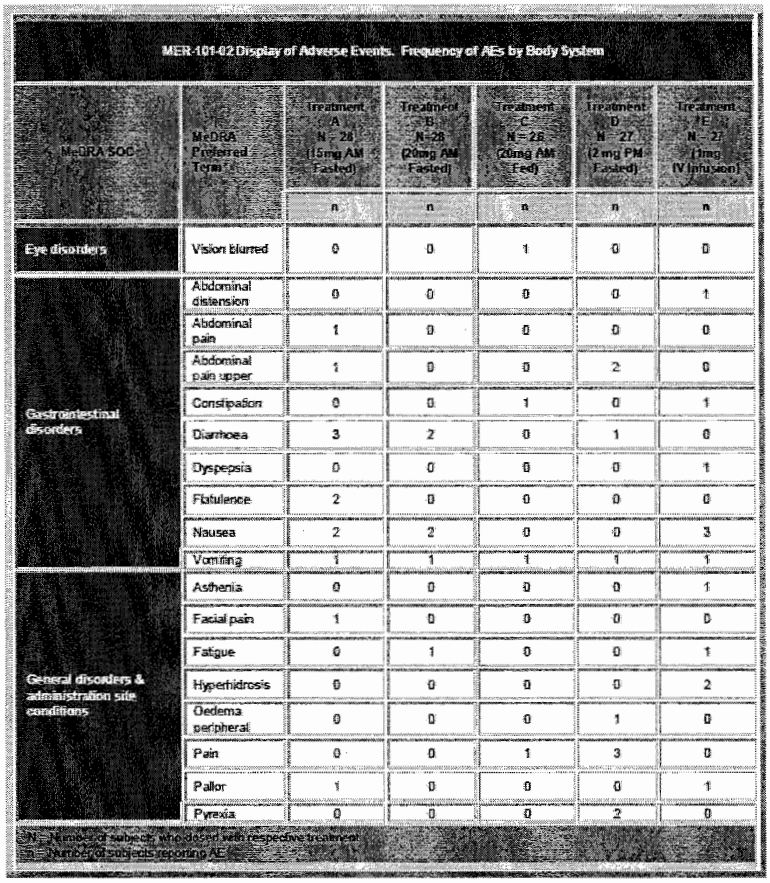
Safety Results

- 103 AEs were reported over the 5 weeks by 23 of 30 subjects:
  - 24 occurred after Treatment A
  - 16 occurred after Treatment B
  - 11 occurred after Treatment C
  - 22 occurred after Treatment D
  - 30 occurred after Treatment E
- 91 AEs were considered "mild" and resolved spontaneously by end of study
- 10 AEs were considered "mild" and resolved with treatment
- 2 AEs were considered "mild" and had not resolved by end of study
- Most frequently reported AE for Treatment A was diarrhea (3 subjects)
- Most frequently reported AE for Treatment B was back pain (3 subjects)
- Most frequently reported AEs for Treatment C were blurred vision (1), constipation (1), vomiting (1), pain (1), decreased blood pressure (1), increased blood pressure (1), back pain (1), joint swelling (1), pain in extremity (1), headache (1), and somnolence (1)
- Most frequently reported AEs for Treatment D were pain (3), and decreased blood pressure (3)
- Most frequently reported AEs for Treatment E were nausea (3), and headache (3)
- The oral tablet was very well tolerated (4 treatment arms were oral)
- No SAEs were reported in this study

MER-101-02 Display of Adverse Events. Frequency of AEs by Body System

MedDRA SOC	MedDRA Preferred Term	Treatment A N = 26 (15mg AM Fasted)	Treatment B N= 28 (20mg AM Fasted)	Treatment C N = 26 (20mg AM Fed)	Treatment D N = 27 (2 mg PM Fasted)	Treatment E N = 27 (1mg IV Infusion)
		n	n	n	n	n
Investigations	Blood pressure decreased	0	0	1	3	1
	Blood pressure increased	2	0	1	1	2
	Body temperature increased	0	1	0	0	0
Musculoskeletal & connective tissue disorders	Arthralgia	1	0	0	1	1
	Back pain	1	3	1	0	2
	Joint swelling	0	1	1	1	1
	Pain in extremity	1	0	1	1	1
Nervous system disorders	Dizziness	1	1	0	1	2
	Headache	1	2	1	2	3
	Somnolence	0	0	1	0	0
	Tremor	0	0	0	0	1

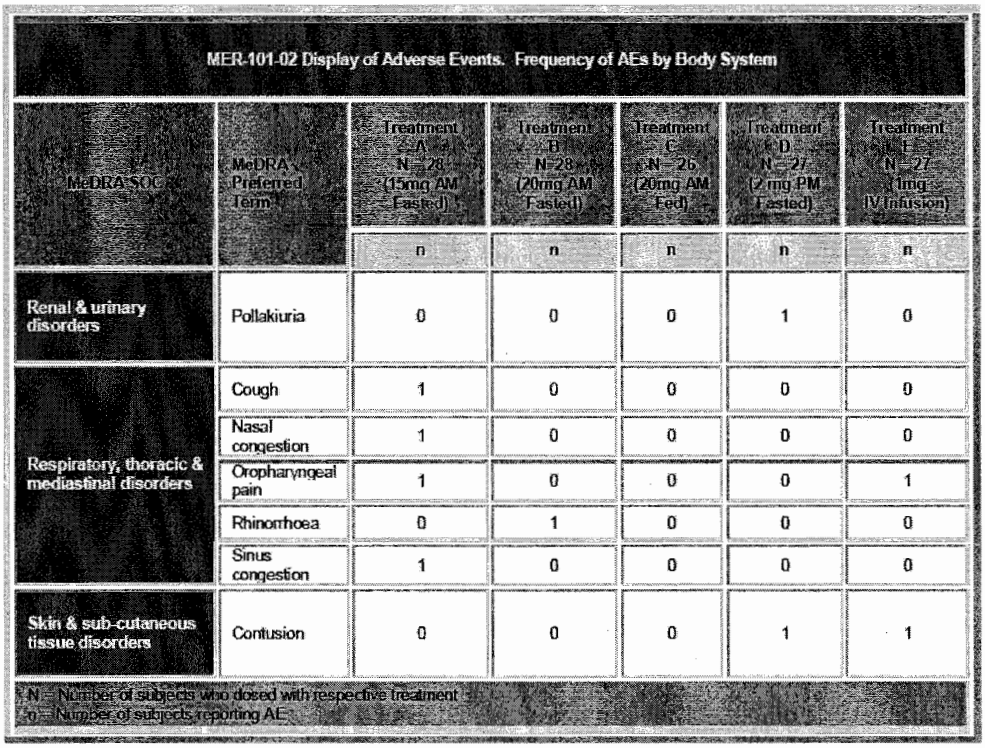
N = Number of subjects who dosed with respective treatment
n = Number of subjects reporting AE



MER-101-02 Display of Adverse Events. Frequency of AEs by Body System

MedDRA SOC	MedDRA Preferred Term	Treatment A N = 28 (15mg AM Fasted)	Treatment B N=28 (20mg AM Fasted)	Treatment C N = 26 (20mg AM Fed)	Treatment D N = 27 (2 mg PM Fasted)	Treatment E N = 27 (1mg IV Infusion)
		n	n	n	n	n
Eye disorders	Vision blurred	0	0	1	0	0
Gastrointestinal disorders	Abdominal distension	0	0	0	0	1
	Abdominal pain	1	0	0	0	0
	Abdominal pain upper	1	0	0	2	0
	Constipation	0	0	1	0	1
	Diarrhoea	3	2	0	1	0
	Dyspepsia	0	0	0	0	1
	Flatulence	2	0	0	0	0
	Nausea	2	2	0	0	3
	Vomiting	1	1	1	1	1
General disorders & administration site conditions	Asthenia	0	0	0	0	1
	Facial pain	1	0	0	0	0
	Fatigue	0	1	0	0	1
	Hyperhidrosis	0	0	0	0	2
	Oedema peripheral	0	0	0	1	0
	Pain	0	0	1	3	0
	Pallor	1	0	0	0	1
	Pyrexia	0	0	0	2	0

N = Number of subjects who dosed with respective treatment
n = Number of subjects reporting AE



MER-101-02 Display of Adverse Events. Frequency of AEs by Body System

MedDRA SOC	MedDRA Preferred Term	Treatment A N = 28 (15mg AM Fasted)	Treatment B N=28 (20mg AM Fasted)	Treatment C N = 26 (20mg AM Fed)	Treatment D N = 27 (2 mg PM Fasted)	Treatment E N = 27 (1mg IV Infusion)
		n	n	n	n	n
Renal & urinary disorders	Pollakiuria	0	0	0	1	0
Respiratory, thoracic & mediastinal disorders	Cough	1	0	0	0	0
	Nasal congestion	1	0	0	0	0
	Oropharyngeal pain	1	0	0	0	1
	Rhinorrhoea	0	1	0	0	0
	Sinus congestion	1	0	0	0	0
Skin & sub-cutaneous tissue disorders	Contusion	0	0	0	1	1

N = Number of subjects who dosed with respective treatment
n = Number of subjects reporting AE

MER-101-03 STUDY

- Phase 2, multi-center, 8 week study
  - Study population was 30 male bisphosphonate-naive, hormone-refractory prostate cancer patients with bone metastases

Objective

- To examine pharmacodynamic effects of 2 different regimens of MER-101 Tablets 20 mg versus Zometa IV infusion 4 mg once-monthly therapy on biomarkers of bone metabolism
- To assess pain and performance status via Brief Pain Index (BPI) short form and ECOG, and analgesic use
- A PK substudy was conducted in a limited number of patients (N=4) on Day 28
- To assess safety profiles of two MER-101 20 mg regimens vs Zometa IV 4 mg infusion

Treatments and Method

- Three treatment cohorts:
  - Cohort A: Zometa IV infusion 4 mg, 15-minute infusion, Day 0 and Day 28
  - Cohort B: MER-101 Tablets 20 mg orally on Days 0, 7, 14, 21, 28, 35, 42, and 49 (weekly regimen)
  - Cohort C: MER-101 Tablets 20 mg orally on Days 0, 1, 2, 3, 28, 35, 42, and 49 (loading dose)
- Medical history and physical examinations were performed at screening and PE was repeated at Day 56
- Safety labs were obtained on Day 0 and Day 56 (hematology, chemistry, and urinalysis)
- Repeat serum creatinine levels were obtained on Day 21 in preparation for dosing on Day 28
- Vital signs were performed and biomarkers (urine NTX, serum CTX, serum bone-specific alkaline phosphatase, and serum calcium) were drawn at Baseline and on Days 0, 7, 14, 21, 28, 35, 42, 49, and 56

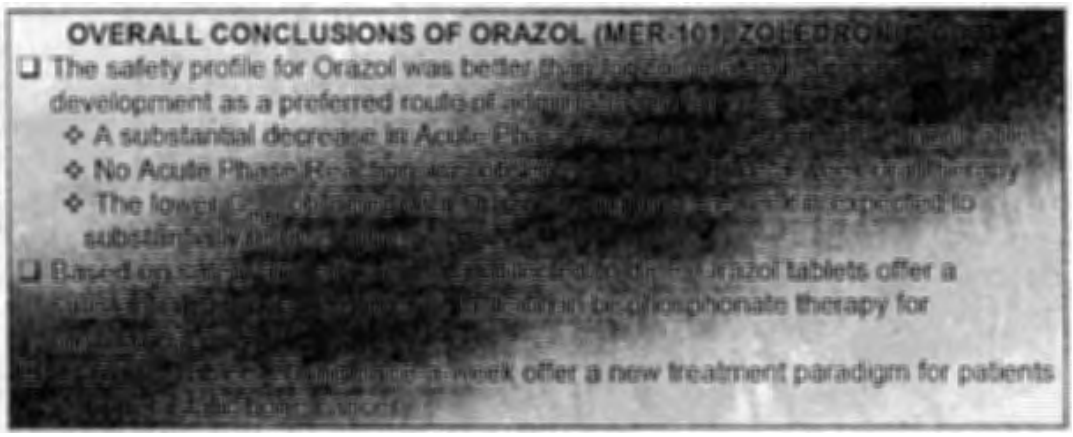
Safety Results

- AEs were reported by 18 of 30 enrolled patients during the study (60%)
- The greatest proportion of AEs per treatment cohort was in Cohort A (75%), compared to Cohort B (46%), and Cohort C (64%)
- The greatest incidence of patients with AEs suspected to be related to study drug occurred in Cohort A (50%)
- Fever was experienced by 4 patients in Cohort A (50%), following study drug administration, which lasted up to 72 hours
  - All fevers reported were suspected to be related to study drug
  - Fever is part of the Acute Phase Reaction associated with zoledronic acid IV infusion
- There was no fever (Acute Phase Reaction) reported in Cohort B
- In Cohort C, 1 patient (9%) experienced fever that was suspected to be related to study drug
  - This event occurred on Day 2 of the four day loading dose and was resolved on Day 4

MER-101-03 Display of Adverse Events. Frequency of AEs by Body System				
System Organ Class (SOC) Preferred Term	Ref. IV Cohort A N = 8 n (%)	MER-101 Tablets 20 mg Cohort B N = 11 n (%)	MER-101 Tablets 20 mg Cohort C N = 11 n (%)	All Patients N = 30 n (%)
Number of Patients with ≥ 1 AE	6 (75)	5 (46)	7 (64)	18 (60)
Gastrointestinal disorders	0	1 (9)	1 (9)	2 (7)
Abdominal pain upper	0	1 (9)	0	1 (3)
Diarrhoea	0	0	1 (9)	1 (3)
Nausea	0	0	1 (9)	1 (3)
General disorders & administration site conditions	4 (50)	2 (18)	2 (18)	8 (27)
Fatigue	0	2 (18)	0	2 (7)
Oedema peripheral	0	0	1 (9)	1 (3)
Pyrexia	4 (50)	0	1 (9)	5 (17)
Infections and infestations	0	0	2 (18)	2 (7)
Herpes zoster	0	0	1 (9)	1 (3)
Influenza	0	0	1 (9)	1 (3)
Musculoskeletal and connective tissue disorders	3 (38)	2 (18)	4 (36)	9 (30)
Arthralgia	0	0	1 (9)	1 (3)
Bone pain	3 (38)	2 (18)	2 (18)	7 (73)
Musculoskeletal chest pain	0	0	1 (9)	1 (3)
Musculoskeletal pain	0	0	1 (9)	1 (3)
Myalgia	1 (13)	0	1 (9)	2 (7)
Nervous system disorders	1 (12)	0	0	1 (3)
Headache	1 (12)	0	0	1 (3)
Renal and urinary disorders	0	0	1 (9)	1 (3)
Urinary retention	0	0	1 (9)	1 (3)
Respiratory, thoracic and mediastinal disorders	0	2 (18)	0	2 (7)
Dyspnoea	0	1 (9)	0	1 (3)
Nasopharyngitis	0	1 (9)	0	1 (3)
N = number of patients per cohort n = number of patients per cohort who reported adverse events				

- The most common classification of adverse events reported was musculoskeletal and connective tissue disorders, which were reported by 9 of 30 patients
- Musculoskeletal-related adverse events were reported by 3 patients in Cohort A (38%), 2 patients in Cohort B (18%), and 4 patients in Cohort C (36%)
- Bone pain was the most commonly reported musculoskeletal AE in 7 of 9 patients (73%)
- The incidence of bone pain reported by patients in Cohort A (38%) was twice that of patients in Cohort B or Cohort C (18% in each)
- Two patients had AEs resulting in discontinuation from the study
  - 1 in Cohort A (13%) due to bone pain
  - 1 in Cohort C (9%) which was considered an SAE due to hospitalization (musculoskeletal pain in the region of ribs and sternum)
- No AEs resulted in death
- The most common AEs attributed to therapy were those associated with the Acute Phase Reaction

MER-101-03 Patients Experiencing ≥ 1 AE by Relationship to Study Drug (Safety Population)				
		Patients Reporting AEs (n)	Not Related	Related
Cohort	# Patients	n (%)	n (%)	n (%)
A	8	6 (75%)	2 (25%)	4 (50%)
B	11	5 (46%)	4 (36%)	1 (9%)
C	11	7 (64%)	4 (36%)	3 (27%)

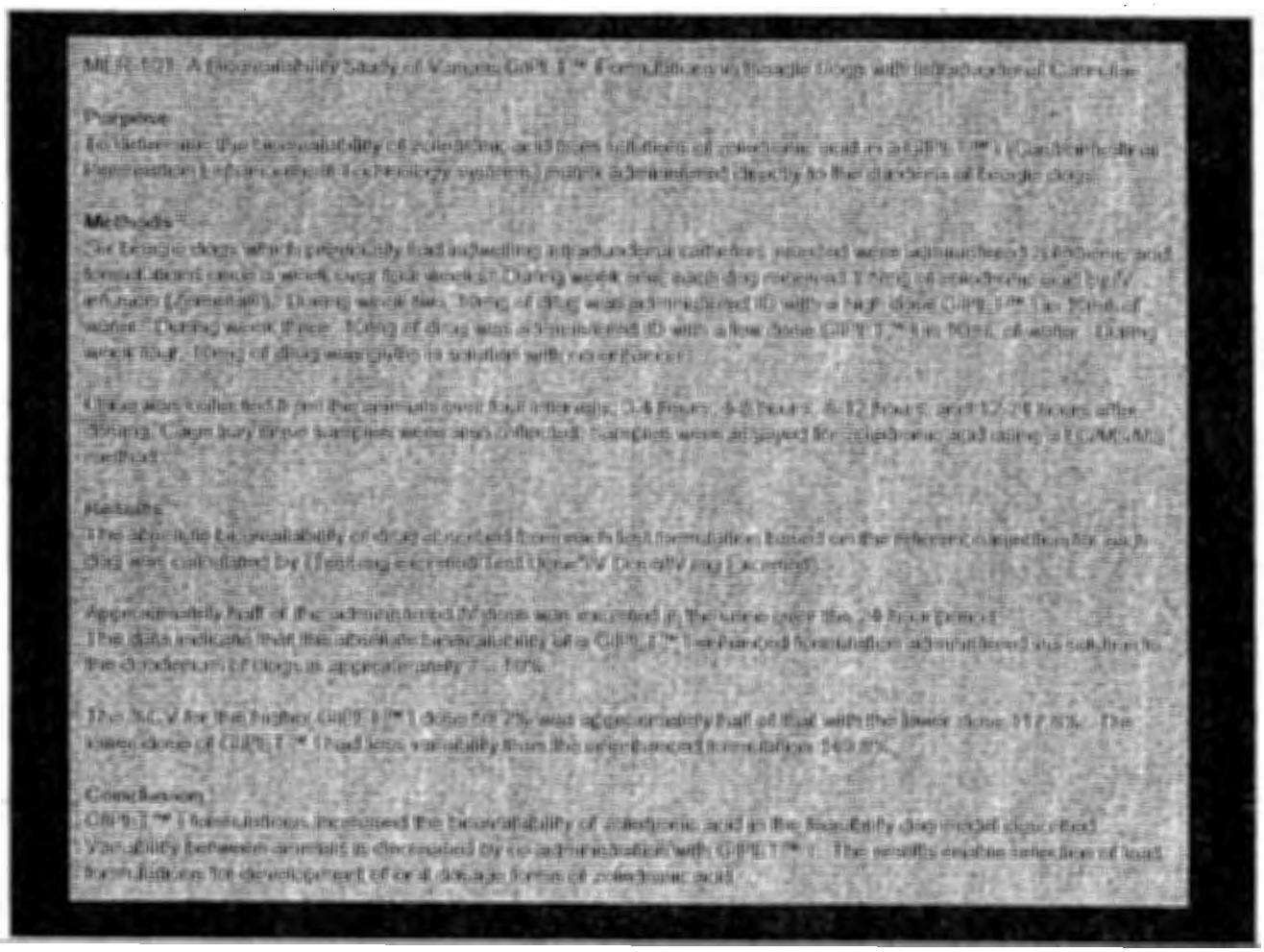

OVERALL CONCLUSIONS OF ORAZOL (MER-101, ZOLEDRO
The safety profile for Orazol was better
development as a preferred route of
A substantial decrease in Acute
No Acute Phase
The lowe
substitu
Orazol tablets offer a
phonate therapy for
offer a new treatment paradigm for patients

9. Cullen et. al, MER-101 A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae, Poster presentation at AAPS (November 2007) ("Cullen").

MER-101: A Bioavailability Study of Various GIPET™ Formulations in Beagle Dogs with Intraduodenal Cannulae

Alan Cullen, Catherine McHugh, Orlagh Feeney, Thomas Leonard

Abstract T3147 - AAPS, November 2007



GIPET™

- Is based on GRAS-listed proprietary penetration enhancers.
- No chemical or physical alteration of the drug molecule is involved.
- Enteric coating eliminates esophageal reflux issues.

OBJECTIVE

To determine the bioavailability of zoledronic acid from solutions of zoledronic acid in a GIPET™I (Gastrointestinal Permeation Enhancement Technology systems) matrix administered directly to the duodena of beagle dogs.

Table 1:
Details of the dose of zoledronic acid, formulation and frequency of dosing administered intraduodenally to beagle dogs.

Test item	Dose of zoledronic acid	Route of administration	Formulation details	Frequency of dosing
1	1.5mg	IV	Zometa®	Single dose
2	10mg	ID	GIPET™ I (high dose form. I)	Single dose
3	10mg	ID	GIPET™ I (low dose form. II)	Single dose
4	10mg	ID	Unenhanced	Single dose

RESULTS

- Approximately half (0.78mg) of the administered IV dose was excreted in the urine over the 24-hour period with a CV of 19.72%. Refer to **Table 2** and **Figure 1.**
- The data indicate that the absolute bioavailability of a GIPET™ I enhanced formulation administered via solution to the duodenum of the dog is approximately 7 – 10%. Refer to **Table 2.**
- The CV for the higher GIPET™ I dose (59.2%) was approximately half of that with the lower dose (117.6%).
- The lower dose of GIPET™ I had less variability than the unenhanced formulation, which was 149.8%.
- No clinical adverse events were observed as a result of the dosing.

Table 2. Zoledronic acid GIPET™ I (Mean % Bio+/- SD, CV%)

	Test Item 1 Ref. (IV)	Test Item 2 High Dose GIPET™I		Test Item 3 Low Dose GIPET™I		Test Item 4 Unenhanced	
	mg	mg	% Bio	mg	% Bio	mg	% Bio
Average	0.78	0.39	**7.3**	0.53	**10.3**	0.18	**3.5**
Std Dev.	0.15	0.26	**4.3**	0.66	**12.16**	0.27	**5.28**
CV	19.72%	66.8	**59.2**	124.2	**117.6**	151.0	**149.8**

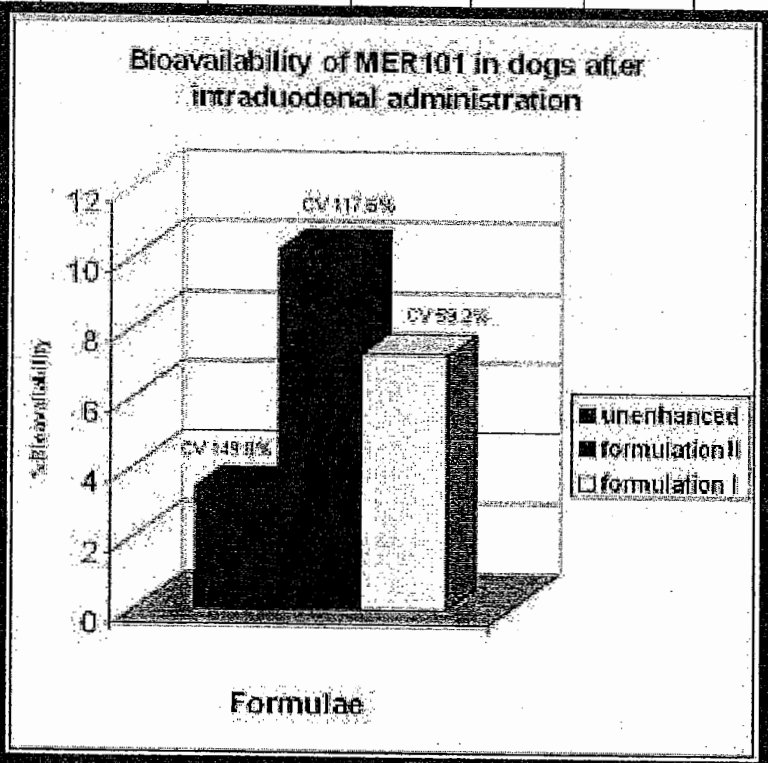


Figure 2.

10. U.S. Patent No. 6,451,815.

US006451815B1

(12) **United States Patent**
Hwang et al.

(10) **Patent No.: US 6,451,815 B1**
(45) **Date of Patent: Sep. 17, 2002**

(54) **METHOD OF ENHANCING BIOAVAILABILITY OF FEXOFENADINE AND ITS DERIVATIVES**

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(73) Assignee: **Aventis Pharmaceuticals Inc.**, Bridgewater, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/353,462**

(22) Filed: **Jul. 13, 1999**

Related U.S. Application Data

(63) Continuation of application No. 09/129,713, filed on Aug. 5, 1998, now abandoned.
(60) Provisional application No. 60/090,103, filed on Aug. 14, 1997.

(51) **Int. Cl.**[7] **A61K 31/445**
(52) **U.S. Cl.** **514/317**; 514/946
(58) **Field of Search** 514/317, 946

(56) **References Cited**

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Primary Examiner—James H. Reamer
(74) *Attorney, Agent, or Firm*—Jiang Lin; Charlotte L. Barney

(57) **ABSTRACT**

The present invention relates to a method of enhancing the bioavailability of a piperidinoalkanol antihistamine in a patient which comprises co-administering to said patient an effective antihistaminic amount of said piperidinoalkanol and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor.

30 Claims, No Drawings

METHOD OF ENHANCING BIOAVAILABILITY OF FEXOFENADINE AND ITS DERIVATIVES

This is a continuation application which is a continuation of application Ser. No. 09/129,713 filed Aug. 5, 1998 now abandoned which claims priority of U.S. Provisional Application Ser. No. 60/090,103 filed Aug. 14, 1997.

BACKGROUND

The term "multidrug resistance" (MDR) describes the phenomenon whereby certain cancerous tumor cells develop a resistance to broad classes of cytotoxic agents when exposed to an individual cytotoxic agent. In other words, after a certain period of treatment with a cytotoxic agent which initially shows efficacy in controlling the growth of the tumor, the tumor develops a resistance not only to the specific agent to which the tumor was exposed, but also to broad classes of structurally and functionally unrelated agents. It has recently been found that MDR tumor cells over express a particular membrane glycoprotein known as p-glycoprotein ("p" for permeability). This p-glycoprotein is a member of the superfamily of ATP-binding cassette (ABC) transporters. It is thought that the exposure of the MDR tumor cells to a cytotoxic agent causes the induction of this p-glycoprotein which mediates a reverse transport system located on the tumor cell membrane that pumps the cytotoxic agent, as well as the other broad classes of cytotoxic agents, out of the tumor cell thus providing mutiple drug resistance for the cell.

P-glycoprotein is not just found in tumor cells. It is also expressed in a variety of normal, non-cancerous, epithelial and endothelial cells including in such tissues as the adreneal cortex, in the brush border of the proximal renal tubule epithelium, on the lumenal surface of biliary hepatocytes, in pancreatic ductules, and in the mucosa of the small and large intestine. For purposes of describing the present invention, the presence of p-glycoprotein in the small and large intestine is of particular interest.

When substances are ingested, they are mixed with digestive substances secreted by the body and are ultimately combined in a mixture in the lumen of the intestine. The lumen of the intestine is in contact with certain special epithelial cells which form the mucosa of the intestine or the intestinal wall. Nutrients and other substances present in the intestinal lumen passively diffuse into these intestinal epithelial cells and later diffuse into the portal circulation which carries the nutrients via the blood stream on to the liver. Thus, nutrients and other substances are absorbed into the body and become bioavailable for use by other tissues in the body.

The intestinal epithelial cells, however, do not just operate as a vehicle for passive diffusion of nutrients and other ingested substances. In addition, there are various active transport mechanisms located in the outer membrane of the epithelial cells which actively transport various nutrients and other substances into the cell. It is now thought that one of the active transport mechanisms present in the intestinal epithelial cells is p-glycoprotein transport mechanism which facilitates the reverse transport of substances, which have diffused or have been transported inside the cell, back into the lumen of the intestine. It has been speculated that the p-glycoprotein present in the intestinal epithelial cells may function as a protective reverse pump which prevents toxic substances which have been ingested and diffused or transported into the epithelial cell from being absorbed into the

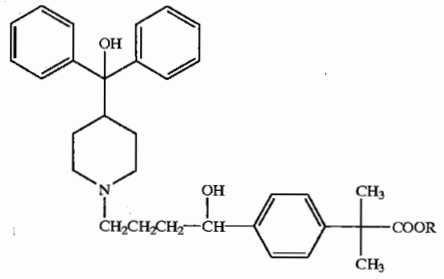
circulatory system and becoming bioavailable. One of the unfortunate aspects of the function of the p-glycoprotein in the intestinal cell however is that it can also function to prevent bioavailability of substances which are beneficial, such as certain drugs which happen to be substates for the p-glycoprotein reverse transport system.

It has now been found that, surprisingly, the antihistamines of the present invention are coincidentally also targeted by the p-glycoprotein reverse transport system in intestinal epiothelial cells and therefore are not fully bioavailable. The present invention successfully provides a method for enhancing the bioavailablilty of these antihistamines.

SUMMARY IF THE INVENTION

The present invention relates to a method of enhancing the bioavailability of a piperidinoalkanol antihistamine of Formula I

Formula I



wherein

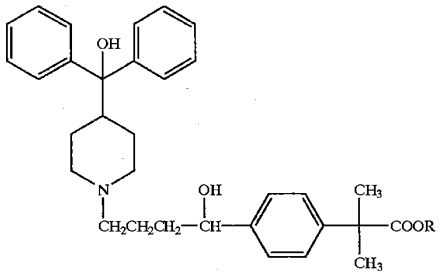
R is hydrogen or C_1–C_6 alkyl,

or a pharmaceutically acceptable salt or an individual optical isomer thereof, in a patient which comprises co-administering to said patient an effective antihistaminic amount of said piperidinoalkanol and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor. The present invention further relates to a method of treating allergic reactions in a patient, which comprises co-administering to said patient an effective antihistaminic amount of antihistamine of Formula I and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor. The present invention also relates composition comprising an effective antihistaminic amount of a piperidinoalkanol antihistamine of Formula I and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of enhancing bioavailability of a piperidinoalkanol antihistamine of Formula I

Formula I



wherein

R is hydrogen or C_1–C_6 alkyl,

or a pharmaceutically acceptable salt or an individual optical isomer thereof.

As used herein, the term "C_1–C_6 alkyl" refers to a saturated hydrocarbyl radical of straight or branched chain configuration of from 1 to 6 carbon atoms. Specifically included within the scope of the term "C_1–C_6 alkyl" are the hydrocarbyl radicals methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like. One skilled in the art would immediately recognize and appreciate that the compounds of Formula I possess a chiral center and as such exist in stereoisomeric forms. The present invention applies to the racemic mixture of these stereoisomeric forms as well as to the isolated individual stereoisomers. The individual stereoisomers can be isolated from the racemic mixture by separation techniques which are well known and appreciated in the art including chromatographic methods and selective crystallization techniques.

The compounds of Formula I may exist in their free form or as pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the compounds of Formula I are those of any suitable inorganic or organic acid. Examples of suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, and phosphoric acids. Examples of suitable organic acids include carboxylic acids, such as, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, cyclamic, ascorbic, maleic, hydroxymaleic, dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranillic, cinnamic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, mandelic acid, and sulfonic acids, such as, methanesulfonic, ethanesulfonic, and β-hydroxyethanesulfonic acid. Non-toxic salts of the compounds of Formula I formed with inorganic or organic bases are also included within the scope of this invention and include, for example, those of alkali earth metals, for example, calcium and magnesium, light metals of group IIIA, for example, aluminum, organic amines, such as, primary, secondary or tertiary amines, for example, cyclohexylamine, ethylamine, pyridine, methylaminoethanol, and piperazine. The salts of compounds of Formula I may be prepared by conventional means as, for example, by treating a compound of Formula I with an appropriate acid or base. The preferred pharmaceutically acceptable salt for compounds of Formula I is the hydrochloric acid salt.

Compounds of Formula I may be prepared as described in U.S. Pat. No. 4,254,129, which is hereby incorporated by reference in its entirety.

The preferred compound of Formula I is the compound (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzeneacetic acid, which is also known as fexofenadine, and its individual stereoisomers. Fexofenadine, as the hydrochloric acid salt, has been recently approved by the United States Food and Drug Administration (FDA) for use as the active ingredient in the antihistamine known as Allegra™. Allegra is indicated for the treatment of seasonal allergic rhinitis with recommended dosing at 60 mg B.I.D.

The present invention provides a method of enhancing bioavailability of the compounds of Formula I. The co-administration of an effective antihistaminic amount of a compound of Fromula I along with an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor provides an enhanced bioavailability for the compounds of Formula I. Bioavailability of a drug is defined as the degree to which a drug becomes available to the target tissue after administration and is conveniently measured as the total amount of drug available systemically. Typically, bioavailability is assessed by measuring the drug concentration in the blood at various points of time after administration of the drug and then integrating the values obtained over time to yield the total amount of drug circulating in the blood. This measurement, called the Area Under the Curve (AUC), is a direct measurement of the bioavailability of the drug. Alternatively, bioavailability may be assessed for fexofenadine by measuring total urine output of fexofenadine, since it is known that fexofenadine is not significantly metabolized after oral administration.

The present invention provides for an enhancement of the bioavailability of the drug of Formula I by co-administration of a p-glycoprotein inhibitor. By co-administration of a compound of Formula I and a p-glycoprotein inhibitor, the total amount of the compound of Formula I is increased over that which would otherwise circulate in the blood in the absence of the p-glycoprotein inhibitor. Thus, co-administration in accordance with the present invention will cause an increase in the AUC of the compound of Formula I over that seen with administration of the compound of Formula I alone.

As used herein, the term "patient" refers to a mammal, such as, for example, a human, mouse, rat, dog, cat, and the like, which is in need of treatment for an allergic reaction. As used herein, the term "allergic reaction" refers to a histamine-mediated allergic disease, such as, for example, seasonal allergic rhinitis, idiopathic urticaria, and the like. Such diseases are generally distinguished by an allergen triggered release of histamine from storage cells in tissues. The released histamine binds certain H_1-histamine receptors which results in the manifestation of the well known allergic symptioms such as sneezing, itching skin, itching eyes, rhinorrhea, etc. An antihistamine, such as the compounds of Formula I, will block manifestation of the allergic symptoms caused by release of histamine by blocking the H_1-histamine receptors in various tissues in the body, such as in the skin, lungs or the nasal mucosa. Antihistamines, such as the compounds of Formula I, are thus well known and effective treatment for allergic reactions in patients.

Enhancement of bioavailability of a compound of Formula I will provide for a more efficient and effective treatment of the patient since, for a given dose, more compound will be available at the tissue sites at which the antihistamine blocks H_1-histamine receptors than in the absence of this enhanced bioavailability.

Administration of the compound of Formula I refers to oral administration. The compound of Formula I may be administered orally in any convenient dosage form including, for example, capsule, tahlet, liquid, suspension, and the like.

An effective antihistaminic amount of a compound of Formula I is that amount which is effective in providing an antihistaminic effect in a patient. An effective antihistaminic amount will vary between about 1 mg to about 600 mg of a compound of Formula I as a daily dose depending upon the type of disease to be treated, the degree of severity of the disease, the species of patient to be treated, the dosage regimen, and other factors which are all well within the abilities of one of ordinary skill in the medical arts to evaluate and assess. A preferred amount however will typically be from about 10 mg to about 240 mg, a more preferred amount will typically be from about 20 mg to about 180 mg, and a further preferred amount will typically be from about 40 mg to about 120 mg. The most preferred amount of a compound of Formula I will be 60 mg or 120 mg. The above amounts of a compound of Formula I can be administered from once to multiple times per day. Typically, doses will be administered on a regimen requiring one, two or three doses per day with one and two being the preferred. The more preferred doseage and regimen will be 40 mg twice per day, 60 mg twice per day, 80 mg twice per day, 80 mg once daily, 120 mg once daily, and 180 mg once daily with the most preferred being 60 mg twice per day and 120 mg once daily.

As used herein, the term "p-glycoprotein inhibitor" refers to organic compounds which inhibit the activity of the p-glycoprotein mediated active transport system present in the gut. This transport system actively transports drugs which have been absorbed from the intestinal lumen and into the gut epithelium back out into the lumen. Inhibition of this p-glycoprotein mediated active transport system will cause less drug to be transported back into the lumen and will thus increase the net drug transport across the gut epithelium and will increase the amount of drug ultimately available in the blood.

Various p-glycoprotein inhibitors are well known and appreciated in the art. These include, water soluble vitamin E; polyethylene glycol; poloxamers including Pluronic F-68; Polyethylene oxide; polyoxyethylene castor oil derivatives including Cremophor EL and Cremophor RH 40; Chrysin, (+)-Taxifolin; Naringenin; Diosmin; Quercetin; and the like.

Polyethylene glycols (PEGs) are liquid and solid polymers of the general formula $H(OCH_2CH_2)_nOH$, where n is greater than or equal to 4, having various average molecular weights ranging from about 200 to about 20000. PEGs are also known as α-hydro-ω-hydroxypoly-(oxy-1,2-ethanediyl)polyethylene glycols. For example, PEG 200 is a polyethylene glycol wherein the average value of n is 4 and the average molecular weight is from about 190 to about 210. PEG 400 is a polyethylene glycol wherein the average value of n is between 8.2 and 9.1 and the average molecular weight is from about 380 to about 420. Likewise, PEG 600, PEG 1500 and PEG 4000 have average values of n of 12.5–13.9, 29–36 and 68–84, respectively, and average molecular weights of 570–630, 1300–1600 and 3000–3700, respectively, and PEG 1000, PEG 6000 and PEG 8000 have average molecular weights of 950–1050, 5400–6600, and 7000–9000, respectively. Polyethylene glycols of varying average molecular weight of from 200 to 20000 are well known and appreciated in the art of pharmaceutical science and are readily available.

The preferred polyethylene glycols for use in the instant invention are polyethylene glycols having an average molecular weight of from about 200 to about 20,000. The more preferred polyethylene glycols have an average molecular weight of from about 200 to about 8000. More specifically, the more preferred polyethylene glycols for use in the present invention are PEG 200, PEG 400, PEG 600, PEG 1000, PEG 1450, PEG 1500, PEG 4000, PEG 4600, and PEG 8000. The most preferred polyethylene glycols for use in the instant invention is PEG 400, PEG 1000, PEG 1450, PEG 4600 and PEG 8000.

Polysorbate 80 is an oleate ester of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides. Polysorbate 80 is made up of sorbitan mono-9-octadecanoate poly(oxy-1,2-ethandiyl) derivatives. Polysorbate 80, also known as Tween 80, is well known and appreciated in the pharmaceutical arts and is readily available.

Water-soluble vitamin E, also known as d-α-tocopheryl polyethylene glycol 1000 succinate [TPGS], is a water-soluble derivative of natural-source vitamin E. TPGS may be prepared by the esterification of the acid group of crystalline d-α-tocopheryl acid succinate by polyethylene glycol 1000. This product is well known and appreciated in the pharmaceutical arts and is readily available. For example, a water-soluble vitamin E product is available commercially from Eastman Corporation as Vitamin E TPGS.

Naringenin is the bioflavonoid compound 2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl) -4H-1-benzopyran-4-one and is also known as 4',5,7-trihydroxyflavanone. Naringenin is the aglucon of naringen which is a natural product found in the fruit and rind of grapefruit. Naringenin is readily available to the public from commercial sources.

Quercetin is the bioflavonoid compound 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy -4H-1-benzopyran-4-one and is also known as 3,3',4',5,7-pentahydroxyflavone. Quercetin is the aglucon of quercitrin, of rutin and of other glycosides. Quercetin is readily available to the public from commercial sources.

Diosmin is the naturally occurring flavonic glycoside compound 7-[[6-O-6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one. Diosmin can be isolated from various plant sources including citrus fruits. Diosmin is readily available to the public from commercial sources.

Chrysin is the naturally occurring compound 5,7-dihydroxy-2-phenyl-4H-1-benzopyran-4-one which can be isolated from various plant sources. Chrysin is readily available to the public from commercial sources.

Poloxamers are α-hydro-ω-hydroxypoly(oxyethylene) poly(oxypropylene) poly(oxyethylene) block copolymers. Poloxamers are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. For example, poloxamer 124 is a liquid with "a" being 12, "b" being 20, and having an average molecular weight of from about 2090 to about 2360; poloxamer 188 is a solid with "a" being 80, "b" being 27, and having an average molecular weight of from about 7680 to about 9510; poloxamer 237 is a solid with "a" being 64, "b" being 37, and having an average molecular weight of from about 6840 to about 8830; poloxamer 338 is a solid with "a" being 141, "b" being 44, and having an average molecular weight of from about 12700 to about 17400; and poloxamer 407 is a solid with "a" being 101, "b" being 56, and having an average molecular weight of from about 9840 to about 14600. Poloxamers are well known and appreciated in the pharmaceutical arts and are readily available commercially. For example, Pluronic F-68 is a commercially available poloxamer from BASF Corp. The preferred poloxamers for use in the present invention are those such as poloxamer 188, Pluronic F-68, and the like.

Polyoxyethylene castor oil derivatives are a series of materials obtained by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil. These polyoxyethylene castor oil derivatives are well known and appreciated in the pharmaceutical arts and several different types of material are commercially available, including the Cremophors available from BASF Corporation. Polyoxyethylene castor oil derivatives are complex mixtures of various hydrophobic and hydrophilic components. For example, in polyoxyl 35 castor oil (also known as Cremophor EL), the hydrophobic constituents comprise about 83% of the total mixture, the main component being glycerol polyethylene glycol ricinoleate. Other hydrophobic constituents include fatty acid esters of polyethylene glycol along with some unchanged castor oil. The hydrophilic part of polyoxyl 35 castor oil (17%) consists of polyethylene glycols and glyceryl ethoxylates.

In polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) approximately 75% of the components of the mixture are hydrophobic. These comprise mainly fatty acid esters of glycerol polyethylene glycol and fatty acid esters of polyethylene glycol. The hydrophilic portion consists of polyethylene glycols and glycerol ethoxylates. The preferred polyoxyethylene castor oil derivatives for use in the present invention are polyoxyl 35 castor oil, such as Cremophor EL, and polyoxyl 40 hydrogenated castor oil, such as Cremophor RH 40. Cremophor EL and Cremophor RH 40 are commercially available from BASF Corporation.

Polyethylene oxide is a nonionic homopolymer of ethylene oxide conforming to the general formula $(OCH_2CH_2)_n$ in which n represents the average number of oxyethylene groups. Polyethylene oxides are available in various grades which are well known and appreciated by those in the pharmaceutical arts and several different types of material are commercially available. The preferred grade of polyethylene oxide is NF and the like which are commercially available.

(+)-Taxifolin is (2R-trans)-2-(3,4-dihydroxyphenyl)-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one. Other common names for (+)-taxifolin are (+)-dihydroquercetin; 3,3', 4', 5,7-pentahydroxy-flavanone; diquertin; taxifoliol; and distylin. (+)-Taxifolin is well know and appreciated in the art of pharmaceutical arts and is readily available commercially.

The preferred p-glycoprotein inhibitor for use in the present invention are water soluble vitamin E, such as vitamin E TPGS, and the polyethylene glycols. Of the polyethylene glycols, the most preferred p-glycoprotein inhibitors are PEG 400, PEG 1000, PEG 1450, PEG 4600 and PEG 8000.

Administration of a p-glycoprotein inhibitor may be by any route by which the p-glycoprotein inhibitor will be bioavailable in effective amounts including oral and parenteral routes. Although oral administration is preferred, the p-glycoprotein inhibitors may also be administered intravenously, topically, subcutaneously, intranasally, rectally, intramuscularly, or by other parenteral routes. When administered orally, the p-glycoprotein inhibitor may be administered in any convenient dosage form including, for example, capsule, tablet, liquid, suspension, and the like.

An effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor is that amount which is effective in providing inhibition of the activity of the p-glycoprotein mediated active transport system present in the gut. An effective p-glycoprotein inhibiting amount will vary between about 5 mg to about 1000 mg of p-glycoprotein inhibitor as a daily dose depending upon the particular p-glycoprotein inhibitor selected, the species of patient to be treated, the dosage regimen, and other factors which are all well within the abilities of one of ordinary skill in the medical arts to evaluate and assess. A preferred amount however will typically be from about 50 mg to about 500 mg, and a more preferred amount will typically be from about 100 mg to about 500 mg. The above amounts of a p-glycoprotein inhibitor can be administered from once to multiple times per day. Typically for oral dosing, doses will be administered on a regimen requiring one, two or three doses per day with one and two being the preferred.

Where water soluble vitamin E or a polyethylene glycol is selected as the p-glycoprotein inhibitor, a preferred amount will typically be from about 5 mg to about 1000 mg, a more preferred amount will typically be from about 50 mg to about 500 mg, and a further preferred amount will typically be from about 100 mg to about 500 mg. The most preferred amount of water soluble vitamin E or a polyethylene glycol will be from about 200 mg to about 500 mg. The above amounts of water soluble vitamin E or polyethylene glycol can be administered from once to multiple times per day. Typically, doses will be administered on a regimen requiring one, two or three doses per day with one and two being preferred.

As used herein, the term "co-administration" refers to administration to a patient of both a compound of Formula I and a p-glycoprotein inhibitor so that the pharmacologic effect of the p-glycoprotein inhibitor in inhibiting p-glycoprotein mediated transport in the gut is manifest at the time at which the compound of Formula I is being absorbed from the gut. Of course, the compound of Formula I and the p-glycoprotein inhibitor may be administered at different times or concurrently. For example, the p-glycoprotein inhibitor may be administered to the patient at a time prior to administration of the compound of Formula I so as to pre-treat the patient in preparation for dosing with the compound of Formula I. Furthermore, it may be convenient for a patient to be pre-treated with the p-glycoprotein inhibitor so as to achieve steady state levels of p-glycoprotein inhibitor prior to administration of the first dose of the compound of Formula I. It is also contemplated that the compound of Formula I and the p-glycoprotein inhibitor may be administered essentially concurrently either in separate dosage forms or in the same oral dosage form.

The present invention further contemplates that the compound of Formula I and the p-glycoprotein inhibitor may be administered in separate dosage forms or in the same combination oral dosage form. Co-administration of the compound of Formula I and the p-glycoprotein inhibitor may conveniently be accomplished by oral administration of a combination dosage form containing both the compound of Formula I and the p-glycoprotein inhibitor.

Thus, an additional embodiment of the present invention is a combination pharmaceutical composition for oral administration comprising an effective antihistaminic amount of a compound of Formula I (the antihistamine) and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor (the inhibitor). This combination oral dosage form may provide for immediate release of both the compound of Formula I and the p-glycoprotein inhibitor or may provide for sustained release of one or both of the compound of Formula I and the p-glycoprotein inhibitor. One skilled in the art would readily be able to determine the appropriate properties of the combination dosage form so as to achieve the desired effect of co-administration of the compound of Formula I and the p-glycoprotein inhibitor.

The antihistamine and the inhibitor may be administered alone or in the form of a pharmaceutical composition in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the antihistamine and inhibitior selected, the dosage regimen desired and standard pharmaceutical practice. The antihistamines, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts, such as the hydrochloride, for purposes of stability, convenience of cystallization, increased solubility and the like. One form of the pharmaceutical composition according to the present invention is a combination pharmaceutical composition where both the antihistamine and the inhibitor are present in the same dosage form.

The pharmaceutical composition may be prepared in a manner well known and appreciated in the pharmaceutical art. The carrier or excipient is pharmacologically inert and may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the antihistamine and the inhibitor. Suitable carriers and excipients are well known in the art. The pharmaceutical compositon may be adapted for oral administration in the form of a tablet, capsule, liquid, syrup, wafer, chewing gum, suspension, or the like. These preparations may contain at least 4% of active ingredient, i.e., the percent by weight of the antihistamine and the inhibitor, but may conveniently be varied depending upon the particular form so that the active ingredients make up from about 4% to about 70% of the weight of the unit dosage form.

Tablets, pills, capsules, and the like may contain one or more of the following carriers or excipients: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose; surfactants such as polysorbate 80, and the like; disintegrating agents such as alginic acid, Primogel™, corn starch, sodium bicarbonate, calcium bicarbonate and the like; lubricants such as magnesium stearate or Sterotex™; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; flavoring agent such as peppermint, methyl salicylate or orange flavoring. Capsules may contain, in addition to the ingredients listed above for tablets, a liquid carrier such as polyethylene glycol or a fatty oil. Tablets and capsules may contain other various carriers and excipients which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredients, sterile water, sucrose as a sweetening agent, preservatives, dyes, and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For purposes of parenteral administration, the inhibitor may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of the active ingredient but may be varied from about 0.1% to about 50% by weight thereof. The amount of the inhibitor should be adjusted in such compositions so that an a suitable dosage will be obtained upon administration.

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water, saline, fixed oils, polyethylene glycols, glycerine, propylene glycols or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates; agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparations may be enclosed in ampules, disposable syringes or multiple dosage vials made of glass or plastic.

More particularly, the combination pharmaceutical composition may be in the form of a tablet, a capsule, a liquid, a suspension, a syrup, and the like. The combination pharmaceutical composition, including in tablet form, may be a simple admixture of the antihistamine, the inhibitor, and any necessary and appropriate carriers and excipients. Alternatively, the composition may be in the form of an admixture of various heterogeneous pellets, beads or other heterogeneous particles which provide an appropriate formulation. In addition, the pharmaceutical composition may be in the form of a multiple compression tablet such as a multilayered tablet or a compression-coated tablet.

Combination pharmaceutical compositions made up of heterogeneous pellets, beads or particles (hereinafter referred to as "heterogeneous pellets"), or made up of multiple compression tablets, are useful for administration of pharmaceutical compositions which provide for different release characteristics for the antihistamine and inhibitor. For example, these compositions may provide for an immediate release of the inhibitor and a sustained release of the antihistamine, or vice versa. These compositions are prepared according to standard techniques which are well known and appreciated in the art such as those described in U.S. Pat. No. 4,996,061 which is hereby incorporated by reference in its entirety.

The following examples illustrate a particularly preferred embodiment of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

EXAMPLE 1

Effect of PEG 400 on the Bioavailabilty of Fexofenadine in the Dog

The effect of polyethylene glycol 400 (PEG 400) on the bioavailability of fexofenadine was determined in two fasted, male beagle dogs. Treatment A consisted of oral administration of one 120 mg fexofenadine hydrochloride sustained release (SR) tablet, and treatment B consisted of oral administration of one SR tablet together with a capsule with 0.5 mL PEG 400 given at −1, 0, 2, 4, 6, and 8 hours before and after the SR tablet. Treatment A was given 10 or 17 days prior to Treatment B. The plasma concentrations of fexofenadine were analyzed to determine relative bioavailability of fexofenadine with and without concomitant treatment with PEG 400.

A mean 2-fold increase in plasma concentrations (Table I) occurred when PEG 400 was co-administered with fexofenadine. This doubling of fexofenadine bioavailability is also shown in FIG. 1, which illustrates the increase in mean plasma concentrations produced during co-administration.

TABLE I

Plasma Concentrations of Fexofenadine in Dogs Given a 120 mg Fexofenadine SR Tablet Dose Alone or with 0.5 mL PEG-400 Capsule Doses

Dose	Time	Fexofenadine Concentration (ng/mL) Dog Number		
Condition	(Hours)	7645	3181	Mean
Fexofenadine Alone	0	0	0	0
	0.5	192.93	221.88	207.41
	1	523.96	1196.64	860.30
	1.5	748.57	1537.07	1142.82
	2	1617.8	2088.09	1852.95
	3	2316.21	1865.81	2091.01
	5	2364.18	793.03	1578.61
	7	1170.93	276.88	723.91
	9	880.07	184.32	532.20
	12	350.02	91.25	220.64
	14	274.33	69.49	171.91
	22	110.33	28.95	69.64
	24	97.87	34.68	66.28
Fexofenadine	0	0	0	0
+ PEG-400	0.5	783.93	154.38	469.16
	1	5866.28	687.3	3276.79
	1.5	7574.3	820.16	4197.23
	2	10116.53	1277.5	5697.02
	3	9794.6	3736.69	6765.65
	5	4794.46	1342.66	3068.56
	7	1400.87	565.14	983.01
	9	890.27	240.76	565.52
	12	585.41	139.86	362.64
	14	293.91	82.72	188.32
	22	108.74	59.66	84.20
	24	93.73	51.54	72.64

EXAMPLE 2

Effect of Water Suluble Vitamin E on the Bioavailability of Fexofenadine in the Dog

The effect of water soluble vitamin E (d-α-tocopheryl polyethylene glycol succinate) on the bioavailability of fexofenadine was determined in two fasted, male beagle dogs in two-way crossover experimental design. Treatment A consisted of oral administration of an aqueous solution of a 1 mg/kg dose of ^{14}C-labeled fexofenadine alone, and Treatment B consisted of oral administration of an aqueous solution of the same dose of ^{14}C-labeled fexofenadine and a 10 IU/Kg dose of water soluble vitamin E. Treatments were given in the opposing order of a crossover design in the two dogs, and a on week washout period occurred between treatments. The radioactivity in plasma and urine was analyzed and is known to represent unchanged fexofenadine in the dog. The results showed a 50% increase in plasma ^{14}C AUC occurred when water soluble vitamin E was co-administered with ^{14}C fexofenadine (Table II). That is, the bioavailability of fexofenadine was increased 50% by water soluble vitamin E. FIG. 2 illustrates the increase in mean plasma concentrations caused by co-administration of water soluble vitamin E.

TABLE II

Plasma Concentrations of [^{14}C]Fexofenadine in Dogs Given a 1 mg/kg [^{14}C]Fexofenadine Oral Solution Dose Alone or with 10 IU/kg Water Soluble Vitamin E

Dose	Time	[^{14}C]Fexofenadine Concentration (ng equiv/mL) Dog Number		
Condition	(Hours)	7645	3181	Mean
Fexofenadine Alone	0	0	0	0
	0.5	509	829	669
	1	546	673	609.5
	1.5	815	743	779
	2	924	559	741.5
	3	882	386	634
	5	330	128	229
	7	155	81	118
	9	82	54	68
	12	40	26	33
	14	33	18	25.5
	22	15	5	10
	24	9	8	8.5
Fexofenadine	0	0	0	0
+ WS Vit E	0.5	853	1472	1162.5
	1	1721	1098	1409.5
	1.5	1974	805	1389.5
	2	1515	572	1043.5
	3	1104	558	831
	5	230	257	243.5
	7	163	120	141.5
	9	90	73	81.5
	12	51	40	45.5
	14	48	31	39.5
	22	14	11	12.5
	24	10	13	11.5

The increase in absorption and bioavailability of fexofenadine that occurred with concomitant administration of water soluble vitamin E was also evident from the urinary excretion of ^{14}C fexofenadine in urine, which increased a mean of 3-fold (Table II).

TABLE III

Percent of [^{14}C]Fexofenadine Excreted in Urine of Dogs Given a 1 mg/kg Oral [^{14}C]Fexofenadine Hydrochloride Dose Without or With Water Soluble Vitamin E Excipient.

Dog Number	Without Excipient (% Dose)	With Excipient (% Dose)	Ratio
7645	2.38	9.88	4.2
3181	2.80	4.79	1.7
Mean	2.59	7.34	3.0

EXAMPLE 3

Effect of PEG 1000 on the Bioavailabilty of Fexofenadine in the Dog

The effect of polyethylene glycol 1000 (PEG 1000) on the bioavailability of fexofenadine was determined in two fasted, male beagle dogs. Treatment A consisted of oral administration of one 120 mg fexofenadine hydrochloride sustained release (SR) tablet, and treatment B consisted of oral administration of one SR tablet together with a capsule containing 0.5 g PEG 1000 dissolved in 2.5 mL water given at −1, −0.1, and 4 hours before and after the SR tablet. Treatment A was given two months prior to Treatment B. The plasma concentrations of fexofenadine were analyzed to determine relative bioavailability of fexofenadine with and without concomitant treatment with PEG 1000.

A mean 2-fold increase in plasma concentrations [AUC (0-24h) values calculated from the concentrations shown in Table IV] occurred when PEG 1000 was co-administered with fexofenadine. The peak concentration was increased a mean of 3-fold. This increased bioavailability in the presence of PEG 1000 is evident in the graph of mean plasma fexofenadine concentrations (FIG. 3).

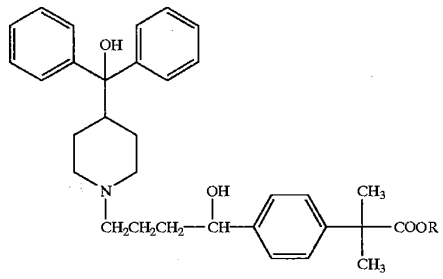
TABLE IV

Plasma Concentrations of Fexofenadine in Dogs Given a 120 mg Fexofenadine SR Tablet Dose Alone or with 0.5 g PEG-1000 Capsule Solution Doses

		Fexofenadine Concentration (ng/mL)		
Dose	Time	Dog Number		
Condition	(Hours)	7645	3181	Mean
Fexofenadine Alone	0	0	0	0
	0.5	192.93	221.88	207.41
	1	523.96	1196.64	860.30
	1.5	748.57	1537.07	1142.82
	2	1617.8	2088.09	1852.95
	3	2316.21	1865.81	2091.01
	5	2364.18	793.03	1578.61
	7	1170.93	276.88	723.91
	9	880.07	184.32	532.20
	12	350.02	91.25	220.64
	14	274.33	69.49	171.91
	22	110.33	28.95	69.64
	24	97.87	34.68	66.28
Fexofenadine	0	0	0	0
+ PEG-1000	0.5	15.28	147.24	81.31
	1	669.27	473.48	571.38
	1.5	1133.02	1687.98	1410.50
	2	4541.31	3963.22	4252.27
	3	7695.42	5595.32	6645.37
	5	3398.34	2035.32	2716.83
	7	1320.73	857.89	1089.31
	9	784.42	377.1	580.76
	12	315.74	202.89	259.32
	24	109.69	112.75	111.22

We claim:

1. A method for enhancing bioavailability of a piperidinoalkanol antihistamine of the formula



wherein

R is hydrogen or C_1–C_6 alkyl,

or a pharmaceutically acceptable salt or an individual optical isomer thereof, in a patient which comprises co-administering to said patient an effective antihistaminic amount of said piperidinoalkanol antihistamine and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor.

2. A method of claim **1** wherein the antihistamine is fexofenadine, or a pharmaceutically acceptable salt thereof.

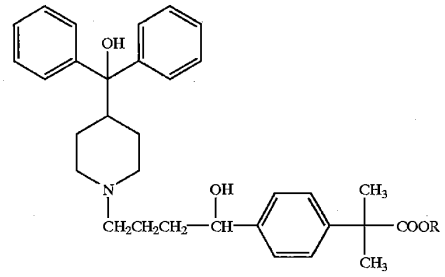
3. A method of claim **2** wherein the p-glycoprotein inhibitor is selected from the group consisting of water soluble vitamin E and polyethylene glycols.

4. A method of claim **3** wherein the p-glycoprotein inhibitor is water soluble vitamin E or is selected from the group consisting of PEG 400, PEG 1000, PEG 1450, PEG 4600 and PEG 8000.

5. A method of claim **4** wherein the p-glycoprotein inhibitor is water soluble vitamin E.

6. A method of claim **4** wherein the p-glycoprotein inhibitor is PEG 1000.

7. A method of treating allergic reactions in a patient which comprises co-administering to said patient an effective antihistaminic amount of a piperidinoalkanol antihistamine of the formula



wherein

R is hydrogen or C_1–C_6 alkyl,

or a pharmaceutically acceptable salt or an individual optical isomer thereof, and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor.

8. A method of claim **7** wherein the antihistamine is fexofenadine, or a pharmaceutically acceptable salt thereof.

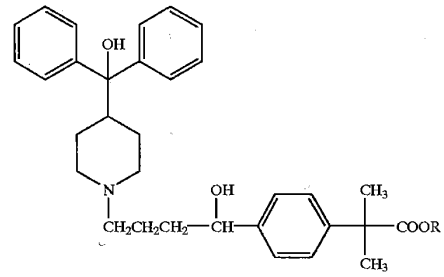
9. A method of claim **8** wherein the p-glycoprotein inhibitor is selected from the group consisting of water soluble vitamin E and polyethylene glycols.

10. A method of claim **9** wherein the p-glycoprotein inhibitor is water soluble vitamin E or is selected from the group consisting of PEG 400, PEG 1000, PEG 1450, PEG 4600 and PEG 8000.

11. A method of claim **10** wherein the p-glycoprotein inhibitor is water soluble vitamin E.

12. A method of claim **10** wherein the p-glycoprotein inhibitor is PEG 1000.

13. A pharmaceutical composition comprising an effective antihistaminic amount of a piperidinoalkanol antihistamine of the formula



wherein

R is hydrogen or C_1–C_6 alkyl,

or a pharmaceutically acceptable salt or an individual optical isomer thereof, and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor.

14. A composition of claim 13 wherein the antihistamine is fexofenadine, or a pharmaceutically acceptable salt thereof.

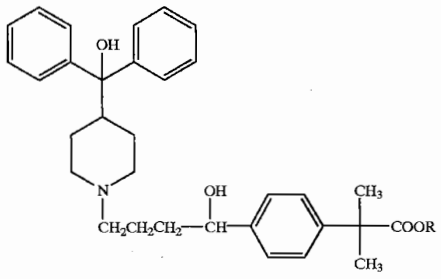
15. A composition of claim 14 wherein the p-glycoprotein inhibitor is selected from the group consisting of water soluble vitamin E and polyethylene glycols.

16. A composition of claim 15 wherein the p-glycoprotein inhibitor is water soluble vitamin E or is selected from the group consisting of PEG 400, PEG 1000, PEG 1450, PEG 4600 and PEG 8000.

17. A composition of claim 16 wherein the p-glycoprotein inhibitor is water soluble vitamin E.

18. A composition of claim 16 wherein the p-glycoprotein inhibitor is PEG 1000.

19. The use of a composition in the manufacture of a medicament for enhancing bioavailability of a piperidinoalkanol antihistamine of the formula



wherein

R is hydrogen or C_1–C_6 alkyl,

or a pharmaceutically acceptable salt or an individual optical isomer thereof, wherein said composition comprises an effective antihistaminic amount of said piperidinoalkanol antihistamine and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor.

20. A use of claim 19 wherein the antihistamine is fexofenadine, or a pharmaceutically acceptable salt thereof.

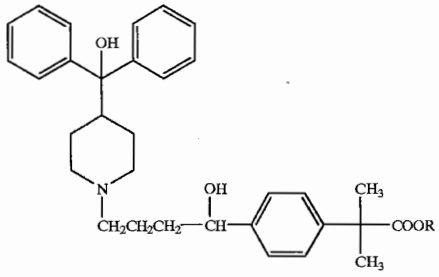
21. A use of claim 20 wherein the p-glycoprotein inhibitor is selected from the group consisting of water soluble vitamin E and polyethylene glycols.

22. A use of claim 21 wherein the p-glycoprotein inhibitor is water soluble vitamin E or is selected from the group consisting of PEG 400, PEG 1000, PEG 1450, PEG 4600 and PEG 8000.

23. A use of claim 22 wherein the p-glycoprotein inhibitor is water soluble vitamin E.

24. A use of claim 22 wherein the p-glycoprotein inhibitor is PEG 1000.

25. The use of a composition in the manufacture of a medicament allergic reactions in a patient wherein said composition comprises an effective antihistaminic amount of a piperidinoalkanol antihistamine of the formula



wherein

R is hydrogen or C_1–C_6 alkyl,

or a pharmaceutically acceptable salt or an individual optical isomer thereof, and an effective p-glycoprotein inhibiting amount of a p-glycoprotein inhibitor.

26. A use of claim 25 wherein the antihistamine is fexofenadine, or a pharmaceutically acceptable salt thereof.

27. A use of claim 26 wherein the p-glycoprotein inhibitor is selected from the group consisting of water soluble vitamin E and polyethylene glycols.

28. A use of claim 27 wherein the p-glycoprotein inhibitor is water soluble vitamin E or is selected from the group consisting of PEG 400, PEG 1000, PEG 1450, PEG 4600 and PEG 8000.

29. A use of claim 28 wherein the p-glycoprotein inhibitor is water soluble vitamin E.

30. A use of claim 28 wherein the p-glycoprotein inhibitor is PEG 1000.

* * * * *

11. Diane A.I. Ashiru-Oredope et al., *The effect of polyoxyethylene polymers on the transport of ranitidine in Caco-2 cell monolayers,* 409 INT'L J PHARM. 164, 167 (2011).

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The effect of polyoxyethylene polymers on the transport of ranitidine in Caco-2 cell monolayers

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ABSTRACT

Previous *in vivo* studies using PEG 400 showed an enhancement in the bioavailability of ranitidine. This study investigated the effect of PEG 200, 300 and 400 on ranitidine transport across Caco-2 cells. The effect of PEG polymers (20%, v/v) on the bi-directional flux of ^{3}H-ranitidine across Caco-2 cell monolayers was measured. The concentration dependence of PEG 400 effects on ranitidine transport was also studied. A specific screen for P-glycoprotein (P-gp) activity was used to test for an interaction between PEG and P-gp. In the absence of PEG, ranitidine transport showed over 5-fold greater flux across Caco-2 monolayers in the secretory than the absorptive direction; efflux ratio 5.38. PEG 300 and 400 significantly reduced this efflux ratio ($p < 0.05$), whereas PEG 200 had no effect ($p > 0.05$). In concordance, PEG 300 and 400 showed an interaction with the P-gp transporter, whereas PEG 200 did not. Interestingly, with PEG 400 a non-linear concentration dependence was seen for the inhibition of the efflux ratio of ranitidine, with a maxima at 1%, v/v ($p < 0.05$). The inhibition of ranitidine efflux by PEG 300 and 400 which interact with P-gp provides a mechanism that may account for the observations of ranitidine absorption enhancement by PEG 400 *in vivo*.

1. Introduction

Many drugs undergo absorption in the small intestine and although it has a large surface area of around 120 m^2, the residence time can be short here. A dosage form will spend an average of 3–4 h in the small intestine (Davis et al., 1986), but this can be very variable (Fadda et al., 2009) and as low as 30 min (Davis et al., 1986). Drug absorption can occur through simultaneous passive diffusion and active mechanisms, involving transcellular and paracellular routes. The paracellular route is controlled by tight junctions, and the transcellular route is influenced by cellular machinery (plasma membrane channels, carriers, exchangers and efflux transporters). Ranitidine is an H_2 receptor antagonist that has an absorption window in the small intestine, but poor absorption in the colon (Williams et al., 1992). The bioavailability of ranitidine has been shown to be improved in male subjects by the administration of low dose PEG 400 (Schulze et al., 2003; Ashiru et al., 2008). At high doses, however, the improvement in bioavailability was not observed. It is currently unknown whether the diminished effect at higher doses is due to the tendency of PEG to accelerate small intestinal transit (Basit et al., 2001; Schulze et al., 2003) or absolution of the PEG 400 absorption-enhancing mechanism.

It has been reported that ranitidine is primarily transported across Caco-2 cells via the paracellular route (Gan et al., 1993; Collett et al., 1996). However, more recent studies have suggested that paracellular transport accounts for 60% of the absorptive transport whilst transcellular processes, including transporters such as human organic cation transporter 1 [OCT], account for the other 40% (Bourdet et al., 2006; Bourdet and Thakker, 2006). The absorption of ranitidine is also affected by efflux transporters. P-glycoprotein (P-gp), multidrug resistance-associated protein 1 and 2 (MRP 1, MRP 2) and breast cancer resistance protein (BCRP) expel drug into the lumen of the intestine and many drugs are substrates of these transporters; consequently the bioavailability and pharmacokinetics of these drugs are controlled by the expression of these carriers. The efflux protein P-gp has been implicated in intestinal ranitidine transport (Collett et al., 1999) whilst cimetidine (another H_2 antagonist) has been identified as both a P-gp and BCRP substrate (Collett et al., 1999; Pavek et al., 2005).

PEG 300 and 400 are commonly used pharmaceutical excipients employed to enhance the solubility of drugs and there is evidence that PEG can inhibit efflux transporters (Hugger et al., 2002a). One group have reported a dose-dependent inhibition of P-gp in excised rat intestine in the presence of PEG 400 (Johnson et al., 2002). PEG 300 and PEG 400 have also been shown to inhibit P-gp in Caco 2 cells (Rege et al., 2001). Based upon our own *in vivo* observations on ranitidine bioavailability (Ashiru et al., 2008), we hypothesise that low molecular weight PEGs can improve ranitidine transport

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by way of P-gp inhibition in a concentration-dependent manner. Therefore, the aim of this study was to investigate the effect of PEG 400 and its lower molecular weight analogues (PEG 200 and 300) on ranitidine transport using the Caco-2 epithelial cell model.

2. Materials and methods

2.1. Materials

The PREDEASY ATPase Kit containing human P-gp membranes from Sf9 insect cells, was obtained from Tebu-bio (Peterborough, UK). Caco-2 cells (human adenocarcinoma cell line) were obtained from the European Collection of Cell Cultures (ECACC) (Wiltshire, UK). Dulbecco's modified Eagle's medium (DMEM), foetal bovine serum, non-essential amino acids, L-glutamine, 0.25% trypsin–EDTA, gentamicin (50 mg/ml), Hanks' Balanced Salt Solution (HBSS), 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES), polyoxyethylene glycol (PEG) 200, 300 and 400 were purchased from Sigma–Aldrich (Dorset, UK). Ranitidine (99.9% purity) was obtained from Zhongnuo Pharmaceutical Co., Ltd. (China). Transwell® Corning Costar Corporation (12-well, 1.13 cm^2 surface area, 0.4 μm pore size) and 162 cm^2 flasks were obtained from Fisher (Leicestershire, UK). ^{14}C-mannitol (specific activity = 61 mCi/mmol) was purchased from Amersham Biosciences (Buckinghamshire, UK). ^{3}H-ranitidine (specific activity = 2.5 Ci/mmol) was purchased from Moravek, CA, USA. Scintillation Cocktail (Emulsifier) was obtained from Perkin Elmer (Buckinghamshire, UK).

2.2. Methods

2.2.1. P-gp ATPase activity

ATPase activity of ranitidine and PEG 400 and its two lower molecular weight analogues (200 and 300) were measured using the PREDEASY ATPase Kit as per manufacturers' instructions. Briefly, the P-gp containing membrane was diluted with assay mix (50 mM Mops–Tris, pH 7.0; 50 mM KCl; 5 mM sodium azide; 2 mM DTT; 0.1 mM EGTA–Tris, pH 7.0; 1 mM ouabainin distilled water). Diluted membrane solution (40 μl) was loaded into the wells of a 96-well plate. Test compounds PEG 200, 300 and 400 were dissolved in DMSO to produce 300 μM solutions. From these solutions 1 μl was taken and added to the membrane suspension. The same volume of DMSO was added to the control wells and the reaction mixtures pre-incubated at 37 °C for 20 min. The reaction was started by the addition of 10 μl ATP (magnesium salt) solution and stopped 10 min later by the addition of 100 μl developer solution. After 2 min 100 μl of blocker solution was added to the wells and then further incubated for 30 min at 37 °C before reading the absorbance at 610 nm in a microplate spectrophotometer. The drug stimulated ATPase activity (nmol/min/mg of protein) was determined as the difference between the amounts of inorganic phosphate released from ATP in the absence and presence of vanadate. Phosphate standards were prepared in each plate and verapamil served as a positive control. Drug-stimulated P-gp ATPase activity was reported as fold-stimulation relative to the basal P-gp ATPase activity in the absence of drug (DMSO control). A compound was classified as an activator if the fold-stimulation was greater than 2-fold over the DMSO control.

2.2.2. Caco-2 cell culture

2.2.2.1. Cell maintenance. Caco-2 cells (passages 25-55) were grown and maintained in culture as previously described (Hidalgo et al., 1989). Briefly, cells were grown in 162 cm^2 cell culture flasks and subcultured weekly on achieving 80–90% confluency. Cell culture growth medium was Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% (v/v) foetal bovine serum, 1% (v/v) non-essential amino acids, 1% (v/v) L-glutamine, and 0.1% (v/v) gentamicin (50 mg/ml). Cells were maintained in an incubator at 37 °C with humidified environment of 95% and 5% CO_2. Medium was changed every 2–3 days.

2.2.2.2. Growth of cell monolayers. For the transport studies, cells were seeded at a density of 60,000 cells/cm^2 onto Transwell® polycarbonate membranes with a 12 mm diameter, pore size of 0.4 μm and a surface area of 1.13 cm^2. Cells grown on Transwell® membranes were maintained by providing 0.5 ml of culture medium to the apical (A) compartment and 1.5 ml to the basolateral (B) compartment. Medium was replaced every 2–3 days until the cells were ready for the permeability experiments (days 21–28).

2.2.2.3. Transepithelial electrical readings (TER). The integrity of the cell monolayers during the growth phase was monitored by taking TER readings using an EVOM™ epithelial voltohmmeter (World Precision Instruments, Hertfordshire, UK). The resistance of the monolayer was determined by subtracting the total resistance (membrane support and cell monolayer) from the membrane support resistance. All cells were used at TER greater than 700 Ω cm^2.

2.2.3. Transport studies

All transport studies were performed on Transwell® grown Caco 2 cells maintained in culture for 21–28 days. Before performing the transport studies the TER was measured to ensure cell monolayer integrity. The cell culture medium was then removed and washed three times with pre-warmed transport buffer (HBSS with HEPES, pH 7.4) prior to the start of the experiment. In all bidirectional transport studies, either HBSS or PEG dissolved in HBSS were present on both sides of the Caco-2 cell monolayers. This was done to maintain osmotic pressure for the duration of the study as the PEG solutions are hyperosmotic (Rege et al., 2001; Hugger et al., 2002a). The integrity of the monolayer during the experiment was confirmed by concomitant addition of ^{14}C-mannitol to all the test solutions.

In the absorptive (A-to-B) transport studies, 1.5 ml of HBSS or PEGs dissolved in HBSS at 20% (v/v), was added to each receiver (B) compartment. Into the donor (A) compartment was added 0.5 ml of HBSS or PEGs dissolved in HBSS, spiked with ^{14}C-mannitol and ^{3}H-ranitidine (along with cold ranitidine to a total concentration of 0.1 mM). For the secretory (B-to-A) transport studies, 1.5 ml mixture of radiolabeled mannitol and ranitidine (total concentration 0.1 mM) were added to the basolateral chamber instead. The transport study was performed under stirring conditions at a speed of 50 rpm (Gyrotory Shaker Model G2, New Brunswick Scientific Co., UK). At 30 min intervals (0, 30, 50, 90, 120, 150 and 180 min), 100 μl samples were removed from the receiver compartment and each compartment was appropriately replenished with HBSS or HBSS containing PEGs. The amount of radiolabeled solute transported across the Caco 2 cell monolayers was determined using a Beckman Coulter LS6500 liquid scintillation counter (Buckinghamshire, UK). The apparent permeability coefficients (Papp; cm/s) for the radiolabeled solute were determined in the absorptive and secretory direction using the equation:

$$\text{Papp} = \left(\frac{1}{AC_o}\right)\left(\frac{dQ}{dt}\right) \quad (1)$$

where dQ/dt is the flux across the monolayer, A is the surface area of the Transwell® membrane (1.13 cm^2), and C_o is the original donor concentration of the radiolabeled solute.

The efflux ratio was determined by dividing the Papp in the B-to-A direction by the Papp in the A-to-B direction. An efflux ratio greater than one indicates predominance of secretory transport suggesting the presence of an efflux transporter.

Table 1
The apparent permeability values for ^{14}C mannitol across Caco-2 cell monolayers in the presence of PEG 200, 300 and 400 (20%, v/v).[a]

Excipient (% v/v)	Mannitol Papp (cm/s $\times 10^{-6}$)
0	0.75 ± 0.05
PEG 200	0.86 ± 0.05
PEG 300	0.93 ± 0.01
PEG 400	0.95 ± 0.06

[a] The bidirectional transport of ^{14}C-mannitol (specific activity – 0.61 Ci/mmol) was examined across Caco-2 cell monolayers in the absence (no PEG, only HBSS) and presence of 20% (v/v) PEG 200, 300 or 400 on both sides of the Caco-2 cell monolayers (grown 21–28 days; $n=3$); experiment performed in triplicate with 3 replicates per variable on each occasion. Samples (100 μl) were taken from the receiver compartments every 30 min for 3 h and each receiver compartment was replenished with the appropriate transport buffer solution (HBSS or PEG in HBSS). The apparent permeability coefficients (Papp) for ^{14}C-mannitol were calculated as described in Section 2.

2.2.4. Statistics

All values were expressed as mean ± SD. Cell culture data are the mean of three separate experiments with replicates of $n=3$ on each occasion. Statistical evaluation of data was performed with SPSS® (version 15.0, SPSS Inc., Chicago, IL, USA). Data were compared using either *t*-test or one-way analysis of variance (ANOVA). In all cases, a difference was considered significant at $p \leq 0.05$.

3. Results

3.1. Effect of PEG on mannitol flux and transepithelial electrical resistance (TER)

Before investigating the effects of PEG on the transport of ranitidine across Caco-2 cell monolayers, it was important to determine whether PEG affects cell monolayer integrity. In these studies, TER measurements and mannitol transport were used to test cellular integrity in the presence of a 20% (v/v) PEG 200, 300 and 400 over a 180 min period. The results showed that the average transport of mannitol in the control monolayers ($0.75 \pm 0.05 \times 10^{-6}$ cm/s) and in those treated with PEG 200, 300, 400 were not significantly different from each other (Table 1; $p > 0.05$). Changes in TER were not considered significant ($p > 0.05$) compared to control for all PEGs. TER values in the presence of PEG were typically >700 Ω cm^2.

3.2. Effect of ranitidine and PEG on P-gp ATPase activity

The interaction between ranitidine and the PEG analogues on P-gp was investigated using a P-gp ATPase activity kit. Of these, only PEG 200 fell below the ATPase stimulation ratio of 2 (Table 2). The other compounds were shown to stimulate P-gp ATPase activity (ratio above 2).

Table 2
Effect of ranitidine and PEG analogues on ATPase activity; screen for P-gp interaction.[a]

Compound	ATPase assay ratio	ATPase activator/interaction with P-gp (Y/N)
Ranitidine	4.15	Y
PEG 200	0.53	N
PEG 300	3.71	Y
PEG 400	3.06	Y

[a] Drug-stimulated Pgp ATPase activity was reported as fold-stimulation relative to the basal Pgp ATPase activity in the absence of drug (DMSO control). A compound is classified as an activator if the fold-stimulation was greater than 2-fold over the DMSO control (Polli et al., 2001).

Table 3
Effects of PEG 200, 300 and 400 (20%, v/v) on ^{3}H-ranitidine transport across Caco-2 cell monolayers.[a]

Excipient	Papp (cm/s $\times 10^{-6}$) A-to-B	Papp (cm/s $\times 10^{-6}$) B-to-A	Papp(B-to-A)/Papp(A-to-B)
0	1.06 ± 0.01	5.72 ± 0.2	5.38
PEG 200	1.07 ± 0.08	5.40 ± 0.65	5.05
PEG 300	2.26 ± 0.09	5.63 ± 0.70	2.49
PEG 400	1.51 ± 0.05	5.91 ± 0.1	3.9

[a] The bidirectional transport of ^{3}H-ranitidine (concentration 0.1 mM; specific activity – 2.5 Ci/mmol) was examined across Caco-2 cell monolayers in the absence (no PEG, only HBSS) and presence of 20% (v/v) PEG 200, 300 or 400 on both sides of the Caco-2 cell monolayers (grown 21–28 days; $n=3$); experiment performed in triplicate with 3 replicates per variable on each occasion. Samples (100 μl) were taken from the receiver compartments every 30 min for 3 h and each receiver compartment was replenished with the appropriate transport buffer solution (HBSS or PEG in HBSS). The apparent permeability coefficients (Papp) for ^{3}H-ranitidine were calculated as described in Section 2.

3.3. Effect of PEG analogues on the bidirectional transport of ranitidine

The Papp values for the absorptive and secretory transport of ^{3}H-ranitidine across Caco-2 cell monolayers in the absence and presence of 20% (v/v) of PEG 200, 300 and 400 are shown in Table 3. The results show that in the absence of PEG (control monolayers), ranitidine exhibited polarised secretory transport (an efflux ratio significantly above 1). In the presence of PEG 300 and 400 (but not PEG 200), the efflux ratio decreased compared to control, although not to a level where efflux is totally abolished, i.e. a ratio of 1. The lowest efflux ratio value was 2.49 for PEG 300; there was an increase in absorptive transport of ranitidine in the presence of PEG 300 and 400, whilst secretory transport remained largely unaffected.

3.4. Effect of PEG 400 concentration on the transport of ranitidine

The Papp for the permeation of ^{3}H-ranitidine across Caco-2 cell monolayers in the absorptive and secretory directions in the presence of various concentrations of PEG 400 are shown in Fig. 1. In the presence of PEG 400 there is predominance of secretory transport of PEG 400 at all concentrations, except for 1% (v/v) where the efflux ratio was at its lowest value of 1.2 (Fig. 2). At concentrations up to 1% (v/v) there was a progressive reduction in secretory and concomitant increase in absorptive transport of ranitidine. At PEG 400 concentrations between 1% (v/v) and 20% (v/v), the inhibition of secretory transport became progressively weaker. All the concentrations of PEG 400 tested had a significant effect on the efflux ratio compared to control (ANOVA, $p < 0.05$).

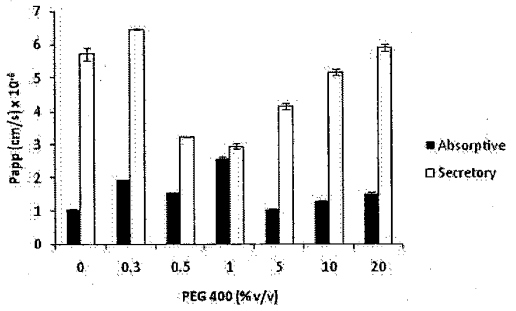

Fig. 1. Effects of different concentrations of PEG 400 on the bidirectional transport of ^{3}H-ranitidine across Caco-2 cell monolayers (mean ± SD, $n=3$). Open bars indicate transport in the secretory direction, closed bars indicate transport in the absorptive direction.

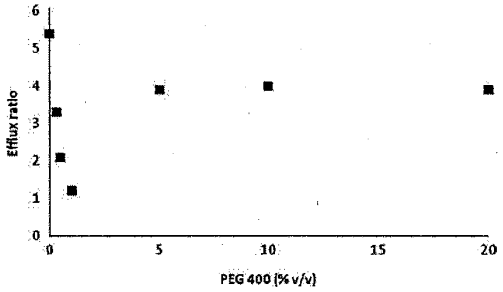

Fig. 2. Effects of different concentrations of PEG 400 on the efflux ratio (Papp secretory/Papp absorptive) of ^{3}H-ranitidine across Caco-2 cell monolayers.

4. Discussion

The bioavailability of ranitidine in male subjects is improved by the administration of low dose – 1% PEG 400 (Schulze et al., 2003; Ashiru et al., 2008). The mechanism for this effect is unknown and the present study investigated whether PEG of different molecular weights produces similar effects *in vitro*, and if so how these are mediated.

PEGs are amphiphilic, non-micelle forming hydrophilic polymers that are considered inert and safe (up to 40%, v/v) for use as pharmaceutical excipients. In this study we verified that PEG does not influence paracellular transport by demonstrating that the permeability of mannitol, a hydrophilic paracellular marker, was unchanged in the presence or absence of PEG 200, 300 or 400 at 20% (v/v). The mannitol Papp $\sim 1 \times 10^{-6}$ cm/s in the presence or absence of PEG was similar to that observed by Rege et al. (2001). As PEG solutions increase osmolality in comparison to standard Caco-2 assay media, the potential to affect drug flux by movement of water across the cell layer was negated by placing PEG in both donor and receiver chambers of the diffusion apparatus to avoid generating a hyperosmotic gradient. The mannitol Papp and TER data confirm that the osmotic pressure did not affect Caco-2 monolayer integrity (Inokuchi et al., 2009).

PEG 300 has no influence on the passive transport of drugs *in vitro* (Hugger et al., 2002a), but there are reports that certain PEG analogues such as PEG 400, PEG 2000 and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) can affect the P-gp transporter (Johnson et al., 2002; Hugger et al., 2002a,b; Shen et al., 2006; Yamagata et al., 2007; Mudra and Borchardt, 2010) although the precise mechanisms by which this occurs remain elusive. Ranitidine is generally regarded to be a substrate for P-gp (Gan et al., 1993; Takamatsu et al., 2001; Bourdet et al., 2006), although Polli et al. (2001) classified ranitidine as a non-substrate. This disparity in defining a compound as a P-gp substrate, or an inhibitor, is not uncommon and can result from different assay sensitivities or inter-laboratory variation in the assays for P-gp transporter–drug interaction. Our data for Caco-2 cell monolayer efflux and P-gp ATPase activity indicate that ranitidine is a P-gp substrate. However, it is noted that the P-gp ATPase assay does not distinguish P-gp substrates from inhibitors and does not measure transport directly. In our studies PEG 300 and 400 stimulated P-gp ATPase and had the ability to inhibit ranitidine efflux in Caco-2 cells, whereas PEG 200 had no effect in either assay. PEG 300 and 400 (20%, v/v) reduced the ranitidine efflux ratio of ~5.5, principally through an increase in absorptive flux. PEG of similar and larger molecular weight (PEG 400, 2000 and 20,000) have been reported to inhibit the polarised efflux of rhodamine 123 when used at concentrations between 0.1 and 20% (v/v or w/v) (Shen et al., 2006).

The effect of PEG 400 concentration on ranitidine efflux ratio was parabolic with a maximum effect of complete inhibition of efflux at 1% (v/v). The reason for the reduced effectiveness at concentrations greater than 1% (v/v) PEG 400 is unclear, but interestingly the concentration effect of PEG 400 on ranitidine transport *in vitro* was similar to the concentration-dependency observed previously for the enhancement of bioavailability of ranitidine *in vivo* (Ashiru et al., 2008). At higher concentrations of PEG 400 there may be competition for the paracellular route between ranitidine and PEG itself. The paracellular route has been reported to contribute 60% of ranitidine flux under certain conditions (Bourdet et al., 2006) and the existence of a saturable paracellular transport pathway has been postulated. PEG has been used as a marker of paracellular permeability (Kim, 1996; Watson et al., 2001; Linnankoski et al., 2010), albeit some reports question its suitability as a paracellular marker as it exhibits higher permeability compared to other markers of comparable molecular weight (Artursson et al., 1993; Iqbal et al., 1993). In this study we did not monitor PEG transport.

The mechanism by which PEG reduces Pgp ATPase activity may involve blocking the binding site or direct interaction of PEG with allosteric sites in the P-gp pump, which have been shown to be present (Dey et al., 1997; Maki et al., 2003). PEG 300 has been reported to inhibit P-gp by alteration of the polar head group regions thus altering membrane fluidity and affecting P-gp activity (Hugger et al., 2002a). Altered membrane fluidity as a result of osmotically-driven water transfer across the mucosa was also suggested to explain the concentration dependent reduction in digoxin efflux in the rat intestine by PEG 400 (Johnson et al., 2002).

5. Conclusion

These *in vitro* data correspond to results from the *in vivo* study in showing that PEG 400 at lower doses enhances the transport of ranitidine. The observation that both ranitidine and PEG interact with P-gp and the efflux of ranitidine in Caco-2 cells is inhibited by PEG 400 suggest that transporter inhibition may be the absorption-enhancing mechanism. Although the mechanism of action for the unusual PEG 400 concentration effect on ranitidine transport was not elucidated conclusively, the effect of PEG on drug transport at concentrations relevant for drug formulation was demonstrated.

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Bioavailability of Hydrochlorothiazide from Pellets, Made by Extrusion/ Spheronisation, Containing Polyethylene Glycol 400 as a Dissolution Enhancer

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KEY WORDS: HCT; hydroflumethiazide; cyclodextrins.

INTRODUCTION

Drugs with limited aqueous solubility such as hydrochlorothiazide (HCT) have a potential for low bioavailability. Several methods which proved to increase the in-vitro release rate of drugs with a low aqueous solubility were tested in-vivo on their ability to increase the bioavailability of the drug. Reduction of the drug particle size (1–3), incorporation of the drug into solid dispersions (4–8) and complexation with cyclodextrins (2,9–10) proved to be suitable methods for increasing the gastrointestinal absorption of drugs with a low aqueous solubility. Vervaet *et al.* (11) demonstrated that the incorporation of a liquid solubiliser into microcrystalline cellulose pellets enabled the enhancement of the in-vitro release rate of HCT. The aim of this study is to evaluate the effect of PEG 400 on the pharmacokinetic parameters of HCT after oral administration of microcrystalline cellulose pellets loaded with HCT and polyethylene glycol 400.

MATERIALS AND METHODS

Materials

Hydrochlorothiazide (HCT)(Ludeco, Brussels, Belgium) was used as a model drug. Polyethylene glycol 400 (PEG 400)(α-Pharma, Vichte, Belgium) was used as a solubilising agent, while microcrystalline cellulose (Avicel PH101®)(FMC Wallington, Little Island, Cork, Ireland) was chosen as a filler and the pellet forming agent. Demineralized water was used as granulation liquid, next to PEG 400.

Formulations

Two pellet formulations were tested in vivo. Type I-pellets consisted of a mixture of HCT and microcrystalline cellulose (ratio: 3.5/96.5; w/w), while PEG 400 was added to form Type I-pellets (HCT/PEG 400/Avicel PH101®—ratio: 3.5/20/76.5; w/w/w). A conventional HCT tablet (Esidrex® 25 mg, Ciba, Basel, Switzerland) was used as the reference formulation.

Preparation of the Pellets

The pellets were prepared using the method described by Vervaet *et al.* (11). The granulation liquid, which was added to the microcrystalline cellulose/HCT mixture, was pure demineralized water in the case of Type I-pellets, while a mixture of demineralized water and PEG 400 was used for Type II-pellets. The batch size of both formulations was 1 kg. After drying the pellets for 48 h at 30°C in a ventilated oven (Heraus, Oberdorf, Germany), the 800–900 μm sieve fraction was isolated.

Dissolution Testing

A dissolution test was performed, using the method described by Vervaet et al. (11), on the HCT tablet and on hard gelatin capsules filled with an amount of Type I- and II-pellets (800–900 μm fraction), equivalent to 25 mg of HCT.

Bioavailability Testing

Eight healthy Caucasian male volunteers, aged 19 to 45 years and weighing between 72 and 112 kg, participated in the study after giving informed consent. The physical state of all volunteers was examined before they were allowed to participate in the study. The subjects had to refrain from taking any other drugs for one week prior to and during the study. Each volunteer was given, in a randomized cross-over study, an oral dose of 50 mg HCT on 3 occasions, once administered as two Esidrex® 25 mg tablets and twice as a two hard gelatin capsule filled with pellets (Type I or II)(800–900 μm fraction). The washout period between the sessions was 1 week (HCT half-life: 5 h). All doses were administered with 200 ml of water at 8 a.m. after overnight fasting. A standard breakfast was given 2 h after administration of the dosage form. A lunch was taken at 12 a.m. No consumption of alcoholic beverages and nicotine was permitted from 12 h before until 24 h after drug intake.

Venous blood samples were collected into glass tubes immediately before and at various time intervals after drug administration. Serum was separated from the blood cells by centrifugation and stored at −20°C until analysis.

Chromatography

HCT serum concentrations were determined using a RP-C18 column (250 × 4 mm − 5 μm)(LiChrospher® 100, Merck, Darmstadt, Germany) equipped with a precolumn (RP-C18 − 4 × 4 mm − 5 μm). Both were kept at a constant temperature of 40°C. The mobile phase was 0.2 M phosphate buffer (pH 7.5)/tetrahydrofuran/acetonitrile (85/10/5; v/v/v). The flow rate was 1 mL/min. The detector wavelength was set at 273 nm.

Hydroflumethiazide (Sigma Chemical Co., St. Louis, MO, USA) was used as the internal standard. 500 μL serum, 100 μL 1.25 μg/ml hydroflumethiazide and 5 mL methyl *tert*-butylether (Sigma Chemical Co., St. Louis, MO, USA) were pipetted into borosilicate glass tubes. After 2 min vortexing and 5 min centrifuging at 2700g, the organic phase was transferred into a new borosilicate glass tube and evaporated until completely dry under a nitrogen stream. The residue was dissolved in 200 μL water, followed by the addition of 3 mL toluene (Vel N.V. Leuven, Belgium). The bulk of the toluene layer was discarded after 2 min of vortexing and 10 min centrifuging at 2700 g.

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Another 3 mL toluene was added, this mixture was again vortexed and centrifuged followed by the removal of the toluene layer. After evaporation of the water fraction under a nitrogen stream, the residue was dissolved in 200 μL mobile phase. A 100 μL aliquot of the homogenized solution was injected into the HPLC system.

HPLC Validation

The HCT recovery (10–1000 ng/ml range) varied between 87.5 and 91.5 %, while 93.5% of the internal standard was recovered. The method was linear between 0 and 1000 ng HCT/mL (r^2 = 0.99987 ± 0.00011)(n = 10). The within-day variability was 0.59–5.01% in the 10–1000 ng/ml range, while the intra-day variability for the same concentration range was determined at 0.68–5.89%. The detection and quantification limit in serum were 3.3 and 11.2 ng/ml, respectively.

Pharmacokinetic Analysis

The C_{max} and t_{max} values were determined from the individual serum concentration—time profiles, while the $AUC_{0\to24h}$ was calculated using the MW/Pharm software package (v. 3.0; Mediware 1987–1991, Utrecht, The Netherlands). The Wilcoxon signed ranked test for paired observations (12) was used to evaluate the pharmacokinetic parameters.

RESULTS AND DISCUSSION

The bioavailability of three HCT formulations was evaluated: a commercially available tablet (Esidrex® 25 mg) and two hard gelatin capsules, one filled with Type I-pellets containing a mixture of HCT and microcrystalline cellulose, while the other capsule contained microcrystalline cellulose pellets to which 20% (w/w) polyethylene glycol 400 was added (Type II-pellets).

Fig. 1 shows the in-vitro release profiles of the different formulations. The incorporation of PEG 400 into the pellet formulation showed a dramatic increase of the in-vitro release rate ($t_{50\%}$ value of 120 and 7 min for Type I- and II-pellets, respectively) due to the solubilising effect of PEG 400 (11). Both the tablet and the Type II-pellet formulation showed similar dissolution profiles for HCT.

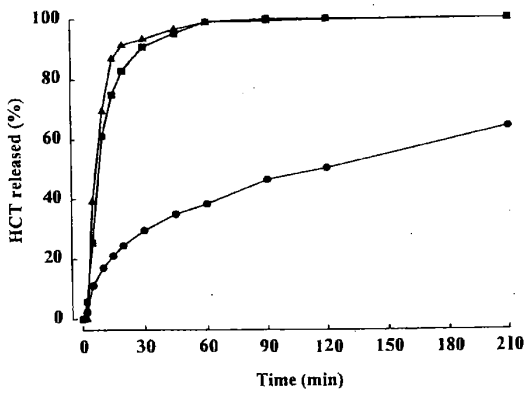

Fig. 1. Dissolution profile of formulations containing 25 mg of HCT. ■: tablet formulation (Esidrex® 25 mg) ●: Type I-pellets (HCT/microcrystalline cellulose 3.5/96.5 (w/w)) ▲: Type II-pellets (HCT/polyethylene glycol 400/microcrystalline cellulose 3.5/20/76.5 (w/w)).

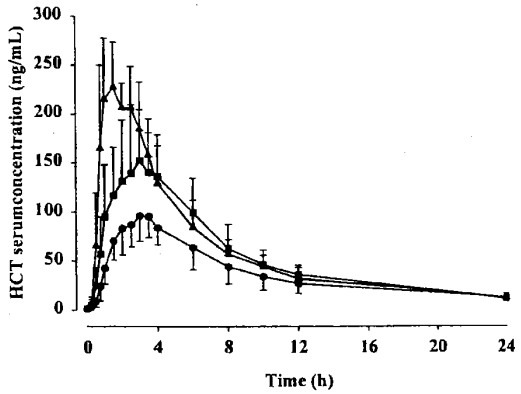

Fig. 2. Mean serum concentration—time profiles (±SD; n = 8) obtained after intake of an oral dose of 50 mg HCT. ■: tablet formulation (Esidrex® 25 mg) ●: Type I-pellets (HCT/microcrystalline cellulose 3.5/96.5 (w/w)) ▲: Type II-pellets (HCT/polyethylene glycol 400/microcrystalline cellulose 3.5/20/76.5 (w/w)).

The mean HCT serum concentration vs. time profiles are presented in Fig. 2. The pharmacokinetic parameters of the different formulations are shown in Table I. The C_{max} values were significantly different ($p \leq 0.01$; Wilcoxon signed ranked test) between all formulations. The t_{max} values of the tablet and the Type I-pellet formulation were not significantly different, while the Type II-pellets showed a significantly shorter t_{max} value ($p \leq 0.01$; Wilcoxon signed ranked test) in comparison to Type I-pellets and the tablet formulation. The calculated $AUC_{0\to24h}$ values were significantly higher ($p \leq 0.01$; Wilcoxon signed ranked test) for the tablet compared to Type I-pellets and for Type II-pellets compared to Type I-pellets. The low relative bioavailability (F_{rel}) of the Type I-pellets (70.4%) compared to the HCT tablet is in accordance with previous results (13), where a F_{rel} of 36.4% was found for HCT when administered as microcrystalline cellulose based pellets compared to a 50 mg HCT tablet. The reduced absorption of HCT was due to the absorption window of HCT in the gastro-intestinal tract,

Table I. Mean Bioavailability Parameters (± SD; n = 8) After Administration of an Oral Dose of 50 mg HCT, Once Administered as Two Esidrex® 25 mg Tablets and Twice as a Two Hard Gelatin Capsule Filled with Pellets

	Tablet	Type I-pellets	Type II-pellets
C_{max} (ng/ml)	180.2 ± 42.1	105.9 ± 24.2[a]	254.5 ± 36.0[a,b]
t_{max} (min)	165 ± 64	195 ± 36	83 ± 31[a,b]
$AUC_{0\to24h}$ (ng.h/ml)	76.5 ± 15.8	53.0 ± 12.8[a]	86.7 ± 19.5[b]
F_{rel} (%)		70.4 ± 13.8	117.3 ± 34.9

[a] Significantly different from tablet ($p \leq 0.01$; Wilcoxon signed ranked test).
[b] Significantly different from Type I-pellets ($p \leq 0.01$; Wilcoxon signed ranked test).

the major part being absorbed in the duodenum and the upper part of the jejunum (14). As the slow in-vitro dissolution rate from Type I-pellets indicated (Fig. 1) only part of the HCT was made available for absorption in the upper parts of the gastro-intestinal tract. This was confirmed by Herman *et al.* (13) who found a high fecal HCT concentration and little of the total dose remaining in the excreted intact pellets, indicating that most of the drug was released from the microcrystalline cellulose pellets in the lower parts of the gastro-intestinal tract.

The higher bioavailability after administration of the tablet, compared to the Type I-pellets, was due to the tablet disintegration, exposing the HCT-crystals to the gastro-intestinal liquids, whereas these liquids had to penetrate the inert microcrystalline cellulose matrix (15) of Type I-pellets to wet and dissolve the drug crystals.

The improvement of the absorption parameters from Type II-pellet compared to the tablet formulation (the mean C_{max} value increased from 180.2 to 254.5 ng/ml, while the mean t_{max} shifted from 165 to 83 min) is to be attributed to the fact that HCT was solubilised in the pellets (11) whereas the drug crystals still had to dissolve when a tablet was administered.

From the results presented it can be concluded that—when formulating a drug with a low aqueous solubility—microcrystalline cellulose pellets loaded with polyethylene glycol 400 yielded a higher bioavailability compared to pellets without PEG 400. The PEG 400 loaded pellets showed only a significantly higher absorption rate in comparison to a disintegrating tablet formulation.

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BIOAVAILABILITY AND EROSIVE ACTIVITY OF SOME NON-STEROIDAL ANTI-INFLAMMATORY DRUGS SOLID-DISPERSIONS.

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ABSTRACT

Solid dispersions of mefenamic acid, azapropazone, glafenine and floctafenine were prepared with PVP K_{25} and PEG 6000 in a ratio of 1:1 w/w. Bioavailability and erosive activity of these drugs were investigated using their solid dispersions. The obtained results revealed that the coprecipitate of such drugs with PVP enhances their bioavailability and significantly inhibits the ulcerogenic effect of the drugs under investigation. However, solid dispersions with PEG enhance bioavailability but slightly reduce their gastric ulceration.

INTRODUCTION

The anti-inflammatory analgesics are often used for long course treatment in patients with chronic and disabling conditions. Most of them cause gastrointestinal toxicity such as peptic ulceration and haemorrhage. A large number of new anti-inflammatory analgesics have been introduced and although their relative efficacy and safety remains to be established, there is evidence that some may produce toxic effects.

Mefenamic acid, azapropazone, glafenine and floctafenine are anti-inflammatory drugs of different chemical structures that have poor solubilities in water[1]. The gastrointestinal

complaints were the most symptoms encountered with medications of these drugs[1,2].

Polyvinyl Pyrrolidone (PVP) and Polyethylene Glycol (PEG) are widely used in the preparation of solid dispersions of insoluble drugs which are applicable in many pharmaceutical preparations. These facts together with the problems encountered with the poor bioavailability of the above mentioned drugs predomenate our investigation to formulate such drugs in solid dispersion with either PVP or PEG.

The surface and histological examination of the gastrointestinal tract of rats fed on these drugs either untreated or in a solid dispersion were also of interest to be investigated.

EXPERIMENTAL

1- Material and Equipment :

Mefenamic acid (El-Nile Co. for Pharmaceuticals, Cairo, Egypt); azapropazone (Siegfried, Zofinen, Switzerland); glafenine and floctafenine (Memphis Chem. Co. Cairo, Egypt). Formalin , sodium chloride, ethyl alcohol, eosin, methyl alcohol, chloroform, hematoxylin, xylol, hard paraffin, PEG 6000 and PVP K_{25} (analytical grades - Prolabo, France). Perkin-Elmer 505 Spectrophotometer and Aminco - Bowman Spectrophotofluorometer.

2- Preparation of Solid Dispersions:

Solid dispersions of each drug in a ratio of 1:1 w/w with PVP or PEG were prepared by solvent and fusion methods for PVP K_{25} and PEG 6000 respectively[3]. In the solvent method, drug-PVP physical mixture was dissolved in an organic solvent then evaporating off the later over a water bath. Methyl alcohol was used to prepare the coprecipitates of azapropazone and mefenamic acid while chloroform was chosen to prepare those of glafenine and floctafenine according to the solubility of drugs under investigation[1].

In the fusion method, each drug was mixed with PEG 6000 in a ratio of 1:1 w/w. The mixtures were carefully heated on electric hot plate till complete melting of PEG, then suddenly cooled in ice bath with continuous stirring. The coprecipitates and the frozen masses were scratched and stored in a desiccator overnight then pulverized, seived and the fractions of 45-63 µm were collected.

3- Bioavailability Study:

Adult male rabbits (2-2.25 Kg) were fasted for 24 hr, while water was allowed freely. The animals were divided into 4 groups each of 6 rabbits. Each group was separately fed with untreated drug and its solid dispersion or coprecipitate in a crossover design. All the administered medications had a particle diameter of 45-63 um and were filled in a hard gelatin capsule in a dose of 50 mg Kg^{-1}. Blood samples were collected at certain time intervals from the congested aural vein into glass tubes and drug concentrations were determined.

4- Methods of Assay of Blood Samples:

a) Mefenamic acid:

Blood samples were taken into heparinized tubes, then centrifuged at 9000 rpm for 10 minutes. The plasma was assayed spectrophotometrically for the total mefenamic acid (parent drug and metabolites, free and conjugated) by the method of Glazko[4].

b) Azapropazone:

Serum was separated from the collected blood samples. The concentration of azapropazone was determined spectrophotometrically as described[5].

c) Glafenine and Floctafenine:

Floctafenine and glafenine have nearly similar chemical structures[1]. Thus, the spectrophotometric method reported by Mallein et al[6].

for assessment of glafenine was adopted to determine both glafenine and floctafenine in heparinized blood samples. The method involves the treatment of serum with n-butanol saturated with concentrated ammonia solution and the butanolic extract was measured spectrophotometrically at 360 nm. The assay was developed for analysing blood samples for both drugs and it was checked for its accuracy for floctafenine[7].

5- Gross-surface and Histological Study:

Male albino rats of 200-250 g weight were randomly divided into 12 groups each of three rats. All animals were fasted 24 hr before experiments but had free access to water. Each three groups received the drug, drug-PVP coprecipitate and drug-PEG solid dispersion. The drugs and their solid dispersions were given in a dose of 20 mg for floctafenine and glafenine. The doses of mefenamic acid and azapropazone were 10 mg of each. All drugs doses were given as suspension in one ml water by means of stainless steel canula. Seven hours after dosing, the animals were killed, stomach was excised, opened out along the lesser curvature and the contents were washed out with 0.9% w/v aqueous sodium chloride solution. Each stomach was stretched out and examined for the presence of ulcerations, fixed in 10% formalin solution. The tissues were processed by the usual paraffin method, sectioned of 6 um, stained by hematoxylin and eosin stain[8], and examined microscopically.

RESULTS AND DISCUSSIONS

a) Bioavailability Study :

The blood plasma concentrations at different time intervals for mefenamic acid, glafenine and floctafenine and the serum concentrations of azapropazone are given in Figures 1 a,c,d and b respectively. Area under blood data curves (AUCS) was

calculated from blood concentrations up to 12 hrs by trapozoidal rule and the values were summarized in Table 1. The obtained data showed that PVP and PEG enhanced the bioavailability of the investigated drugs from their solid dispersions. The blood level profiles were almost parallel to the untreated drug.

The peak time of blood concentrations was not affected by the type of polymer and the technique of dispersion used, however, the peak heightwas increased (Table 1).

The maximum blood concentrations (Table 1 and Figure 1) were in the following order : PVP coprecipitate > PEG solid dispersion > untreated drug. Statistical analysis of the obtained data using Student 't' test[9] revealed that a highly significant difference existed between coprecipitates and untreated drugs. These data indicated that the mean blood drug concentrations over 0-12 hour interval were affected by the type of polymer and method of its incorporation with drug.

The increase in bioavailability of the tested drugs from their solid dispersions may be due to particle size effect and the increase in the wettability of drugs during dissolution. This results are in agreement with the previously reported data[3].

2- Gastric Ulcerogenic activity:

The rats which received untreated drugs exhibited a considerable mortality within 7 hours and gastrointestinal haemorhage was established to be the cause of death, but no mortality was identified for those animals given the solid dispersions (Table 2). The oral administration of the selected drugs either untreated or in solid dispersion to rats showed quitely different effects on the gastric mucosa. Focal erosions in the corpous and body with evidence of bleeding in or around the eroded

areas after administration of the untreated drugs occurred. Some lesions were seen from the serosal surface as small brown areas. No erosions were evident after dosing of solid dispersions but there was extensive sloughing of the mucous layer The erosions were clearly visible to the naked eye and were generally focal or extended lengthwise down the mucosa. No damage occurred in the middle of the greater curvature in the fore-stomach. Most of the damage occurred in the middle of the greater curvature in the corpus with occasional damage in the antrum and pylours.

The microscopic examination of stomachs of all groups showed stricking abnormalities (Figs. 2-13). Extensive damage occurred, and the damaged cells in the mucosa below erosions stained poorly in stomach of rats receiving untreated mefenamic acid, azapropazone, glafenine and floctafenine (Figs. 2, 5, 8 and 11).

The solid dispersions of the tested drugs with either PVP or PEG seemed to decrease the ulcerogenic effects of all drugs (Figs. 2-13). The figures indicate that PVP inhibits the ulcerogenicity of azapropazone, glafenine and floctafenine (Figs. 7, 10, and 13). A typical gastric mucosa with normal gastric pits and oxyntic cells were observed in the stomach of rats receiving PVP coprecipitates of azapropazone, glafenine and floctafenine. However, mefenamic acid-PVP showed damaged and erosion area w which are still less delterious than untreated drugs (Figs. 2 and 4).

The oral administration of the tested drugs in the form of solid dispersion with PEG inhibits their ulcerogenic activities to certain extent with different variances (Figs. 3, 6, 9, and 12). Enlargement of the area between damaged and undamaged

cells (Fig. 3) was found in animals receiving mefanamic acid-PEG solid dispersions. However, there is a sharp distinction between damaged and undamaged cells (Fig. 6) for azapropazone-PEG solid dispersion. Meanwhile, few cells have been sloughed away but the remainder had been clearly either damaged severely in the erodded area or remained intact as in case of glafenine-PEG (Fig. 9). The damage is confined to the superfacial mucosal cells occurred and the internal cytoplasm of the superfacial mucous cells distrupted as a consequence of discharging large number of mucous granules (Fig. 9). In contrast the gastric mucosa of the rats receiving floctafenine-PEG solid dispersion showed absence of any ulceration in the mucosal surface. Only inflammatory infiltrate, consisted of eosinophils, lymophocytes and plasma cells was found (Fig. 12).

It is noteworthy that the used anti-inflammatories induce peptic ulceration and bleeding when administered orally, which is in agreement with the reported findings[1,2].

Several mechanisma have been proposed to account for the development of gastric damage [10-15]. Among these explanations is the direct physical damage by the drug particles and loss of the protective mucous layer[10] and acidity influence of the drugs[11]. Many attempts were reported to inhibit these ulcerogenic activities utilizing different routes of administration, microencapsulation and different dosage forms[16-19]. In this study, it was found that coprecipitation of such drugs with PVP inhibits these peptic ulceration. In addition, the dispersion of such drugs with PEG decreased this effect. The drug may be in the molecular form (coprecipitate) or in very fine crystalline particles thet convyed with PEG (solid dispersion), and consequently enhancement in the dissolution and absorption of such drugs may occurs[3].

Accordingly, the time of contact of such drugs with the mucosal surface is decreased, and hence their local effects may be inhibited. In conclusion solid dispersions and coprecipitates of the tested drugs with PVP and PEG can be recommended in the oral therapy with NSAID.

Table 1: Blood level[X] data of rabbits administered different NSAID untreated and as solid dispersions.

Drug	Mefenamic acid			Azapropazone			Glafenine			Flocta fenine		
Form-	Untreated	PVP coppt	PEG S.d	Untreated	PVP coppt	PEG S.d.	Untreated	PVP coppt.	PEG S.d.	Untreated	PVP coppt.	PEC S.d
Peak hight ug/ml	52 ±3.20	89 ±3.17	64 ±3.09	1160 ±6.14	1220 ±8.12	1150 ±7.15	85.33 ±4.11	157.95 ±6.3	122.15 ±5.2	66.4 ±3.12	83.75 ±6.7	76.3 ±4.1
Peak time (hrs)	2±0	2±0	2±0	3±0	3±0	3±0	2±0	2±0	2±0	2±0	2±0	2±0
AUC_{0-12} µg/ml.hr	324.75 ±14.1	524** ±16.3	369* ±14.7	7497 ±12.7	8257** ±20.5	7767* ±16.2	769.69 ±15.3	999.84*** ±20:4	862.33* ±17.7	401.93 ±8.2	532.6** ±9.7	465.85* ±8.3

x Average of 6 rabbits for each treatment.

± Standard deviation (plasma or serum)

* Insignificant difference (P>0.05)

** Significant difference (P<0.1)

*** Very high significant difference (P<0.001) on comparing with untreated drug by student's t-test .

coppt. = coprecipitate

S.d. = solid dispersions.

Table 2: Mortality rate of rats administered different NSAID untreated and as solid dispersion.

Drug Form	Mefenamic acid			Azapropa-zone			Glafenine			Floctafenine		
Mortality time (hr)	A	B	C	A	B	C	A	B	C	A	B	C
2	1	-	-	1	-	-	-	-	-	1	-	-
4	1	-	-	1	-	-	2	-	-	1	-	-
7	1	-	-	-	-	-	1	-	-	1	-	-
Total*	3	-	-	2	-	-	3	-	-	3	-	-

* : Number of died animals.

A : Untreated drug.

B : PVP corecipitate.

C : PEG solid dispersion.

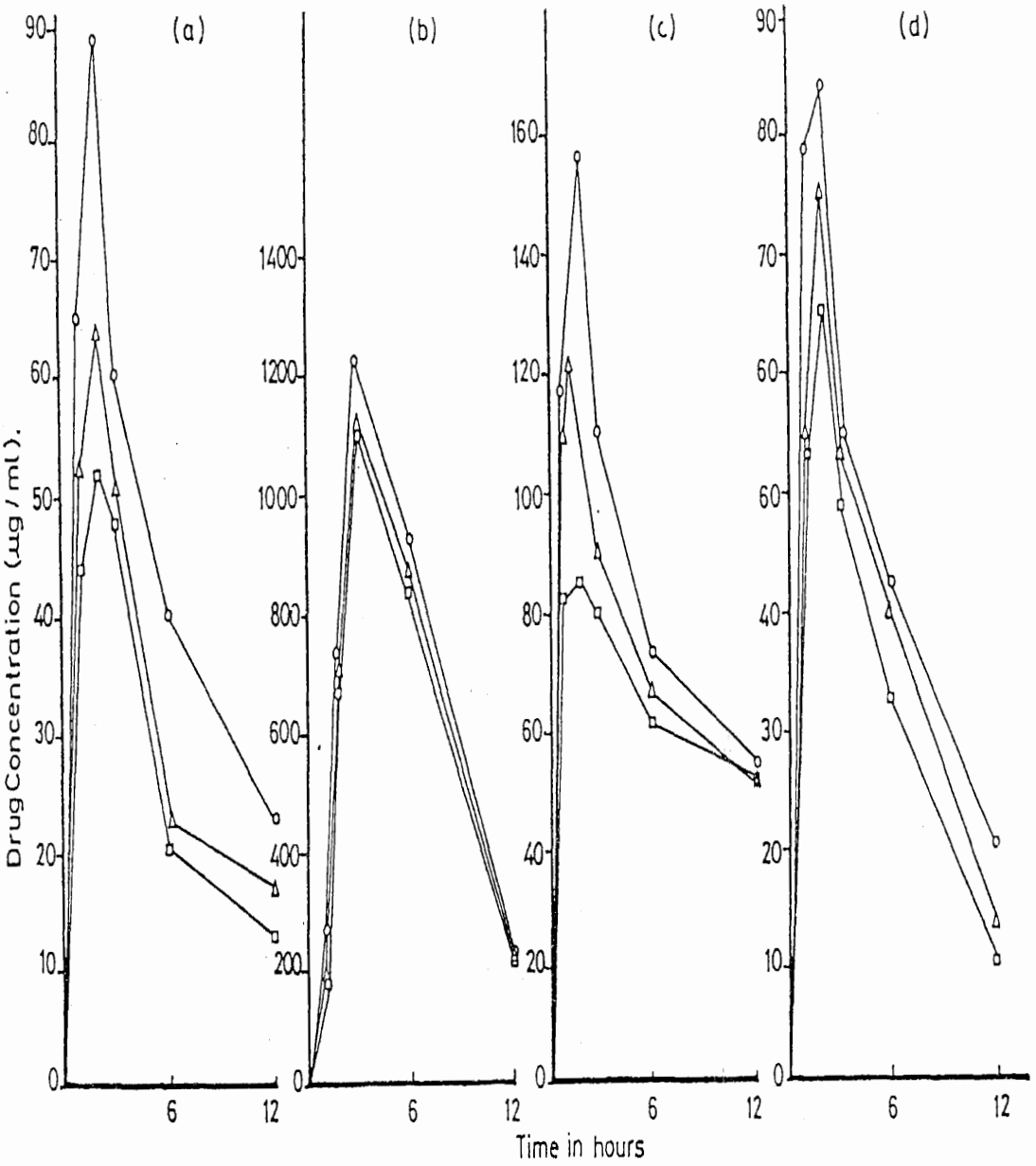

Figure 1. Mean blood concentration of mefenamic acid(a), azapropazone(b), glafenine (c), and floctafenine(d).

▫ Untreated drug
△ Drug - PEG solid dispersion
○ Drug - PVP coprecipitate

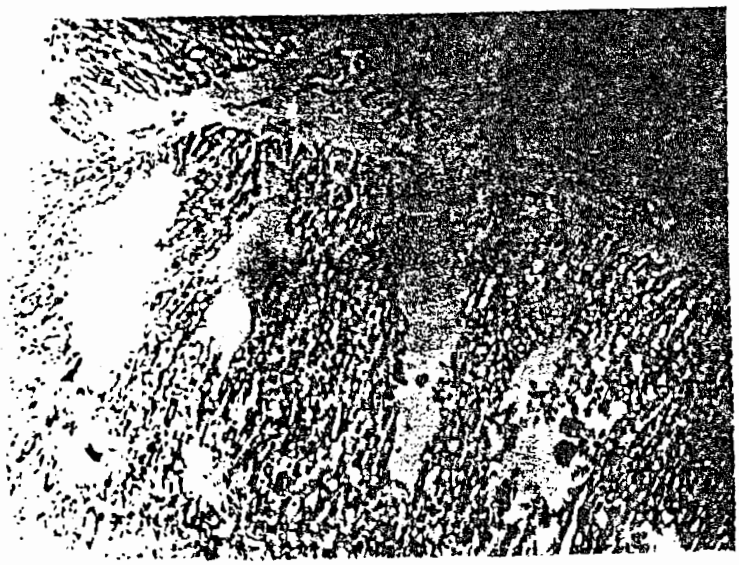

Fig. 2: Gastric mucosa of a rat after oral administration of 10 mg untreated mefenamic acid (Hx. & E.X 100).

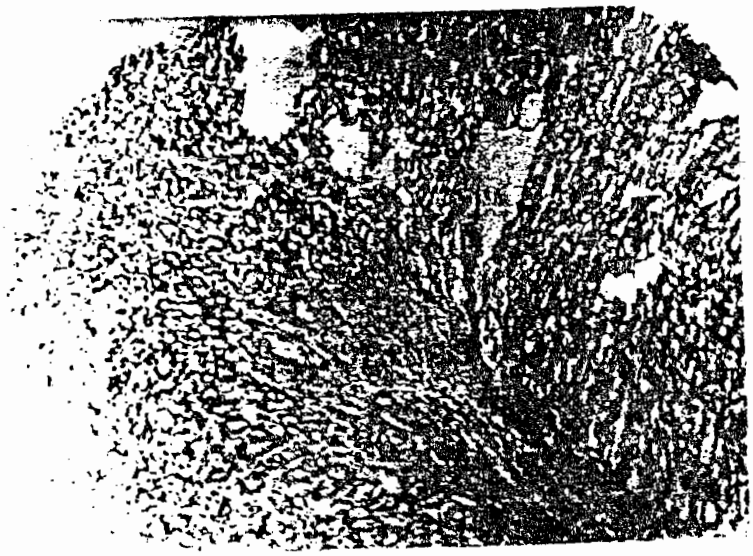

Fig. 3: Gastric mucosa of a rat after oral administration of 20 mg mefenamic acid-PEG solid dispersion (Hx & E.X 100).

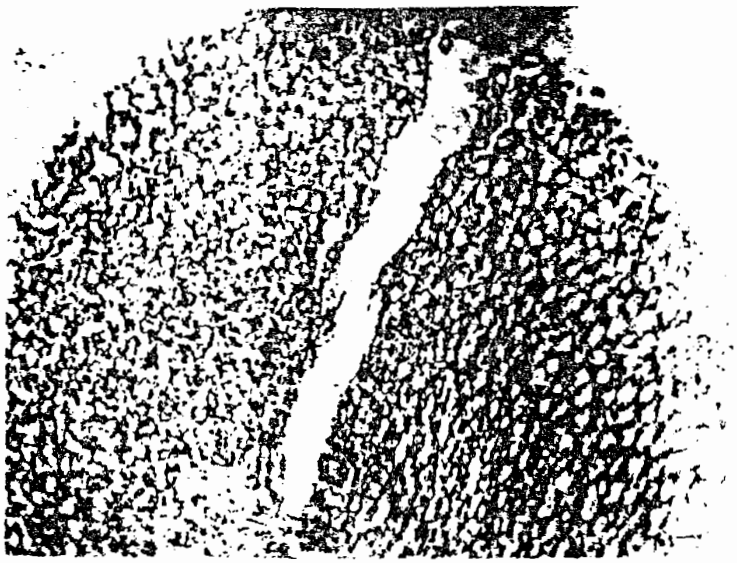

Fig. 4: Gastric mucosa of a rat after oral administration of 20 mg mefenamic acid-PVP coprecipitate (Hx & E.X 100).

Fig. 5: Gastric mucosa of a rat after oral administration of 10 mg untreated azapropazone (Hx. & E.X 100).

Fig. 6: Gastric mucosa of a rat after oral administration of 20 mg azapropazone-PEG solid dispersion (Hx & E.X 100).

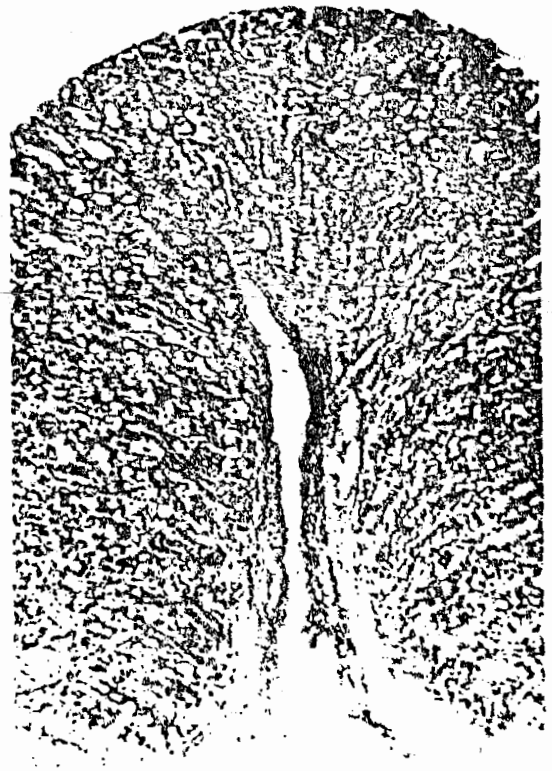

Fig. 7: Gastric mucosa of a rat after oral administration of 20 mg azapropazone-PVP coprecipitate (Hx & E.X 100).

Fig. 8: Gastric mucosa of a rat after oral administration of 20 mg untreated glafenine (Hx. & E.X 100).

Fig. 9: Gastric mucosa of a rat after oral administration of 40 mg glafenine-PEG solid dispersion (Hx. & E.X 100).

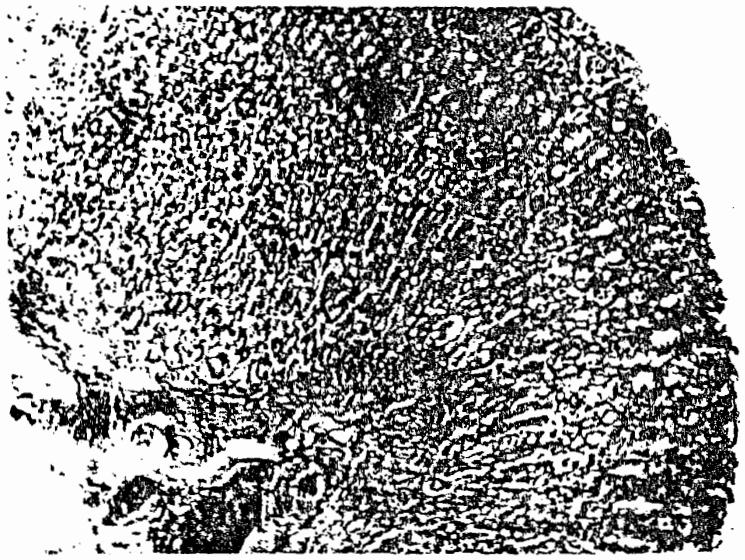

Fig. 10: Gastric mucosa of a rat after oral administration of 40 mg glafenine-PVP coprecipitate (Hx & E.X 100).

Fig. 11: Gastric mucosa of a rat after oral administration of 20 mg untreated floctafenine (Hx & E.X 100).

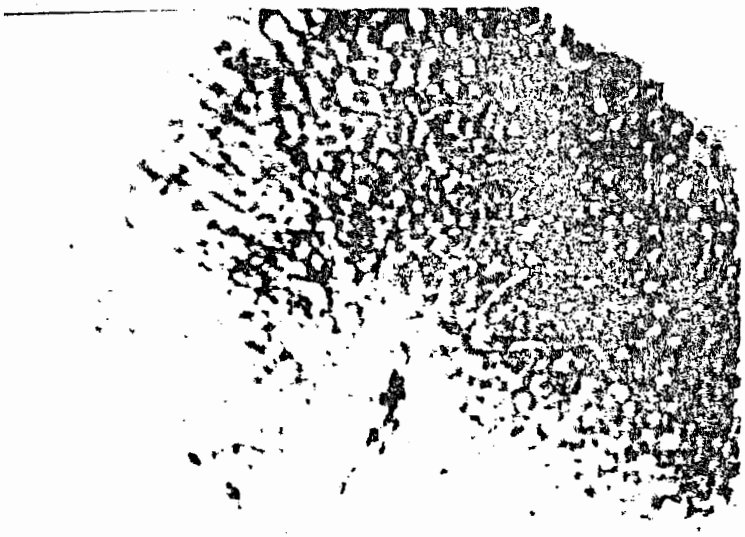

Fig. 12: Gastric mucosa of a rat after oral administration of 40 mg floctafenine-PEG solid dispersion (Hx & E.X 100).

Fig. 13: Gastric mucosa of a rat after oral administration of 40 mg floctafenine-PVP coprecipitate (Hx & E.X 100).

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الاتاحة الحيوية والنشاط التآكلى لبعض المنتشرات الصلبة للادوية المضادة للالتهابات

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حضرت المنتشرات الصلبة لحامض الميفيناميك والاذابرباذون والجلافينين والفلوكتافينين مع عديد فينيل البيروليدون ك ٢٥ وعديد الايثيلين جليكول ٦٠٠٠ بنسبة ١ : ١ وقد تناول البحث دراسة الاتاحة الحيوية لهذه الادوية ومنتشراتها الصلبة بالاضافة الى دراسة النشاط التآكلى لهذه الادوية ومنتشراتها الصلبة على معدة الفئران .

وقد اشارت النتائج الى وجود زيادة واضحة فى الاتاحة الحيوية لهذه الادوية من منتشراتها الصلبة بينما قلت خطورتها التآكلية على معدة الحيوانات .

وقد كان هذا التأثير واضحا من المنتشرات الصلبة للادوية مع عديد فينيل البيروليدون عنه فى حالة عديد ايثيلين جليكول .

. *received in 3/6/1986 & accepted in 8/11/1986*

14. European Medicines Agency Scientific Assessment Report-Aclasta® (zoledronic acid, Novartis) Injection (Mar. 4, 2006) ("EMA Scientific Assessment").

SCIENTIFIC DISCUSSION

1. Introduction

The adult form of Paget's disease of the bone (PDB) is a common condition with a strong genetic component, characterised by focal increases in bone turnover, involving one or more bones throughout the skeleton. In affected areas, excessive osteoclastic bone resorption is followed by disorganised bone formation resulting in low-quality (woven) bone of reduced mechanical integrity. The cited prevalence of PDB varies considerably by geographic area and criteria for diagnosis. A positive family history increases the risk markedly, but the exact mode of inheritance remains to be established.

While the majority of patients remain asymptomatic, active PDB is associated with bone pain and risk of bone deformity, pathological fracture, osteoarthritis, and deafness. There is also a small but defined risk of the development of osteosarcoma. The activity of PDB is reflected in serum and urine levels of biochemical markers of bone turnover. Currently available literature does not provide any clear evidence that any marker is superior to serum total alkaline phosphatase (SAP) for sensitivity or specificity.

Pharmacological therapy of PDB aims to reduce bone turnover and is currently based on the use of second- or third-generation bisphosphonates. It should be noted that none of the treatments used in PDB have been shown to prevent complications such as deafness, fracture or deformity, or alter the natural history of the disease.

The Applicant Novartis Europharm Ltd submitted a complete stand-alone application for Marketing Authorisation for Aclasta for the proposed indication of "Treatment of Paget's disease of the bone". The active substance of Aclasta, zoledronic acid (zoledronate)is a nitrogen-containing bisphosphonate with a mode of action involving inhibition of the enzymatic activity of farnesyl diphosphate synthase (FPP synthase). Inhibition of FPP synthase is considered a main mechanism by which osteoclast activity is inhibited and apoptosis is promoted. Zoledronic acid, has been previously approved within the EU as Zometa (EMEA/H/C/336) for the treatment of malignancy-induced hypercalcaemia and prevention of skeletal-related events in patients with advanced malignancies involving bone. In the oncology indications, zoledronic acid is given repeatedly as an intravenous infusion of 4 mg over at least 15 minutes every 3-4 weeks. For Paget's disease, on the other hand, zoledronic acid is proposed to be given as a single intravenous infusion of 5 mg to induce a long-lasting biochemical remission. The Applicant uses a separate invented name and label for the benign indication to avoid any potential confusion between the different doses and dosing interval, compared with the oncology indications.

2. Quality aspects

Introduction

Aclasta contains zoledronic acid as the active substance. It is presented as a clear, colourless aqueous solution for infusion containing 5.33 mg /100 ml of zoledronic acid monohydrate, which is equivalent to 5 mg /100 ml of anhydrous zoledronic acid.

Other ingredients include mannitol, sodium citrate and water for injections. The container is a plastic vial with rubber stopper and aluminium with flip off component. An overfill is filled to the vials to permit withdrawal of the labelled amount of zoledronic acid.

Drug Substance

The active substance is identical to the one used for the centrally authorised product Zometa, powder and solvent for solution for infusion (EMEA/H/C/336). The details of the manufacturing process, purification, specifications and stability have already been assessed for the above-mentioned application and are briefly summarised below.

The chemical name of zoledronic acid is (1-hydroxy-2-imidazol-1-ylphosphonoethyl) phosphonic acid.

The active substance does not contain any chiral centers and thus it does not exhibit any optical isomers. The monohydrate form of zoledronic acid was selected, because of its good chemical and physical stability in the solid state at ambient temperature. The structure of the active substance has been confirmed using an array of suitable methods.

- Manufacture

The active substance is synthesised by multiple steps and purified. The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.

- Specification

The active substance specification is in accordance with the one accepted for the powder for solution for infusion formulation.

Drug Product

- Pharmaceutical Development

Due to the poor absorption of zoledronic acid after oral administration the pharmaceutical development was aimed at developing a parenteral formulation. In order to facilitate the administration to patients by health professionals a "ready to infuse-solution" was found more safe and easy to use. The excipients used are mannitol and water for injection. The amount of excipients has been optimised to develop an isotonic solution and a stable buffering system for zoledronic acid. All excipients used in the product are of non-animal origin and comply with their corresponding European Pharmacopoeia monographs.

The immediate packaging materials are commonly used for these types of formulations and are made from the same material as the one used for Zometa 4 mg/5ml concentrate for infusion (plastic colourless vials with bromobutyl rubber stoppers).

- Manufacture of the Product

The manufacturing process is a standard process for these kind of formulations and sterilisation is performed in line with the requirements of the Ph.Eur. All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from production scale batches demonstrates that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification, assay, pH, impurities, particulate matter, degradation products, bacterial endotoxins and sterility. All tests included in the specification have been satisfactorily described and validated.
Batch analysis data from 6 batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were carried out according to ICH requirements.

In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Aclasta is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is the same as the one used in the already centrally authorised product Zometa, powder and solvent for solution for infusion (EMEA/H/C/336). It is well characterised and documented. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The

manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3. Non-clinical aspects

Introduction
Pivotal non-clinical pharmacology and toxicology studies, conducted between 1987 and 2004, were in accordance with principles of GLP.

Pharmacology
- Primary pharmacodynamics (*in vitro/in vivo*)

In cultures of freshly isolated rabbit and human osteoclasts zoledronic acid (10-100 μM) induced morphological features similar to apoptosis and caspase-3-like activation. Osteoclastogenesis was inhibited in a dose-dependent manner with an IC_{50} of 15 nM *in vitro* in cultures of murine bone marrow cells stimulated to form osteoclasts by addition of macrophage-colony stimulating factor and ligand for the receptor activator NF-κB (RANKL).

Zoledronic acid also inhibited proliferation of human foetal osteoblastic cell line (hFOB) with an IC_{50} of 40 μM. In cultures of primary human trabecular osteoblasts, zoledronic acid increased osteoprotegerin, a decoy receptor that binds to RANKL and inhibits interaction with RANK, inhibiting osteoclastogenesis.

Inhibition of bone loss was investigated in ovariectomised (OVX) estrogen-deficient rats and monkeys. Efficacy and bone safety of zoledronic acid were evaluated in a 12-month study in the rat and in a 16-month study in the rhesus monkey. Treatment started immediately after ovariectomization in both studies and subcutaneous doses of up to 12.5 μg/kg/week were used. The cumulative doses were 390 μg/kg in rat and 862.5 μg/kg in monkey, as compared with an approximately 100 μg/kg human yearly dose. A higher skeletal turnover in rat and possibly in monkey could result in that drug exposure in bones in OVX animals might not have reached human exposure levels. These issues as well as potential indications of "frozen bone", were discussed during CHMP scientific advice procedures. It was concluded that the available studies plus an 8-month study in OVX rats (see below), together with clinical data could be accepted as sufficient for addressing bone safety in non-oncology indications.

Parameters assessed in the 12- and 16-month studies included bone mass, bone mechanics, bone histomorphometry and biochemical markers of bone metabolism. In the rat, a dose of 1.5 μg/kg/week often resulted in full efficacy as determined by the parameters studied. Bone mechanical parameters, femoral neck fracture, femur 3-point bending and vertebra compression were dose-dependently increased by zoledronic acid towards levels in intact controls.

Comparable effects were noted in monkey, but mechanical parameters did not attain statistical significance. Histomorphometry of vertebral cancellous bone showed that zoledronic acid increased trabecular area, trabecular number, node number in comparison with OVX control, while trabecular separation was decreased. Bone formation rate and mineral apposition rate were decreased dose-dependently by zoledronic acid. In monkey, ovariectomization had no remarkable effect on histomorphometric parameters of cancellous bone in the vertebra, radius and femur at week 69. Cancellous bone structure was not affected by zoledronic acid, but the activation frequency and bone formation rate were decreased at all doses, while mineral apposition rate was decreased at the high dose (12.5 μg/kg/week), only. In cortical bone, zoledronic acid had no effect on mineral apposition rate or on total Haversian bone. Porosity and bone formation rate were decreased by zoledronic acid in cortical bone of femoral shaft.

An 8-month study in OVX rats given a single iv injection of 0.8, 4, 20, 100 or 500 μg/kg of zoledronic acid or 200 μg/kg of alendronate 4 days prior to ovariectomy was conducted to evaluate the duration of a bone protective effect. Zoledronic acid dose-dependently reduced plasma osteocalcin. At week

32, levels were suppressed in the 100 and 500 µg/kg groups, only. Bone mineral density analysis of the proximal tibial metaphysis indicated that zoledronic acid from 20 µg/kg protected completely against bone loss up to 24 weeks. Alendronate had a similar but weaker effect. Analysis of cortical and cancellous bone separately showed that 4 µg/kg partially protected against cortical thinning up to 12 weeks and against cancellous bone loss for at least 32 weeks. Histomorphometric parameters in cancellous bone of the proximal tibia were not affected by zoledronic acid up to doses of 20 µg/kg, while the two higher doses decreased bone formation to 45 and 21%, respectively, of the sham control level. Zoledronic acid dose-dependently prevented loss of cancellous bone of proximal tibia as indicated by 3D-µCT images at week 32. Zoledronic acid prevented loss of strength of femoral metaphysis and diaphysis with effects at 20 µg/kg generally comparable with 200 µg/kg of alendronate. High doses of zoledronic acid 100-500 µg/kg tended to increase bone strength above sham control levels.

In a study in male 7-week old rats with bone histomorphometry assessed using static and dynamic parameters, mineralised bone tissue was increased dose-dependently by zoledronic acid. There was a dose-dependent decrease in the osteoid perimeter in the cancellous bone. The significance of the osteoid changes is unclear but could result from a decrease in the activation frequency of new remodelling bone units. Retardation of longitudinal bone growth was reported but apparently not related to a mineralisation disturbance of the growth plate.

Mineralisation parameters in monkey indicated that a continued loss of bone density (humerus and vertebra) occurred in both intact control and OVX control and was counteracted in OVX animals by doses ≥2.5 µg/kg. Reduction of the central and distal radius bone mineral density was prevented by zoledronic acid in OVX at 12.5 µg/kg/week. Zoledronic acid dose-dependently increased carbonate content, reduced serum calcium at week 26 at the high dose and increased parathyroid hormone (PTH) at week 52. Femoral neck stiffness was dose-dependently increased and activation frequency of new remodelling sites decreased. No evidence of a mineralising defect, no osteoid accumulation, and no woven bone was reported. The decline of bone mineral density (BMD) of the distal and central radius in both OVX and control groups was unexpected and could not be explained, however, it was prevented by doses of 12.5 µg/kg/week. Additionally, zoledronic acid dose-dependently decreased levels of biochemical markers of osteoblastic bone formation (alkaline phosphatase, osteocalcin) and of osteoclastic bone resorption (N-telopeptide, pyridinoline), compared with OVX control. In general, similar effects were seen in both rat and monkey.

- Safety pharmacology

Safety pharmacology studies of zoledronic acid covered major organ systems such as the cardiovascular and autonomic, respiratory, gastrointestinal and renal systems, and no remarkable effects were reported.

- Pharmacodynamic drug interactions

No studies were submitted.

Pharmacokinetics

The pharmacokinetics of zoledronic acid has been studied in rat and dog. No data are available for rabbit and mouse, species used in reproduction toxicity and safety pharmacology studies. The compound does not seem to be metabolised and, in view of the low tolerability in rabbits, the lack of data in the rabbit is not considered a significant problem for the interpretation of data.

- Absorption- Bioavailability

The primary parameters characterised indicate that the pharmacokinetics of zoledronic acid are overall similar to other bisphosphonates. In rats exposure was comparable after intravenous and subcutaneous doses with negligible gender differences.

- Distribution

Distribution studies in rat showed, as expected, that most of the dose was taken up by bone with tibia having the highest levels followed by vertebra and cranium. Initially about 60% of the dose is taken up

in the bones and 40% still remains in bone after 1 year. The apparent half-life of zoledronic acid in bone appears to be over 360 days. Quantitative analysis showed that, with the exception of long-term retention in bone, transient high levels were also observed in kidney and spleen.

After repeated intravenous doses of 0.15 mg/kg in rat, accumulation was evident both in bone and soft tissue. Steady-state levels were not attained after 16 days of daily dosing. Accumulation in soft tissues was, however, more than 2 orders of magnitude lower than in bone and declined with an apparent half-life of 150 to 200 days after treatment had stopped. In a 3-month study in rats given subcutaneous doses of 0.1 mg/kg/day, no accumulation in plasma was recorded.

- Metabolism (in vitro/in vivo)

Zoledronic acid is not metabolised. There is no evidence of metabolites circulating in plasma or being excreted in urine.

- Excretion

Zoledronic acid is primarily excreted unchanged through the kidneys after intravenous administration with less than 3% in the feces in rat and dog. Most of the radioactivity was excreted during the first 24 hours (renal plus fecal 33% of dose in rats and 23% in dogs) after which excretion proceeded at low rates so that approximately 60% of the dose was excreted after 12 months. No true elimination of radioactivity could be determined from selected bones such as tibia.

Toxicology

- Single dose toxicity

In single dose toxicity studies in rats, a minimum lethal dose of 8 mg/kg was identified after intravenous bolus injection. The cause of death at high single doses quite likely involved cardiac and/or renal effects.

- Repeat dose toxicity (with toxicokinetics)

The toxicity of zoledronic acid after repeated doses was investigated in rat and dog in studies up to 1 year using subcutaneous and intravenous (bolus or infusion) administration routes and various dosing schedules. The toxicological profile of zoledronic acid showed similarities with that of other bisphosphonates. The most common effects in toxicity studies were increased primary spongiosa in the metaphyses of long bones (non-proliferative hyperostosis) in growing animals, a finding reflecting pharmacological antiresorptive activity. At high doses, effects possibly irritant, in organs such as GI-tract (haemorrhage, erosions, also after iv administration), liver (hepatocellular necrosis, haemorrhage, inflammation), spleen (inflammation, haemorrhage), lungs (inflammatory lesions) were reported, as well as irritation at injection sites. Effects, possibly secondary to poor physical condition, were noted in lymphoid organs and reproductive tract. Renal effects were seen in rat and dog studies and were characterised by renal tubular necrosis/regeneration and inflammation with increased blood urea nitrogen (BUN) and creatinine values. Effects on renal function and integrity seemed to occur at decreasing doses with increasing study duration. In rat studies, males appeared more sensitive than females. Recently bisphosphonates have been associated with a potential to cause eye disorders in clinical use. Ophthalmological examinations in preclinical studies did not however indicate any untoward ocular effects.

Renal effects in rats (tubular necrosis, regeneration, hyaline casts, focal tubular basophilia) were reported in 10-day iv bolus (6 mg/kg/d), 2-week iv (3.2 mg/kg/d), 10-day sc (0.6 mg/kg/d) and 12-month sc (0.003 mg/kg/d) studies. No kidney effects were reported in the 13-week sc rat study at the high dose of 0.1 mg/kg/d. Renal effects in dogs (e.g. tubular degeneration/necrosis, inflammation, increase in connective tissue, cellular casts, tubular basophilia and urothelial hyperplasia) were noted in 3-month iv (0.2 mg/kg/d), 13-week iv infusion (0.25 mg/kg/3x week), 26-week iv infusion (0.25 mg/kg/3x week) and 26/52-week iv bolus (0.1 mg/kg/every 2nd or 3rd day) studies. In dog, kidney effects seemed to develop after cumulative doses of 2.2 g/kg both after injection and infusion. Renal effects appeared reversible after a 26 weeks recovery period. In a 26-week intravenous infusion study in dogs with administration every third week, kidney effects were recorded in all groups after 9 doses of 0.25 mg/kg. A renal NOEL of 0.25 mg/kg after 3 doses was proposed.

The dog studies indicate that infusion time is one factor that is involved in the expression of kidney toxicity, such that a shortening of the infusion time appeared to be coupled to less adverse renal effects. Furthermore, local kinetics of zoledronic acid in the kidney may influence potential for renal toxicity. The reason for the differences in the potential of zoledronic acid to cause kidney toxicity in various rat studies is not clear. Zoledronic acid used in malignancy indications that involve daily dosing may have significant renal toxicity. Although the current indication entails a single dose therapeutic regimen, a slow release of zoledronic acid from bone after a single dose and elimination via kidneys may represent a situation comparable to local repeated low exposure. However it is likely, that the exposure will be low enough for kidney toxicity not to be manifested in the time periods in question.

In rat studies, common clinical chemistry changes included elevated alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), cholinesterase, $\alpha 2$, β globulin levels, increased alkaline phosphatase (AP), creatinine, BUN and Mg. After subcutaneous administration of doses over 0.6 mg/kg reduced erythrocytic parameters, increased granculocytic and coagulation parameters were noted. In a rat 1-month subcutaneous toxicity study, doses of 0.2 mg/kg increased white blood cells (WBC), decreased Ca, P, AP and AP liver isozymes. All changes were reversible except for AP. Increased levels of creatinine kinase were noted from 0.02 mg/kg/d. Histopathological target organs included GI-tract (gastric mucosal degeneration, multifocal necrosis of glandular epithelium), liver (degeneration, increased hepatocyte and Kupffer cell mitosis, periportal hepatocellular hypertrophy, phagocytic activity), adrenal (hypertrophy), spleen (clear macrophages, lymphocytolysis), lymph nodes (lymphocytolysis), thymus (lymphocytolysis, clear macrophages) and lung (increased cellular infiltration). Vasculitis and cellulitis fasciitis at the injection site were described. Skeletal muscle lesions in the thigh muscle were reported at doses over 0.06 mg/kg.

In view of the thymus lymphocytosis, increases of macrophages in spleen, lymph nodes, thymus atrophy, duodenum inflammation reported in a number of toxicity studies, the Applicant presented an evaluation and discussion on possible immunotoxic effects of zoledronic acid. The review of data, also considering dosing regimens in relation to the once yearly intended in clinical therapy, did not indicate any unexpected immunotoxicity. Bisphosphonates in the clinic are however known to have the potential to cause an acute-phase reaction.

In a 3-month subcutaneous toxicity study at doses $\geq$0.03 mg/kg/day, broken/shortened incisors were noted in males during the recovery period. Bisphosphonates have been reported to produce mineralisation defects specifically in rat incisor dentine. There was a non dose-dependent lengthening of metaphyseal primary spongiosa, increased metaphyseal bone diameters in femur and tibia (non-reversible) and a compensatory bone marrow hypercellularity. In a 6/12-month subcutaneous study, testicular atrophy was reported in the 0.01 mg/kg group at 12 months with changes showing reversibility. Examination of tibia from selected rats showed that mineralised tissue at the distal border changed to primary spongiosa. The changes were paralleled by a strong reduction in bone formation at the cellular and tissue levels. The effects were consistent with inhibition of bone resorption and consequent reduction of bone turnover, related to the pharmacological effect of zoledronic acid.

In dog studies, common clinical chemistry changes included elevated activated partial thromboplastin time (APTT), creatinine kinase, increased ASAT, ALAT, lactate and glutamate dehydrogenase, Mg and decreased erythrocytic parameters, AP bone isozyme activity and albumin levels. At doses over 0.02 mg/kg P, Ca and K were decreased. Increases in urea, bilirubin, total lipids, cholesterol, triglycerides and total protein were findings in several studies. Injection site lesions (cellulitis, phlebitis) were present in most studies. Stomach changes (gastric inflammation, mineralisation, ulceration, atrophy, oedema), bone changes (increased mesenchymatous tissue and/or bone deposition in medullary cavities of femur, sternum, rib) and slight mineralisation in the bone marrow were noted. The bone findings were not reversible and the effects were in part ascribed to the pharmacological activity of zoledronic acid. In a 26/52-week study, testicular changes, focal atrophy, degeneration and mineralisation of the seminiferous tubules were noted in some dogs at doses of 0.03 mg/kg at the end of 26 weeks, only.

Bone physical chemistry, morphometry and mechanical properties were studied in dogs after 6, 12 months treatment and following a 6-month recovery period. Physical chemistry parameters indicated a shift towards greater mineralisation between 6 and 12 months. At 12 months, the mineralisation profile in vertebrae had shifted towards higher densities. This was not noted in the femur, probably due to lower turnover in cortical bone. Tetracycline labelling was inadequate to assess dynamic parameters. At 6 and 12 months no difference in the structural parameters such as bone volume, trabecular thickness, cortical areas, cortical thickness were reported with regard to the proximal tibial side. Osteoid surface and volumes were decreased consistent with decreased bone turnover. Osteoid thickness and osteoid volume were not increased, indicative of the absence of mineralisation defect. Bone formation resumed after the 6-month recovery period, suggesting reversibility. Biomechanics indicated a significant increase in density and mechanical properties of trabecular bone with zoledronic acid treatment, prominent at 0.03 mg/kg. Cortical bone density and mechanical properties of cortical or trabecular bone structures were not affected. After 12 months, there was a trend towards an increase in density and mechanical properties of trabecular core. A significant increase in density and mechanical properties of whole vertebrae was also evident. The NOEL for bone safety was considered to be 0.1 mg/kg when given on alternating days for 16 weeks and then every 3rd day through week 52.

Interspecies comparisons were based on renal NOAEL in various studies, and for comparison a human systemic exposure of 1001 ngxhour/ml after 5 mg was used. Based on AUC after a single dose margins of exposure in dog studies was <1 to 3-fold higher than human exposure, while based on cumulative AUC values, exposure multiples of 4 tol2 were obtained. In rat studies corresponding values ranged from 1 to 9 based on cumulative AUC, and <1 to 4 based on AUC values after a single dose. Exposure multiples based on Cmax values were generally higher for rat, but lower for dog.

- Genotoxicity in vitro and in vivo

Zoledronic acid was assessed for genotoxic potential in a standard battery of tests. There was no indication of the compound having genotoxic activity either in vitro or in vivo.

- Carcinogenicity

Long-term carcinogenicity studies in mouse and rat by oral gavage at doses up to 2.0 mg/kg/day showed an increased incidence of Harderian gland tumours in male mice, but the increase was within historical control limits since the Harderian gland tumours have no human correlate, such that the clinical relevance of this observation is limited.

- Reproductive and developmental studies

The reproductive toxicity of zoledronic acid was studied in rat and rabbit. The fertility and early embryonic developmental study was terminated early due to deaths/sacrifices linked to difficulties at parturition (dystocia) observed at doses as low as 0.01 mg/kg; effects partly ascribed to the calcium depleting effects of the compound. Toxicity was also evident in embryo/foetal development studies in rat. A marked increase in pre and post implantation loss, increased resorptions and a decreased number of viable foetuses was recorded at 0.6 mg/kg. In the second rat study foetal weights were decreased at doses over 0.2 mg/kg and post implantation increased at 0.4 mg/kg. Zoledronic acid was teratogenic in rat at doses ≥0.2 mg/kg with malformations such as cleft palate, displaced ventricle and dilatation of major vessels, dilated lateral brain ventricles, thickening or curving of the clavicle, humerus and ulna. The teratogenicity was considered a direct effect and not a consequence of maternal toxicity although evident.

Zoledronic acid was not well tolerated in rabbits and in a dose range finding study in pregnant rabbits doses over 0.2 mg/kg resulted in severe clinical signs, body weight loss and animals had to be sacrificed. In a second study doses over 0.01 mg/kg caused maternal toxicity. Signs of hypocalcaemia were recorded. Overall, the compound did not appear to be teratogenic in rabbits since the incidence of malformations was comparable in all groups.
No prenatal and postnatal development study was conducted as the findings in the fertility and early embryonic development study indicated this would not be meaningful. In general, effects noted in the studies were not unexpected. These observations have been adequately reflected in the SPC.

- Local tolerance

Similar to other bisphosphonates, zoledronic acid had local irritating effects upon subcutaneous or intravenous administration.

Ecotoxicity/environmental risk assessment

The potential for ecotoxicity, risk to the environment has been addressed in separate reports. Calculated predicted environmental concentrations do not indicate any cause for immediate concern.

Discussion on the non-clinical aspects

There are no validated animal models of Paget's disease. The etiology of the disease is unknown although it appears to be generally accepted that abnormal osteoclasts are central to the pathophysiology. As well as inhibiting bone resorption, zoledronic acid had less marked inhibitory effects on osteoblasts and decreased bone formation *in vivo*. Thus, inhibition of bone resorption and bone formation may occur concomitantly, but effects were dose-dependent with some maintenance of function and bone formation, although at levels lower than in controls.

Studies in estrogen-deficient animals indicated that bone mass was maintained and reduction of bone mechanic parameters of femur, tibia and vertebra in rat were dose-dependently prevented by zoledronic acid, and the effects were evident only when starting treatment prior to induction of bone loss. A study in which zoledronic acid treatment of OVX rats was initiated 8 weeks after ovariectomy demonstrated that the compound does not exert a "curative" effect. Animal bone studies generally showed expected effects with no significant undesirable changes occurring at relevant doses. Taken together the studies available for zoledronic acid are considered sufficient from the preclinical point of view.

In a case with a compound such as zoledronic acid subject to rapid sequestration and retention in bone, the clinical relevance of animal models used in toxicology studies would not seem appropriately assessed using conventional methods based on e.g. metabolite comparisons and exposure levels. Considering excretion routes and distribution pattern, the species used seem generally relevant.

Data from the toxicology programme indicated that the most frequent effect induced by zoledronic acid was an increase in primary spongiosa in the metaphyses related to the pharmacological activity in addition to adverse effects that were primarily directed at the kidney, liver and gastrointestinal tract.

4. Clinical aspects

Introduction

The clinical study programme is summarised in the Table below.

Table Summary of all studies in Paget's disease

Study No.	Study objective, population	Treated Patients	Study Duration	Medication, Dosing scheme	Type of control
Large efficacy trial (completed)					
2305	Ph III, double-blind, randomized safety/efficacy trial in Paget's disease	178	6 months	1 x 5 mg Zol (single 15 min iv infusion) 30 mg risedronate/day (2 months)	active control
2304	Ph III, double-blind, randomized safety/efficacy trial in Paget's disease	171	6 months	1 x 5 mg Zol (single 15 min iv infusion) 30 mg risedronate/day (2 months)	active control
Large dose-ranging trial					
002	Ph II, double-blind, randomized dose-ranging trial in Paget's disease	176	3 months	1 x 50, 100, 200, 400 µg Zol 1 x placebo (60 min iv infusion)	placebo control
Small dose-ranging trial					
001	Ph I, open, rising dose	16	2 weeks	1 x 24, 72, 216, 400 µg Zol	no

All clinical trials were GCP-compliant as claimed by the company.

- Pharmacokinetics

Pharmacokinetic data are mainly from previous studies in cancer patients. There are no specific pharmacokinetic data for patients with Paget's disease, but the disease state is not expected to affect the pharmacokinetics and conclusions from previous studies can be extrapolated to the present application.

- Absorption

Not applicable

- Distribution

At the end of infusion, plasma concentrations showed a rapid, multiphasic decline reaching < 1% of peak levels after 24 hours. Thereafter, low plasma levels persisted over a long period (≤ 0.1% of peak levels at day 29 after a 16 mg dose). The initial rapid decline is suggested to reflect the combined processes of binding and uptake in bone and renal elimination. The persisting, low levels thereafter reflect the slow re-distribution from bone. The long-term binding of zoledronic acid to bone is the rationale for the single-dose administration proposed for Paget's disease of the bone.

In vitro, ^{14}C-zoledronic acid in blood showed no major affinity for red blood cells. Plasma protein binding was moderate (approximately 56%) and did not vary with concentration. Animal data and the low recovery of ^{14}C-zoledronic acid in humans indicate that most of the drug is bound to bone tissue.

- Elimination

Study 506, with ^{14}C-zoledronic acid, indicated no metabolism in humans. The compound was primarily eliminated unchanged via renal excretion, but recovery of radioactivity was low. Most of the recovered radioactivity was excreted within 24 hours after end of infusion (29%). After 72 hours, 32% was recovered and at later timepoints the concentrations in urine were generally below the detection limit. In a pooled data set of 64 patients from studies J001, 503 and 506, the CL_R of zoledronic acid represented 75±33% of the estimated creatinine clearance (CLcr), which averaged 84 ml/min. The renal and total plasma clearances of zoledronic acid were strongly correlated to CLcr.
In preclinical studies, less than 5% of a dose was excreted in faeces.

Due to the slow re-distribution of zoledronic acid from bone, which may be dependent on bone re-modelling, the terminal t1/2 could not be adequately determined. A t1/2 γ of 146 hours was estimated from the population pharmacokinetic analysis, but was thought likely to be an underestimation. The AUC area under the curve 0-24 hours ($AUC_{0-24\ hours}$) was therefore used for estimation of key pharmacokinetic parameters.

In a new study no. 1101 in 10 cancer patients, the half-life after a single 4 mg dose was estimated to be 198 hours. Cumulative excretion of drug in urine after 24 hours was 32.6% of the dose. Plasma clearance was 4.85 L/hr and CL_R 2.44 L/hr. Thus, CL_R was about 50% of the total clearance and the remainder is likely to be binding to bone.

- Dose proportionality and time dependencies

The $AUC_{0-24\ hour}$ was dose proportional between doses of 2 and 16 mg. According to the population pharmacokinetic analysis, the predicted plasma clearance at doses 2, 8 and 16 mg was 108%, 92% and 79%, respectively, of the clearance at a 4 mg dose. Thus, clearance appeared to decrease slightly with increasing doses.

There was no significant accumulation in plasma at multiple doses given every 28 days. The $AUC_{0-24\ hours}$ at later doses was 1.13-fold higher than after the first dose. Assessment of time-dependency was not considered to be important for the present application, since only a single dose is recommended.

- Special populations

Impaired renal function

The exposure was about 30-40% higher in patients with mild to moderate impairment. In a population pharmacokinetic analysis, CL_R in patients with CLcr of 20, 50 and 140 ml/min was estimated to be 37%, 72% and 149%, respectively, of that for a patient with CLcr of 80 ml/min. No dose adjustment is considered necessary at mild to moderate impairment while due to paucity of data, zoledronic acid is not recommended to patients with severe renal impairment.

Impaired liver function

No study was performed in patients with hepatic impairment, as zoledronic acid is not metabolised in the liver nor excreted via bile, and hepatic impairment is therefore not expected to affect the pharmacokinetics of the compound.

Gender, Race, Weight and Age

In the population pharmacokinetic analysis on the pooled data set of 64 patients from three studies, there were no effects of gender, race, body weight or age that would warrant specific dose adjustments.

Children

No data are available, and Aclasta is not recommended in children and adolescents.

- Pharmacokinetic interaction studies

Previously submitted studies indicated no inhibition of hepatic enzymes *in vitro* by zoledronic acid (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11).

No *in vivo* interaction studies have been performed, since zoledronic acid is not metabolised, and shows no potential for inhibition of cytochrome P450 enzymes.

Induction was not discussed, but has not been identified as a problem for other bisphosphonates and, moreover, would not be expected to occur at a single dose administration.

The risk for pharmacokinetic drug-drug interactions is expected to be low.

Pharmacodynamics

- Mechanism of action

Like other bisphosphonates, zoledronic acid inhibits bone resorption by osteoclasts and, secondarily, bone turnover by binding to bone surfaces, especially in areas of high bone turnover. As demonstrated in the Zometa dossier, zoledronic acid reduces the osteoclastic hyperactivity of lytic or blastic bone lesions.

- Primary and secondary pharmacology

Preclinical and clinical data showed that zoledronic acid has potent bisphosphonate effects on bone turnover, which should make it potentially useful for the indication treatment of PDB. The clinical studies submitted in Paget's disease provided additional information concerning pharmacodynamics in this population and separate PK/PD studies were not considered necessary. Relevant biomarkers for studying the efficacy of zoledronic acid were chosen.

Combined data from PDB studies 2304 and 2305 showed that the median levels of serum and urine resorption markers C-telopeptide (CTx) were decreased to within normative ranges by 10 days of dosing.

Bone histomorphometry data from a limited number of M6 bone biopsies obtained within trial 2304 demonstrated the expected reduction in bone turnover with an anti-resorptive agent. Osteoblast function as evaluated by fractional mineralising surfaces indicated continued bone turnover with zoledronic acid. No mineralisation defects were evident and the mineral apposition rate was also unchanged relative to placebo. Qualitative assessment indicated no evidence of abnormal bone quality.

Additional histomorphometric data will be made available from the post menopausal osteoporosis programme (POP) studies with zoledronic acid 5 mg annually.

Clinical efficacy

- Dose response studies

The two early dose-ranging trials 001, 002 contributed little data of interest. The studies showed no clinically relevant efficacy to reduce bone markers at doses under 200 µg. Although signs of efficacy were noted with the highest dose of 400 µg (47% reduction of serum alkaline phosphatase at 3 months), this extrapolates to changes that are considerably less than the ≥75% reduction of SAP excess or SAP normalisation, which is required to meet the definition of a clinical responder.

The dose selected for the pivotal PDB trials is the same as that being evaluated for once yearly administration within the ongoing POP for zoledronic acid. It could be noted that the CHMP, during scientific advice, expressed reservations whether this would be the optimal dose for POP and that it might carry an unnecessary risk of over-suppression of bone turnover in POP. Whether this argument is of relevance for (extralesional) bone safety in PDB remains speculative. It may be relevant to note that the 5 mg dose recommended for PDB is substantially less than the annual cumulative dose administered in the majority of oncology patients.

In summary, the choice of dose of zoledronic acid in Paget's disease has not been properly justified by dose-response or other preparatory studies. Nevertheless, the benefit/risk of the proposed regimen has been assessed from the two available controlled studies in the target population, and in addition some safety data from the ongoing POP trials.

- Main studies

Two largely identical Phase III studies (2305, 2304) have been performed in support of the indication for the treatment of PDB, focusing on effects on alkaline phosphatases over six months of a single dose of 5 mg zoledronic acid and aiming to demonstrate non-inferiority of this regimen *vs.* an approved regimen of risedronate 30 mg *q.d.*, dosed during 60 days.

Studies 2305 and 2304

METHODS

Study Participants

Trials 2305, 2304 enrolled male and female patients >30 years with a confirmed diagnosis of PDB and serum alkaline phosphatases (SAP) at baseline ≥2xULN. The minimum washout periods for prior calcitonin and bisphosphonate therapy were set at 90 and 180 days, respectively. Patients with calculated GFR <30 ml/min or urine protein ≥2+ were excluded from participation.

Demographic and baseline disease characteristics are summarised in the tables below. The trials enrolled similar populations

Table Baseline demographic characteristics trials 2305, 2304 (ITT population)

	Study 2304		Study 2305	
	Zoledronic acid (N=90)	Risedronate (N=82)	Zoledronic acid (N=92)	Risedronate (N=93)
Sex – n (%)				
Male	62 (68.9)	61 (74.4)	62 (67.4)	57 (61.3)
Female	28 (31.1)	21 (25.6)	30 (32.6)	36 (38.7)
Race – n (%)				
Caucasian	84 (93.3)	80 (97.6)	84 (91.3)	84 (90.3)
Black	6 (6.7)	2 (2.4)	3 (3.3)	3 (3.2)
Other	0 (0.0)	0 (0.0)	5 (5.4)	6 (6.5)
Age (years)				
Mean (SD)	70.4 (10.25)	72.1 (9.91)	71.3 (9.42)	68.2 (11.15)
Median	72.0	74.0	72.5	70.0
Range	42.0 – 94.0	44.0 – 87.0	45.0 – 92.0	34.0 – 88.0
Age – n (%)				
<65 years	25 (27.8)	17 (20.7)	21 (22.8)	29 (31.2)
≥65 years	65 (72.2)	65 (79.3)	71 (77.2)	64 (68.8)

Table Baseline disease characteristics trials 2305, 2304 (ITT population)

	Study 2304		Study 2305	
	Zoledronic acid (N=90)	Risedronate (N=82)	Zoledronic acid (N=92)	Risedronate (N=93)
Baseline SAP (U/L)				
Mean (SD)	424.5 (335.35)	423.0 (267.35)	431.0 (308.11)	427.4 (348.56)
Median	329.0	321.0	342.5	301.0
Range	229.0 - 2822.0	214.0 - 1971.0	230.0 - 2338.0	222.0 - 2377.0
Baseline SAP – n (%)				
< 3xULN	47 (52.2)	45 (54.9)	46 (50.0)	56 (60.2)
≥ 3xULN	43 (47.8)	37 (45.1)	46 (50.0)	36 (38.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Creatinine clearance at baseline (mL/min)				
Mean (SD)	86.8 (36.51)	84.5 (36.34)	84.2 (28.75)	89.2 (30.26)
Median	77.7	79.2	81.6	88.2
Range	30.6 - 217.8	29.4 - 228.0	(36.0 - 180.0)	(34.2 - 192.6)
Creatinine clearance at baseline – n (%)				
< 30 mL/min	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
30 to < 40 mL/min	3 (3.3)	2 (2.4)	2 (2.2)	1 (1.1)
40 to 50 mL/min	10 (11.1)	7 (8.5)	8 (8.7)	9 (9.7)
> 50 mL/min	77 (85.6)	72 (87.8)	82 (89.1)	83 (89.2)
Last Paget's disease therapy before randomisation - n (%)				
Bisphosphonates	39 (43.3)	39 (47.6)	50 (54.3)	52 (55.9)
Oral	23 (25.6)	28 (34.1)	33 (35.9)	35 (37.6)
IV	13 (14.4)	10 (12.2)	14 (15.2)	16 (17.2)
Clodronate	3 (3.3)	1 (1.2)	3 (3.3)	1 (1.1)
Other	2 (2.2)	2 (2.4)	6 (6.5)	5 (5.4)
None	49 (54.4)	41 (50.0)	36 (39.1)	36 (38.7)
Washout for bisphosphonates - n (%)				
<180 days	1 (1.1)	0 (0.0)	2 (2.2)	2 (2.2)
180 to < 365 days	4 (4.4)	1 (1.2)	5 (5.4)	3 (3.2)
≥365 days	34 (37.8)	38 (46.3)	43 (46.7)	47 (50.5)

Additional baseline disease characteristics of interest were presented by the Applicant. The distribution with respect to the proportion of patients with polyostotic/monostotic disease is consistent with the characteristics of the general population with Paget's disease.

Treatments

A single dose of zoledronic acid 5 mg given as an infusion over 15 min (followed by risedronate placebo) *vs.* risedronate 30 mg *q.d.* for 60 days. The regimen for risedronate is that approved throughout Europe.

All patients were supplemented with calcium and multivitamins, including vitamin D.

Objectives

The primary objective was to show non-inferiority of zoledronic acid relative to risedronate with respect to the primary efficacy variable, proportion of responders at six months. See also below

(statistical methods). The objective was considered to be acceptable by the CHMP during scientific advice.

Outcomes/endpoints
The primary efficacy variable was the proportion of patients who achieved therapeutic response, defined as normalisation of SAP or at least 75% reduction from baseline of *excess* SAP at the end of six months.

Secondary efficacy variables included (log transformed values for bone markers)
- Relative change in SAP at D28
- Relative change in serum and urine CTx at D10
- Time to first therapeutic response
- Proportion of patients achieving SAP normalisation at D28
- Change in pain scores (BPI-SF) over time

Exploratory analyses included
- Proportions of patients who achieved SAP normalisation at D 10, 63, 91, 182

Sample size
Sample size calculations were based on the non-inferiority criterion of –0.16 for the primary efficacy variable. This margin is argued to maintain at least 75% of the effect of risedronate *vs.* etidronate. See also below (statistical methods).

Randomisation and blinding (masking)
The two main efficacy trials 2304 and 2305 were carried out double-blinded and randomized. Standard tools (IVRS) and procedures were used.

Statistical methods
The following analysis sets were defined: ITT (all randomised), MITT (randomised patients with baseline and at least one post baseline SAP determination) Safety (all patients who received at least one dose of study drug) and PP (exclusion of all major protocol violations).

Missing data were handled as follows:
For the proportion of patients who achieved therapeutic response and the proportion who achieved SAP normalisation, LOCF was used. No imputation was used for other efficacy parameters.

According to the SAP, non-inferiority of zoledronic acid vs. risedronate could be concluded if a Δ of greater than –0.16 (two-sided 95% CI) was observed. In addition, and as a pre-planned strategy to test superiority of zoledronic acid, between-treatment difference in the proportion of patients who achieved therapeutic response at six months was evaluated by logistic regression with treatment and baseline SAP (<3xULN or ≥3xULN) as explanatory variables

A closed testing procedure was used for secondary efficacy claims (CTx at D10, SAP change at D28, SAP normalisation at D28, BPI-SF, time to first therapeutic response).

RESULTS
Patient disposition is given in the Table below.

Table Subject disposition trials 2305, 2304 (ITT population)

	Study 2304		Study 2305	
	Zoledronic acid n (%)	Risedronate n (%)	Zoledronic acid n (%)	Risedronate n (%)
Total no. of patients - n(%)				
Randomized	90 (100)	82 (100)	92 (100)	93 (100)
Completed	86 (95.6)	76 (92.7)	85 (92.4)	89 (95.7)
Discontinuations – n(%)				
Total	4 (4.4)	6 (7.3)	7 (7.6)	4 (4.3)
Primary reason				
Adverse event	2 (2.2)	2 (2.4)	1 (1.1)	0 (0.0)
Protocol violations	1 (1.1)	0 (0.0)	3 (3.3)	2 (2.2)
Patient withdrew consent	1 (1.1)	2 (2.4)	3 (3.3)	2 (2.2)
Lost to follow up	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)

Numbers analysed

The analysis populations are summarised in the Table below.

Table Patients in analysis populations by treatment, trial 2305 and 2304

	Zoledronic acid 5 mg single IV infusion n (%)		Risedronate 30 mg/day x 60 days n (%)	
	2304	2305	2304	2305
ITT	90 (100)	92 (100)	82 (100)	93 (100)
MITT	88 (97.8)	88 (95.7)	82 (100)	89 (95.7)
PP	75 (83.3)	69 (75.0)	67 (81.7)	81 (87.1)
Safety	89 (98.9)	88 (95.7)	82 (100)	90 (96.8)

The lower fraction included in PP (zoledronic acid) was explained by lower compliance to oral placebo.

Outcomes and estimation

Primary efficacy data are given in the Table below. The primary efficacy variable was the proportion of patients who achieved therapeutic response at 6 months. A therapeutic response was defined as the normalization of SAP or a reduction of at least 75% from baseline (Visit 1) in SAP excess (difference between measured level and midpoint to the normal range).

Table Proportion of patients with therapeutic response at 6 months, trials 2305, 2304 (MITT population)

Treatment	N	Proportion	Difference [1] 95% CI	Odds ratio [2] 95% CI	p-value [3]
2305					
Zoledronic acid	88	0.95	0.20 (0.09, 0.31)	7.13 (2.56, 25.41)	< 0.0001
Risedronate	89	0.75	---	---	---
2304					
Zoledronic acid	88	0.97	0.23 (0.12, 0.35)	10.37 (3.40, 45.21)	< 0.0001
Risedronate	82	0.73	---	---	---

[1] Difference of zoledronic acid minus risedronate.
[2] Odds ratio of zoledronic acid over risedronate and its 95% CI is based on the logistic regression model.
[3] P-value given by the likelihood ratio test for the treatment comparison in the logistic regression model.

The lower limit of the one-sided 97.5% CI for the difference between the treatment groups was greater than –0.16 in both studies 2305 and 2304, meeting the non-inferiority criterion. When testing for superiority, the lower limit of the CI was greater than 0, indicating that zoledronic acid had a significantly higher proportion of patients who achieved therapeutic response compared to risedronate (20% higher). The results of the 95% CI were confirmed by the statistically significant treatment effect in the logistic regression model from both studies (all $p<0.001$), and odds ratio of 7.13 (95% CI: 2.56, 25.41) in Study 2305, and odds ratio of 10.37 (95% CI: 3.40, 45.21) in Study 2304. Consistent, statistically significant results were shown in the PP-population.

The relevant variable proportion of subjects with SAP normalisation was tested as a secondary variable at D28 (2305: zoledronic acid 0.09, risedronate 0.01, $p<0.01$; 2304: zoledronic acid0.06, risedronate 0, $p<0.01$).

Data for SAP normalisation at six months (tested as exploratory variable) are summarised below.

Table Proportion of subjects with SAP normalisation at 6 months (MITT population)

Treatment	N	Proportion (%)	Difference (95% CI)	Odds ratio (95% CI)	p-value
2305					
Zoledronic acid	88	0.89 (89%)	0.32 (0.19, 0.46)		< 0.0001
Risedronate	89	0.56 (56%)			
2304					
Zoledronic acid	88	0.89 (89%)	0.29 (0.15, 0.43)		< 0.0001
Risedronate	82	0.60 (60%)			

Findings for serum and urine CTx (secondary variables) and serum P1NP (exploratory) were consistent with those for SAP.

Time to first therapeutic response (secondary variable) was significantly shorter with zoledronic acid, compared with risedronate (62.7 *vs.* 108.2 days (ITT), risk ratio 3.31 [2.28;4.81]) in Study 2305 and (62.7 vs. 103.1 (ITT), risk ratio [2.54, 5.58]) in Study 2304.

BPI-SF scores declined over time on study in both treatment arms in both trials, without significant differences or trends to superiority of zoledronic acid. In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline were observed over 6 months for Aclasta and risedronate.

Experience with retreatment is non-existent.

Ancillary analyses

Subgroup analyses for key efficacy variables were performed for

- Baseline SAP <3xULN or ≥3xULN
- Race
- Sex
- Last PDB therapy (oral bisphosphonate, IV bisphosphonate, clodronate, others, none)
- Washout period for bisphosphonates (<180, 180 to <365, ≥365D)
- Age (<65, 65-74, ≥75 years)

The findings for the primary efficacy criterion in these subgroup analyses were very similar between trials 2305 and 2304.

The findings for the primary efficacy criterion for the combined trials are summarised in the tables below.

Table Proportion of patients who achieved therapeutic response at 6 months by demographic factor – combined active-controlled studies (MITT population)

Subgroup	Zoledronic acid n/N (Proportion)		Risedronate n/N (Proportion)	
Age				
< 65 years	45/45	(1.00)	37/45	(0.82)
65-74 years	62/64	(0.97)	46/59	(0.78)
≥75 years	62/67	(0.93)	44/67	(0.66)
Sex				
Female	117/121	(0.97)	86/116	(0.74)
Male	52/55	(0.95)	41/55	(0.75)
Race				
Caucasian	158/163	(0.97)	120/161	(0.75)
Black	7/8	(0.88)	1/4	(0.25)
Other	4/5	(0.80)	6/6	(1.00)

Table Proportion of patients who achieved therapeutic response at 6 months by disease factors – combined active-controlled studies (MITT population)

Subgroup	Zoledronic acid n/N (Proportion)		Risedronate n/N (Proportion)	
Baseline SAP				
< 3xULN	87/90	(0.97)	74/99	(0.75)
≥ 3xULN	82/86	(0.95)	53/72	(0.74)
Last Paget's therapy				
Oral bisphos.	53/55	(0.96)	33/60	(0.55)
IV bisphos.	22/25	(0.88)	21/26	(0.81)
Clodronate	6/6	(1.00)	2/2	(1.00)
Others	8/8	(1.00)	6/7	(0.86)
None	80/82	(0.98)	65/76	(0.86)
Washout for bisphosphonates				
< 180 days	3/3	(1.00)	1/2	(0.50)
180-<365 days	8/8	(1.00)	2/4	(0.50)
≥ 365 days	70/75	(0.93)	53/82	(0.65)

When the baseline SAP > 3xULN category is divided into two groups (3-6 xULN, >6xULN) the therapeutic response rate remains consistent across the zoledronic acid subgroups with 96% and 93%

of the patients in the two subgroups achieving therapeutic response compared to a 95% therapeutic response rate in the overall group.

- Clinical studies in special populations

There were no studies performed in special populations.

- Analysis performed across trials (pooled analyses and meta-analysis)

None

- Supportive studies

None

- Discussion on clinical efficacy

The pivotal clinical trials were performed essentially in accordance with CHMP scientific advice. The study samples are considered reasonably representative of the intended target population, although of mild to moderate average disease severity. Short-term efficacy on the accepted surrogate variable SAP is robust with 95% response rate for the primary responder criterion, consistent over subgroups and corroborated by findings for other bone turnover markers. The attainment of 89% response rate for SAP normalisation at six months is also reassuring, is significantly superior to what was achieved with the approved comparator risedronate, and appears to be considerably in excess of what has been published for other bisphonates.

In the primary efficacy analysis (MITT), zoledronic acid was clearly superior to risedronate in both trials (proportions of responders 2305: 0.95 *vs.*0.75; OR 7.13 [2.56; 25.41]; 2304: 0.97 *vs.* 0.73, OR 10.37 [3.40; 45.2]). This was consistent in PP analysis. Normalisation of SAP at six months (exploratory) was noted in the proportions 0.89 *vs.* 0.56 and 0.89 *vs.* 0.60 in the two studies. Changes in SAP corroborated those for serum and urine CTx. Findings in subgroups (demographics, baseline disease severity, prior bisphosphonate exposure yes/no) were consistent with the primary analysis.

Time to first therapeutic response was shorter with zoledronic acid, compared with risedronate in both trials.

There was no difference between treatments regarding response in BPI-SF pain scores in either study.

The lack of radiographic data is acknowledged as a deficiency, but such data has not been requested in other applications for this indication.

Follow-up data in responders are currently being collected in extensions to both trials for patients who were classified as therapeutic responders at the end of the 6-month core study. Data for a median follow-up of 18 months from time of dosing were made available in response to CHMP Day 120 List of Questions (D120 LOQ). In this analysis, 141/143 zoledronic acid-treated patients maintained their therapeutic response, compared with 71/107 of the risedronate-treated patients. Additional long-term data will be reported to the CHMP post-marketing.

There is currently no actual experience of retreatment with zoledronic acid in PDB.

Clinical safety

- Patient exposure

Taking into account data supplied in the response to CHMP D120 LOQ, the safety assessment considered data obtained in approximately 541 patients with PDB: 157 patients in early-phase trials who received doses less than 5 mg zoledronic acid (24-400 µg), 177 patients in trial 2305 and 2304 who received 5 mg of zoledronic acid, 172 patients who received the active comparator, risedronate, and 35 patients in early phase studies who received placebo.

Pooled data from the four trials in the target population constituted the major safety population. Further, post-marketing data for Zometa in oncology indications were taken into account.

- Adverse events (AE)

Adverse events (≥5%) in the major safety population are summarised per System Organ Class (SOC) in the Table below.

Table Adverse events overall and by body system (≥ 5% patients in any group) (Paget's disease, safety population)

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid <5 mg (24-400 µg) n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100.0)	172 (100.0)	157 (100.0)	35 (100.0)
Total no. with an AE	146 (82.5)	133 (77.3)	120 (76.4)	29 (82.9)
System organ class				
General disorders & administrat. site conditions	69 (39.0)	35 (20.3)	43 (27.4)	9 (25.7)
Musculoskeletal & connective tissue disorders	66 (37.3)	55 (32.0)	71 (45.2)	17 (48.6)
Nervous system disorders	51 (28.8)	35 (20.3)	32 (20.4)	9 (25.7)
Gastrointestinal disorders	50 (28.2)	41 (23.8)	20 (12.7)	6 (17.1)
Infections & infestations	50 (28.2)	46 (26.7)	31 (19.7)	6 (17.1)
Respiratory, thoracic & mediastinal disorders	19 (10.7)	18 (10.5)	16 (10.2)	3 (8.6)
Injury, poisoning & procedural complications	17 (9.6)	21 (12.2)	9 (5.7)	1 (2.9)
Metabolism & nutrition disorders	17 (9.6)	10 (5.8)	5 (3.2)	0 (0.0)
Skin & subcutaneous tissue disorders	15 (8.5)	13 (7.6)	15 (9.6)	3 (8.6)
Investigations	11 (6.2)	9 (5.2)	14 (8.9)	1 (2.9)
Renal & urinary disorders	10 (5.6)	12 (7.0)	6 (3.8)	1 (2.9)
Eye disorders	8 (4.5)	3 (1.7)	9 (5.7)	0 (0.0)
Vascular disorders	8 (4.5)	5 (2.9)	5 (3.2)	4 (11.4)
Psychiatric disorders	5 (2.8)	8 (4.7)	5 (3.2)	2 (5.7)

Studies : 2304, 2305, 001, 002

A tabulation of the most frequent AEs suspected to be drug-related (investigator's assessment) in the PDB population is given below.

Table Most frequent AEs (≥ 2% patients in any group) suspected to be drug related (Paget's disease, safety population)

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid <5 mg (24-400 µg) n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100)	172 (100)	157 (100)	35 (100)
Total no. with an AE	92 (52.0)	43 (25.0)	65 (41.4)	16 (45.7)
Adverse events				
Flu-like symptoms	16 (9.0)	9 (5.2)	4 (2.5)	0 (0.0)
Pyrexia	13 (7.3)	1 (0.6)	3 (1.9)	0 (0.0)
Rigors	13 (7.3)	1 (0.6)	4 (2.5)	0 (0.0)
Headache	12 (6.8)	6 (3.5)	7 (4.5)	2 (5.7)
Myalgia	11 (6.2)	6 (3.5)	3 (1.9)	0 (0.0)
Nausea	10 (5.6)	3 (1.7)	6 (3.8)	1 (2.9)
Bone pain	9 (5.1)	2 (1.2)	8 (5.1)	2 (5.7)
Fatigue	9 (5.1)	3 (1.7)	12 (7.6)	0 (0.0)
Arthralgia	7 (4.0)	3 (1.7)	16 (10.2)	3 (8.6)
Lethargy	7 (4.0)	1 (0.6)	1 (0.6)	1 (2.9)
Influenza	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	6 (3.4)	4 (2.3)	2 (1.3)	0 (0.0)
Hypocalcemia	5 (2.8)	1 (0.6)	0 (0.0)	0 (0.0)
Asthenia	4 (2.3)	1 (0.6)	2 (1.3)	0 (0.0)
Diarrhea	4 (2.3)	0 (0.0)	1 (0.6)	1 (2.9)
Dyspepsia	4 (2.3)	4 (2.3)	0 (0.0)	0 (0.0)
Dyspnea	4 (2.3)	0 (0.0)	1 (0.6)	0 (0.0)
Back pain	3 (1.7)	2 (1.2)	13 (8.3)	1 (2.9)
Paraesthesia	2 (1.1)	0 (0.0)	3 (1.9)	1 (2.9)
Body temperature increased	1 (0.6)	2 (1.2)	4 (2.5)	0 (0.0)
Hot flush	1 (0.6)	0 (0.0)	1 (0.6)	2 (5.7)
Night sweats	1 (0.6)	0 (0.0)	0 (0.0)	1 (2.9)
Chest wall pain	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Flushing	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Muscle cramp	0 (0.0)	1 (0.6)	4 (2.5)	0 (0.0)
Edema peripheral	0 (0.0)	0 (0.0)	1 (0.6)	1 (2.9)
Pain in extremity	0 (0.0)	2 (1.2)	11 (7.0)	3 (8.6)

Studies : 2304, 2305, 001, 002

Generally, the AE profile appears to be that expected with an IV bisphosphonate and also consistent with findings in other trials of zoledronic acid in benign conditions (0041, 0041E1, 2201). Flu-like symptoms, headache and fatigue frequently occurred within the first 3 days of administering zoledronic acid. The majority of these symptoms resolved within 4 days of the event onset. A majority of the patients (95/177) in the zoledronic acid 5 mg group reported their adverse events in the first 3 days after initiating study drug. Thereafter, more adverse events were reported in the risedronate group.

Adverse events of special interest

Renal adverse events

Renal abnormality was defined as a serum creatinine rise of > 0.5 mg/dL from baseline, or a > 2+ protein value by dip-stick. In the original submission, there were no events of raised serum creatinine at D9-11 post infusion in the PDB population (protocol-defined analysis) and only one episode of transient, asymptomatic proteinuria. In study 2304 there were no renal adverse events associated with deterioration of renal function or renal abnormalities reported for zoledronic acid. For risedronate, there were three adverse events that met the definition of deterioration of renal function. An overview of clinical renal AEs in the major safety population is given in the Table below.

Table Renal adverse events (Paget's disease, safety population)

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg	Risedronate	Zoledronic acid <5 mg (24-400µg)	Placebo
Patients studied				
Total no. studied	177 (100.0)	172 (100.0)	157 (100.0)	35 (100.0)
No. with renal AEs	2 (1.1)	3 (1.7)	0	0
Adverse event				
Creatinine clearance decreased	1 (0.6)	0 (0.0)	-	-
Urinary retention	1 (0.6)	0 (0.0)	-	-
Hematuria	0 (0.0)	2 (1.2)	-	-
Renal impairment	0 (0.0)	1 (0.6)	-	-

Studies: 2304, 2305, 001, 002

A subject with multiple occurrences within an AE is counted only once in the AE category.

The two events reported with zoledronic acid 5 mg relate to one case of protocol-defined increase in serum creatinine occurring at six months post administration, and one case of urinary retention, respectively.

Available data in the PDB population create no specific concern regarding renal safety of IV zoledronic acid. Renal adverse events will be specifically monitored post-marketing.

Upper gastrointestinal adverse events

In the PDB safety database, there was no marked difference between zoledronic acid and risedronate regarding reporting rates for upper gastrointestinal AEs (18.6% and 16.3%, respectively).

Uveitis/iritis/scleritis

There were no reports of these events in the PDB population.

Osteonecrosis of the maxillofacial region

This has recently been highlighted in the literature as a complication of pamidronate and zoledronic acid when used in oncology indications. No events of this type are reported in the current dossier. Post-marketing surveillance is considered to be necessary.

Bone safety

Available data create no specific concerns (see section on Pharmacodynamics).

- Serious adverse event/deaths/other significant events

The only SAEs assessed as potentially related involved one report of cerebrovascular accident, occurring 69 days post administration of 5 mg zoledronic acid in study 2305, and one report of ECG changes 9 days following 100 µg of zoledronic acid in trial 002.

SAEs suspected to be drug-related in other completed trials in benign indications included isolated cases of flu-like symptoms.

Table Serious adverse events (excluding death) (Paget's disease, trials 2305, 2304)

Patient Identity	Age/Sex	Preferred term	Day of onset	Relation to drug
zoledronic acid 5 mg (study 2304)				
0303/00125	71/M	Embolic stroke	114	Not suspected
0604/00095	75/M	Peripheral ischemia	125	Not suspected
		Sympathectomy	131	Not suspected
		Leg amputation	157	Not suspected
0401/00037	79/F	Arthritis	2	Suspected
0504/00117	53/M	Cellulitis orbital	132	Not suspected
0507/00046	76/M	Difficulty in walking	3	Not suspected
		Spinal column stenosis	3	Not suspected
		Asthenia	3	Suspected
Risedronate (study 2304)				
0303/00272	73/M	Lower limb fracture	19	Not suspected
0107/00252	76/M	Dysphagia	60	Not suspected
0605/00190	79/F	Abdominal pain upper	101	Suspected
0605/00199	81/F	Renal impairment	173	Not suspected
		Lower resp. tract infection	173	Not suspected
		Confusional state	173	Not suspected
		Urinary tract infection	173	Not suspected
		Staphylococcal infection	224	Not suspected
0401/00118	77/M	Acute coronary syndrome	73	Not suspected
0401/00157	72/M	Hepatic cyst	154	Not suspected
		Pyrexia	154	Not suspected
		Rigors	154	Not suspected
0504/0065	52/F	Hypocalcemia	12	Suspected
0507/0136	87/F	Abdominal pain	80	Not suspected
		Constipation	80	Not suspected
		Abdominal Pain	88	Not suspected
		Back pain	88	Not suspected
zoledronic acid 5 mg (study 2305)				
0104/00250	77/M	Femur fracture	98	Not suspected
0305/00058	83/M	Back pain	93	Not suspected
		Cerebrovascular accident	93	Suspected
		Spinal fracture	93	Not suspected
0308/00369	77/F	Asthma	101	Not suspected
		Dyspnea	101	Not suspected
		Enterobacter sepsis	157	Not suspected
0501/00137	76/F	Escherichia infection	104	Not suspected
Risedronate (study 2305)				
0254/00054	73/M	Chest pain	54	Not suspected
0455/00295	52/F	Endometrial hyperplasia	95	Not suspected
0601/00187	83/F	Humerus fracture	84	Not suspected

No unexpected signal has been created by these data.

In the major safety population (all patients with PDB given ≥ 1 dose of study drug) there was a total of four deaths, all occurring in trial 002 using sub-therapeutic doses of zoledronic acid, and none assessed to be related to study drug.

- Laboratory findings

Clinically notable hypocalcaemia (serum calcium <1.87 mmol/l) or AE of hypocalcaemia was reported in 8/177 patients in studies 2305 and 2304 following zoledronic acid 5 mg and with serum calcium nadir usually occurring before or by D10 post injection. Truly symptomatic hypocalcaemia was reported in two patients, both of which showed non-compliance with calcium and vitamin D supplementation.

- Safety in special populations

No specificities regarding the AE profile were noted in predefined subgroups or in relation to specific concomitant drug intake.

- Safety related to drug-drug interactions and other interactions

As noted in the section on pharmacokinetics, the potential for pharmacokinetic drug – drug interactions is low. No specific dynamic interactions of concern are foreseen apart from those related to known class effects.

- Discontinuation due to adverse events

There was only one discontinuation due to AE in the major safety population. Corresponding data from the finalised trials in benign indications are unremarkable.

- Post marketing experience

The data available refers to zoledronic acid as Zometa, indicated in oncology patients. As already discussed, dosage regimens for zoledronic acid and co-morbidity spectrum are quite different in the oncology setting compared with for the currently sought indication. Apart from the recently identified issue of maxillofacial osteonecrosis, the safety experience with Zometa is not considered to have raised unexpected concerns.

- Discussion on clinical safety

The main adverse effects of zoledronic acid by intravenous infusion are flu-like symptoms in the first 3 days following administration. These symptoms occur very commonly, are usually transient and resolve spontaneously within 2-4 days. Bone pain, arthralgia, myalgia, fever, and hypocalcaemia have also been observed commonly. All of these symptoms have been reported previously with other bisphosphonates.

The occurrence of symptomatic hypocalcaemia with zoledronic acid despite vitamin D and calcium supplementation created concern in the primary assessment. In response to CHMP D120 LOQ, the applicant provided additional data and discussion on this issue. In the pivotal trials, transient hypocalcaemia, usually with the nadir at or before D10 post injection was noted in eight patients treated with zoledronic acid. The two cases with the lowest serum calcium values were truly symptomatic and were associated with non-compliance with calcium and vitamin D supplementation. The wording in the SPC of sections 4.2 and 4.4 has been strengthened, in order to emphasise the importance of adequate calcium supplementation post infusion; this approach should ensure manageable safety in clinical practice. Hypocalcaemia is targeted for focused surveillance within PSURs.

Based on preclinical and clinical data, there is a concern for renal toxicity of IV bisphosphonates. Monitoring of renal function was performed 9-11 days following the initial dose in pivotal trials, and such monitoring is also specified per protocol in ongoing trials in non-malignant indications. No renal abnormalities (increase in serum creatinine or proteinuria $\geq$2+) occurred due to zoledronic acid infusion in the PDB population. Due to the concern for potential renal events, individuals with creatinine clearance below 30 ml/min were excluded from the trials. The exclusion of patients with severe renal impairment has been reflected in the SPC. Renal toxicity is targeted for focused surveillance within PSURs.

Events of iritis/uveitis/scleritis were not seen in the PDB population so far, but are, appropriately, listed in the SPC as occurring with bisphosphonate therapy. This area will also be focused on in PSURs.

The limited amount of (extralesional) bone safety data available was discussed in the pharmacodynamic section. Additional biopsy data from POP trials will be reported to the CHMP. The specific bone safety issue of maxillofacial osteonecrosis, highlighted for pamidronate and zoledronic acid in oncology indications has so far not been reported in non-malignant indications. Targeted surveillance within PSURs is considered necessary.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality
The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit/Risk balance of the product.

Non-clinical pharmacology and toxicology
Overall, the primary pharmacodynamic studies provided adequate evidence that zoledronic acid had inhibitory effects on osteoclasts inhibiting bone resorption and as well as reducing bone turnover. The general safety pharmacology studies showed no remarkable effects. The pharmacokinetics of zoledronic acid has been studied in rat and dog. The findings revealed in the toxicology programme have been adequately reflected in the SPC.

Efficacy
The pivotal clinical trials were performed in accordance with CHMP scientific advice and in an acceptable sample of the patient population. Short-term efficacy on the accepted surrogate variable SAP is robust. The attainment of replicated 89% response rate for SAP normalisation at six months is reassuring, is significantly superior to what was achieved with the approved comparator risedronate, and also appears to be considerably in excess of what has been published for other bisphosphonates. Follow-up data are still preliminary, as regards to maintenance of long-term response.

Safety
The updated safety database has been adequately presented. Hypocalcaemia appears to occur more frequently in patients receiving i.v. zoledronic acid compared with oral risedronate, even if usually mild and without clinically significant consequences. Hypocalcaemia is included in the SPC as a common side effect for Aclasta. Renal adverse events and osteonecrosis of the maxillofacial region will be specifically monitored post-marketing.

Benefit/risk assessment
Aclasta (zoledronic acid) is the first i.v. bisphosphonate proposed for the treatment of Paget's disease in the EU. Zoledronic acid is a potent bisphosphonate. The dose claimed is poorly substantiated. However, efficacy on usually accepted intermediary endpoints was demonstrated to be superior to that of an approved regimen of oral risedronate in two adequate clinical trials, and the safety profile is considered to be manageable within the restrictions imposed by the agreed SPC.

Data on maintenance of effect after a single dose are preliminary. The available data on long-term efficacy/safety and their limitations have been pointed out in the SPC. The Applicant intends to collect further data from the ongoing extension program in order to define these parameters. These data will be reported to CHMP when the 2-year follow up data is available.

Overall, and taking into account the commitments to provision of additional efficacy and safety data post-marketing, the benefit/risk balance is acceptable.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by a unanimous decision that the benefit/risk ratio of Aclasta in the treatment of Paget's disease of bone was favourable and therefore recommended the granting of the marketing authorisation.

15. Conte et al., *Safety of intravenous and oral bisphosphonates and compliance with dosing regimens*, 9(4) ONCOLOGIST 28 (2004) ("Conte").

Safety of Intravenous and Oral Bisphosphonates and Compliance With Dosing Regimens

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Safety of Intravenous and Oral Bisphosphonates and Compliance With Dosing Regimens

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Key Words. *Advanced cancer · Bone metastases · Bisphosphonates · Zoledronic acid*

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the differences between oral and i.v. bisphosphonate therapy in terms of safety and side effects.
2. Explain the renal effects of long-term i.v. bisphosphonate treatment.
3. Discuss the importance of patient compliance in long-term disease management.

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ABSTRACT

Patients with advanced cancers—particularly breast and prostate cancers—are at high risk for bone metastasis, leading to accelerated bone resorption and clinically significant skeletal morbidity. Bisphosphonates are effective inhibitors of bone resorption and reduce the risk of skeletal complications in patients with bone metastases. The standard routes of administration for bisphosphonates used in clinical practice are either oral or i.v. infusion. Oral administration of bisphosphonates is complicated by poor bioavailability (generally <5%) and poor gastrointestinal tolerability. First-generation bisphosphonates, such as clodronate (Bonefos®; Anthra Pharmaceuticals; Princeton, NJ), must be administered at high oral doses (1,600-3,200 mg/day) to achieve therapeutic effects, which leads to poor tolerability and compliance with oral dosing regimens. Infusion of bisphosphonates is associated with dose- and infusion-rate-dependent effects on renal function. In particular, high bisphosphonate doses (e.g., 1,500 mg clodronate) can cause severe renal toxicity unless infused slowly over many hours. In contrast, the newer, more potent bisphosphonates effectively inhibit bone resorption at micromolar concentrations, and the small doses required can be administered via relatively short i.v. infusions without adversely affecting renal function. Zoledronic acid (Zometa®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) is a new generation bisphosphonate, and the recommended dose of 4 mg can be safely infused over 15 minutes. The 90-mg dose of pamidronate (Aredia®; Novartis Pharmaceuticals Corp.) and the 6-mg dose of ibandronate (Bondronat®; Hoffmann-La Roche Inc.; Nutley, NJ) require 1- to 4-hour infusions. Intravenous bisphosphonates require less frequent dosing (once a month) and are generally well tolerated with long-term use in patients with bone metastases. Zoledronic acid has demonstrated the broadest clinical activity in patients with bone metastases. *The Oncologist 2004;9(suppl 4):28-37*

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Introduction

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and are effective in the treatment of malignant bone disease [1]. Intravenous bisphosphonates are the current standard of care for the treatment of hypercalcemia of malignancy (HCM) and for the prevention of skeletal complications associated with bone metastases. Currently, zoledronic acid (Zometa®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) (4 mg via a 15-minute infusion) and pamidronate (Aredia®; Novartis Pharmaceuticals Corp.) (90 mg via a 2-hour infusion) are the only agents recommended by the American Society of Clinical Oncology (ASCO) for the treatment of bone lesions from breast cancer and multiple myeloma [2]. Furthermore, zoledronic acid is approved by both the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the prevention of skeletal complications in patients with multiple myeloma or bone metastases secondary to a variety of solid tumors, including breast, prostate, and lung cancer [3].

Bisphosphonates have undergone considerable evolution since the early 1970s, and the potency of these compounds has been steadily improved with each successive generation [4]. The first-generation bisphosphonates, etidronate (Didronel®; Procter and Gamble Pharmaceuticals, Inc.; Cincinnati, OH) and clodronate (Bonefos®; Anthra Pharmaceuticals; Princeton, NJ)—which lack a nitrogen atom—require relatively high molar concentrations to achieve clinical activity. Etidronate and clodronate also have low therapeutic ratios. Therefore, at the high doses required to effectively inhibit bone resorption, etidronate has the potential to adversely affect bone mineralization and may cause osteomalacia [5]. The i.v. infusion of etidronate and clodronate has also been associated with acute renal failure [6]. Therapeutic doses of etidronate and clodronate must be infused slowly over many hours with careful monitoring of serum creatinine to ensure renal safety. The first nitrogen-containing bisphosphonates, pamidronate and alendronate (Fosamax®; Merck and Company, Inc.; West Point, PA), were developed in the early 1980s and were found to be 10- to 100-fold more potent inhibitors of bone resorption than etidronate and clodronate [7, 8]. Ibandronate (Bondronat®; Hoffmann-La Roche Inc.; Nutley, NJ) was subsequently developed and shown to be approximately 10-fold more potent than pamidronate. Zoledronic acid and risedronate (Actonel®; Proctor and Gamble Pharmaceuticals, Inc.) are members of the newest generation of bisphosphonates that contain heterocyclic side chains. Zoledronic acid is unique in that it contains two nitrogen atoms, and it has been shown to be 40- to 850-fold more potent than pamidronate in various preclinical models of osteoclast-mediated bone resorption [7].

The development of highly potent nitrogen-containing bisphosphonates improved the convenience of i.v. administration because it allowed infusion times to be dramatically shortened. Infusion of all bisphosphonates is associated with dose- and infusion-rate-dependent effects on renal function as evidenced by increases in serum creatinine [9, 10]. Therefore, the more potent agents, which achieve therapeutic activity at micromolar concentrations, require lower doses and shorter infusion times. Zoledronic acid has the shortest approved infusion time of any bisphosphonate (15 minutes), compared with the 1-4 hours required for pamidronate and ibandronate. In addition, zoledronic acid (4 mg) is unique among other bisphosphonates because it effectively reduces the incidence and delays the onset of skeletal complications in patients with osteolytic, mixed, and osteoblastic bone lesions from a wide range of primary malignancies, including multiple myeloma, breast, prostate, and lung cancer, as well as a variety of other solid tumors [11-15].

Bisphosphonates used to treat malignant bone disease are administered either orally or via an i.v. infusion. Each route has it advantages and disadvantages, and this review focuses on those issues. Although daily oral bisphosphonate therapy can be administered at home and may seem more convenient than i.v. administration for the patient, oral bisphosphonate therapy appears to be less effective and may not be any more convenient than monthly infusions [16-18]. Oral bisphosphonates are less effective for the treatment of HCM (i.e., less rapid and sustained normalization of serum calcium) and appear to have limited activity in patients with bone metastases compared with i.v. therapy [16, 17] (reviewed by *Coleman* [19]). Furthermore, the oral administration of bisphosphonates is limited by poor bioavailability (<5%) and gastrointestinal (GI) toxicities (primarily esophagitis and diarrhea) [16, 18, 20]. Because of poor GI tolerability, compliance with oral bisphosphonate therapy is also an issue, and many patients require dose adjustments or discontinue therapy as a result, which can adversely affect efficacy. Therefore, in line with the updated ASCO guidelines on bisphosphonate therapy in breast cancer and multiple myeloma [2], as well as consensus guidelines and recommendations for bisphosphonate therapy in prostate cancer [21-23] and lung cancer [24], most physicians prefer i.v. bisphosphonates for the treatment of malignant bone disease, wherein strict compliance with the regimen is critical to achieve maximum therapeutic benefit.

Safety Profile of Bisphosphonate Therapy

Both the i.v. and oral administration of bisphosphonates are associated with adverse events, but the safety profile varies somewhat depending on the route of administration. Intravenous administration is associated with mild-to-moderate flu-like symptoms following the initial infusions,

whereas oral administration is associated with a significant incidence of GI adverse events. Oral administration is generally not associated with adverse effects on renal function, whereas renal function can be affected by i.v. administration. However, when bisphosphonates are administered at the recommended doses and infusion rates, the incidence of elevated serum creatinine is generally low (<10%), and severe renal adverse events are rare.

Intravenous Bisphosphonates

In general, the i.v. administration of bisphosphonates is well tolerated with a predictable and manageable side-effect profile that may include acute-phase responses, fluctuations in serum ion levels (calcium, magnesium, and phosphorus), and occasional elevations in serum creatinine [9, 10]. However, i.v. bisphosphonates are associated with a low incidence of serious adverse events. In addition, there are no known interactions between bisphosphonates and anticancer agents. Self-limiting, transient, acute-phase reactions resulting in mild to moderate flu-like symptoms have been reported in approximately one-third of patients—primarily after the first infusion [9]. These reactions occur with similar frequencies among patients treated with all i.v. bisphosphonates and are characterized by transient low-grade fever, fatigue, arthralgia or myalgia, nausea, and increased bone pain. In the comparative phase III trial of 4 mg zoledronic acid versus 90 mg pamidronate in patients with breast cancer or multiple myeloma, the most common adverse events in both treatment groups were mild to moderate bone pain, nausea, fatigue, and fever, and these events occurred with similar frequencies in both treatment groups (Table 1) [11, 12]. In a recent study of i.v. ibandronate (2 or 6 mg) in patients with breast cancer, serious adverse events related to the study drug included bone pain, lung edema, and asthenia [25]. Intravenous bisphosphonates are also associated with a slightly higher incidence of mild anemia [13] and with serum electrolyte imbalances. The latter can be minimized with administration of vitamin D and calcium (500 mg/day) supplements [11, 13]. Ibandronate has also been associated with lymphocytosis [9].

Table 1. Most frequently reported adverse events regardless of relationship to study drug

	n of patients (%)	
Adverse event	Zoledronic acid (4 mg) (*n* = 563)	Pamidronate (90 mg) (*n* = 556)
Bone pain	325 (58)	316 (57)
Nausea	270 (48)	266 (48)
Fatigue	241 (43)	240 (43)
Fever	213 (38)	172 (31)
Vomiting	187 (33)	183 (33)
Anemia	181 (32)	175 (32)
Myalgia	153 (27)	143 (26)

Adapted with permission from *Rosen et al.* [12].

Recently, retrospective case studies have reported an association between long-term bisphosphonate therapy and osteonecrosis of the jaws [26-28]. The incidence of osteonecrosis was very rare, occurring in <1 in 10,000 patients receiving i.v. bisphosphonate therapy since 2001. Historically, the risk of developing osteonecrosis (at any site) is four times higher in cancer patients than in the normal population and has multiple risk factors, including previous/concomitant chemotherapy, steroid therapy, or radiation therapy, as well as trauma, infection, and a history of dental procedures [29]. Therefore, it is recommended that physicians assess the dental status of patients before administration of bisphosphonate therapy, avoid invasive dental procedures in patients receiving bisphosphonate therapy, and monitor patients for good oral hygiene and the occurrence of jaw osteonecrosis. Importantly, a causal relationship between bisphosphonate use and osteonecrosis has not been established, and it is unclear as to why this condition develops preferentially in the jawbones. Furthermore, cases of osteonecrosis in patients receiving bisphosphonates have only been observed since 2001, indicating that new concomitant anticancer therapies could be contributing to the development of the disease.

Renal Effects of i.v. Bisphosphonates

All i.v. bisphosphonates are associated with dose- and infusion-rate-dependent effects on renal function [6, 9, 30]. Therefore, bisphosphonates should always be infused at the recommended doses and schedules, and renal function should be monitored. Doses of pamidronate higher than the recommended 90 mg have been associated with a higher risk of nephrotoxicity [31]. In addition, the infusion time for zoledronic acid was lengthened from 5 to 15 minutes and the 8-mg dose was discontinued because of renal safety concerns [11, 13, 14]. Patients receiving long-term bisphosphonate therapy may experience a rise in serum creatinine. In general, however, clinically significant serum creatinine increases are rare among patients treated with i.v. bisphosphonates.

The long-term safety of zoledronic acid was investigated in three large clinical trials involving more than 3,000 cancer patients with multiple myeloma, breast cancer, prostate cancer, and lung cancer or other solid tumors [12, 13, 32]. These trials used prospectively applied conservative criteria to evaluate notable serum creatinine

increases after bisphosphonate infusion (defined as an increase ≥0.5 mg/dl for patients with normal baseline serum creatinine levels [<1.4 mg/dl], an increase ≥1.0 mg/dl for patients with abnormal baseline serum creatinine levels, or ≥2 times the baseline value). Importantly, changes in serum creatinine were defined according to baseline measurements. After 2 years of monthly infusions, overall renal safety was similar for patients with breast cancer and multiple myeloma who were treated with either zoledronic acid or pamidronate [12]. More importantly, the renal safety profile of zoledronic acid was not significantly different than that of placebo in patients with prostate cancer or lung cancer and other solid tumors [13, 32].

In the comparative trial in patients with multiple myeloma or breast cancer, Kaplan-Meier estimates of time to first notable serum creatinine increase (Fig. 1) demonstrated comparable risks for decreased renal function (risk ratio = 1.057; $p = 0.839$) for patients treated with zoledronic acid (4 mg via a 15-minute infusion) or pamidronate (90 mg via a 2-hour infusion) [12]. Furthermore, among patients with breast cancer receiving 4 mg zoledronic acid via a 15-minute infusion ($n = 181$), there were no National Cancer Institute Common Toxicity Criteria (CTC) grade 3 or 4 serum creatinine increases, and the percentage of patients receiving zoledronic acid who experienced a notable serum creatinine increase was similar to that of pamidronate (9.4% versus 6.5% for pamidronate) (Table 2) [33]. The long-term safety of zoledronic acid and pamidronate has also been demonstrated beyond 2 years of therapy. A subset analysis in 22 patients with multiple myeloma or breast cancer who received i.v. zoledronic acid or pamidronate therapy for a median of 3.6 years (range 2.2-6 years) showed no clinically relevant changes in complete blood cell count, platelet count, calcium analysis, electrolyte analysis, or kidney function tests, thus demonstrating that prolonged bisphosphonate therapy is well tolerated [34]. The renal safety of long-term zoledronic acid was confirmed by a recent analysis performed at our institution; 53 patients with breast cancer (44), multiple myeloma (7), or other tumor types (2) were treated with i.v. bisphosphonates for a median of 30 months (range 24+ to 124+ months), with CTC grade 1 renal toxicity observed in 7.5% of patients.

Recently, the renal safety profile of i.v. ibandronate (6 mg via a 1- to 2-hour infusion every 3-4 weeks) in patients with breast cancer was reported, and it was similar to that of zoledronic acid in the breast cancer subset [25, 35]. In a post-hoc analysis using the same criteria defined in the zoledronic acid trials, 6% of patients receiving either ibandronate or placebo experienced a notable increase in serum creatinine after 2 years of therapy (Table 2) [35]. The incidences of clinically significant renal adverse events

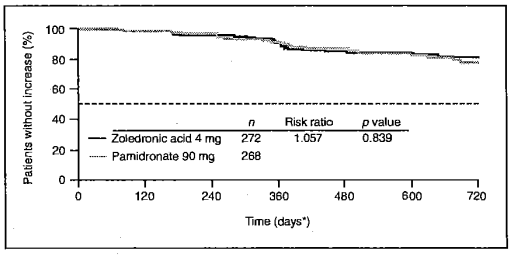

***Figure 1.** Kaplan-Meier estimates of time to first notable serum creatinine increase in patients with multiple myeloma or breast cancer with bone metastases receiving 4 mg zoledronic acid or 90 mg pamidronate and Andersen-Gill multiple event analysis of the risk of elevated serum creatinine between treatment groups. *After start of study drug.*

Table 2. Percentage of breast cancer patients with notable serum creatinine increases* after 2 years of i.v. bisphosphonate therapy

Treatment	*n* of patients	Patients with an increase (%)
Zoledronic acid [33] (4 mg over 15 minutes)	181	9.4
Pamidronate (90 mg over 2 hours)	184	6.5
Ibandronate [35] (6 mg over 1 hour)	152	6
Placebo	158	6

*Notable serum creatinine increase defined as an increase of ≥0.5 mg/dl for patients with baseline serum creatinine levels ≤1.4 mg/dl, an increase of ≥1.0 mg/dl for patients with baseline serum creatinine levels >1.4 mg/dl, or any increase ≥2 times the baseline value.

were also similar between the ibandronate and placebo groups (4.5% for ibandronate versus 4.0% for placebo), and none of these were considered serious adverse events [36]. However, the percentage of patients experiencing a decrease in creatinine clearance was twofold higher in the ibandronate group (2.6% versus 1.3% for placebo).

Zoledronic acid (4 mg via a 15-minute infusion) has also demonstrated a favorable renal safety profile when compared with placebo in two long-term, randomized trials [13, 32, 37]. In a study of 643 men with advanced prostate cancer, Kaplan-Meier estimates of time to first notable serum creatinine increase (Fig. 2) demonstrated comparable risks of elevated serum creatinine for patients treated with zoledronic acid and those given placebo for 24 months (risk ratio = 1.137; $p = 0.752$) [37]. Similarly, in a study in patients with lung cancer or other solid tumors, the incidences of serum creatinine increases in patients with non-small cell lung cancer were similar in the zoledronic acid and placebo groups after 21 months of treatment ($p = 0.920$) [38]. Only

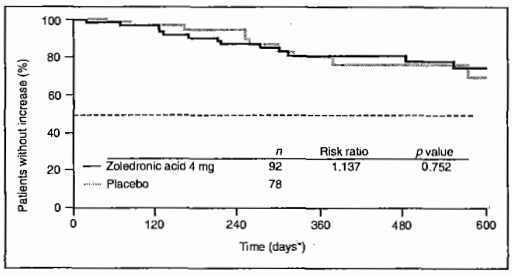

Figure 2. Kaplan-Meier estimates of time to first notable serum creatinine increase in patients with prostate cancer and bone metastases receiving 4 mg zoledronic acid or placebo and Andersen-Gill multiple event analysis of the risk of elevated serum creatinine between treatment groups. *After start of study drug.

one patient in each treatment group had a grade 3 serum creatinine increase, and no patient experienced a grade 4 increase.

Because of the potential for decreased renal function, guidelines for the long-term use of i.v. bisphosphonates in patients with malignant bone disease recommend that serum creatinine levels be monitored before each infusion [2]. In addition, the prescribing information for pamidronate, zoledronic acid, and ibandronate recommends monitoring serum creatinine or creatinine clearance [10, 39, 40]. If a patient receiving zoledronic acid or pamidronate has a notable serum creatinine increase, as defined in the zoledronic acid trials, infusion of the next dose should be withheld until serum creatinine returns to within 10% of baseline. Moreover, zoledronic acid and pamidronate are not recommended for patients with baseline serum creatinine levels >3.0 mg/dl unless the clinical benefit outweighs the risk [10, 39]. Infusion of ibandronate at a lower dose (2 mg) is recommended for patients with creatinine clearance <30 ml/minute; however, there is no evidence that this dose has clinical activity [25, 40]. In general, the use of i.v. bisphosphonates in patients with significantly impaired renal function is not recommended. Otherwise, i.v. bisphosphonates may be used in patients at risk for decreased renal function as long as serum creatinine is closely monitored. In particular, patients with multiple myeloma are at increased risk of renal failure because of the nature of their disease and use of nephrotoxic chemotherapy. Increasing the infusion time and addition of hydration therapy may be appropriate in some clinical situations to reduce the risk.

Oral Bisphosphonates

Oral bisphosphonates, including clodronate and ibandronate, are used for the treatment of bone metastases in patients with advanced breast cancer. However, bisphosphonates are poorly absorbed in the GI tract (<5% of the oral dose is typically absorbed) and can cause esophagitis and other GI adverse events [41]. Because of their low bioavailability, high oral doses may be required. This is particularly problematic for clodronate, which is one of the least potent bisphosphonates available. Consequently, patients must swallow several large tablets or capsules. In addition, oral bisphosphonates must be administered on an empty stomach to improve bioavailability. The typical daily dosing regimen specifies that the tablets be taken on an empty stomach with 6-8 ounces of water, and patients must fast and remain upright for at least 30 minutes to avoid epigastric pain. If not taken properly, oral bisphosphonates can cause a high incidence of GI adverse events, including esophagitis, mucositis, nausea, vomiting, and diarrhea, and may exacerbate the side effects of anticancer therapy.

Evidence of GI toxicity associated with oral bisphosphonate therapy is available from studies of clodronate and ibandronate in cancer patients and in postmenopausal women with osteoporosis. In a long-term trial of oral clodronate (1,600 mg/day for 2 years) in patients with breast cancer, GI adverse events were significantly more common for patients receiving oral clodronate than for those receiving placebo (Table 3) [42, 43]. Although the overall incidences of adverse events were similar in the two treatment groups, the incidence of GI adverse events was significantly higher among patients treated with clodronate (57% versus 45% for placebo; $p < 0.05$). The incidence of upper GI adverse events was only slightly higher in the clodronate group (22% for clodronate versus 19% for placebo) [43], but diarrhea was significantly more common in the clodronate group, particularly during the treatment period (15% versus 7%; $p < 0.05$). In a pooled analysis of two recent trials of oral ibandronate in breast cancer patients with bone metastases,

Table 3. Most common gastrointestinal adverse events associated with oral clodronate therapy

Adverse event	*n* of patients (%) Clodronate (1,600 mg/day) (*n* = 538)	Placebo (*n* = 541)
GI system disorders*	307 (57.1)	245 (45.3)
Upper GI [43]	120 (22.3)	104 (19.3)
Diarrhea*	81 (15.1)	37 (6.8)
Nausea	120 (22.3)	126 (23.3)
Dyspepsia	56 (10.4)	49 (9.1)
Vomiting	60 (11.2)	53 (9.8)
Abdominal pain	39 (7.2)	27 (5.0)

*Statistically significant difference between groups ($p < 0.05$).

Modified with permission from *Atula et al.* [42].

patients receiving ibandronate (50 mg/day) were twice as likely to experience treatment-related GI adverse events, including abdominal pain, dyspepsia, nausea, and esophagitis, than those receiving placebo (Table 4) [44]. A randomized trial of oral ibandronate in 240 postmenopausal women with osteoporosis also demonstrated that diarrhea was more common in patients receiving ibandronate than in those receiving placebo (10% and 11% for two different schedules of ibandronate versus 1% for placebo) [45, 46]. In addition, a higher percentage of patients in the daily ibandronate group experienced constipation than in the placebo group (6% versus 0%).

Table 4. Most common treatment-related gastrointestinal adverse events associated with oral ibandronate therapy

Adverse event	*n* of patients (%)	
	Ibandronate (50 mg/day) (*n* = 287)	Placebo (*n* = 277)
GI system disorder	42 (14.6)	21 (7.6)
Abdominal pain	6 (2.1)	2 (0.7)
Dyspepsia	20 (7.0)	13 (4.7)
Nausea	10 (3.5)	4 (1.4)
Esophagitis	6 (2.1)	2 (0.7)

Data from *Body et al.* [44].

Compliance With Oral Bisphosphonate Therapy

A major issue with the use of oral bisphosphonate therapy is patient compliance with the dosing regimen. Compliance with oral medication is influenced by a variety of factors, including age, disease type and duration, lifestyle, treatment regimen, and tolerability [47, 48]. In addition, compliance rates reported from well-controlled clinical trials might be higher than those observed in "real-world" situations. Oral medications that elicit GI or other side effects that significantly affect quality of life are less likely to be taken than treatment regimens without major side effects. In addition, when the adverse events associated with an oral therapy can be directly attributed to the drug—for example, if adverse events occur in close temporal proximity to dosing—patients are less likely to comply. Oral bisphosphonate therapy has been associated with a fairly high rate of noncompliance and early study withdrawal because of its complicated treatment regimen and high rate of GI adverse events [40, 49-52].

The global rate of noncompliance with long-term oral bisphosphonate therapy for osteoporosis has been reported as >50% [53]. However, there are limited data on the rate of noncompliance with oral bisphosphonate therapy among patients with bone metastases from advanced cancer, which also involves chronic dosing. The only available data regarding compliance with oral bisphosphonate therapy in patients with bone metastases are from clinical trials of oral clodronate conducted in Europe. Because clodronate has a low potency and thus requires high doses to achieve therapeutic concentrations, treatment with oral clodronate (1,600 mg/day) is further complicated by the large tablets that are difficult for many patients to swallow. Although there are no studies that were specifically designed to evaluate compliance, several studies have reported data on compliance. In a clinical trial of oral clodronate in breast cancer patients with bone metastases (n = 173), compliance was evaluated in 78% of patients in the clodronate group who survived longer than 6 months. Of these, 74% were partially or fully compliant (i.e., self-administered the study medication during part or all of the study, respectively) and 26% were completely noncompliant with the oral regimen [49]. In addition, 16% of patients receiving clodronate and 18% of patients receiving placebo reported difficulty swallowing the capsules. In another study of oral clodronate in patients with metastatic bone pain (n = 55), overall compliance was reported as >90%, but a number of patients withdrew prematurely because of difficulty swallowing the capsules [50].

Another way to assess noncompliance is to examine the reasons for study termination and the extent to which bisphosphonate-related adverse events contribute to early withdrawal (Table 5). In the study cited above in 173 patients with breast cancer, 34% of patients in the clodronate group

Table 5. Summary of oral bisphosphonate studies and most common reasons for early study withdrawal

Study	*n*	Study drug (*n*)	Patients discontinuing study drug (%)	Most common reasons for discontinuing study drug
Paterson et al. [49]	173	Clodronate (85)	34	Early noncompliance (22%)
Robertson et al. [50]	55	Clodronate (27)	37	Difficulty swallowing capsules (11%)
Kristensen et al. [51]	100	Clodronate (49)	35	GI adverse events (14%)
Aiula et al. [42]	1,079	Clodronate (538)	NR	GI adverse events (11%)
Coleman et al. [52]	110	Ibandronate (77)	NR	GI adverse events (8%)

Abbreviation: NR = not reported.

discontinued the study drug, including 22% of patients who withdrew because of early noncompliance (i.e., <6 weeks) [49]. A recent randomized trial of oral clodronate in the adjuvant setting for the prevention of bone metastasis in patients with breast cancer demonstrated higher incidences of GI adverse events and early study discontinuation due to adverse events in the clodronate group than in the placebo group [42]. In that large, multicenter trial, 1,079 patients were randomized to receive either oral clodronate (1,600 mg/day) or placebo for 2 years. GI adverse events resulted in early study withdrawal for 6.3% of patients in the clodronate group and for 3.9% of patients in the placebo group. Two additional studies have also reported high rates of study discontinuation among breast cancer patients receiving oral clodronate for the treatment of bone metastases [50, 51]. In one study involving 100 patients, 35% of patients discontinued the study drug, and 14% of patients treated with clodronate discontinued treatment because of GI adverse events (primarily nausea and diarrhea) [51]. In a study involving 55 patients, 37% of patients receiving oral clodronate withdrew from the study, and difficulty swallowing the capsules was reported to contribute to study withdrawal in 11% of patients [50]. These studies suggest that as many as one-third of patients may not receive the full benefit of oral clodronate either because of early withdrawal or noncompliance.

A high rate of early study withdrawal due to GI adverse events was also reported in a study of oral ibandronate in patients with metastatic bone disease [52]. That study involved 110 patients with bone metastases secondary to a variety of cancers, who received either oral ibandronate at doses ranging from 5-50 mg/day or placebo; 8% of patients discontinued within 1 month because of GI intolerability. During the first month of treatment, a dose-dependent incidence of GI adverse events was reported; 50% of patients treated with the 50-mg ibandronate dose experienced GI toxicity compared with 30% of patients in the placebo group. Notably, one patient treated with the 20-mg ibandronate dose developed radiographically confirmed esophageal ulceration. Similarly, in a pooled analysis of two recent trials of oral ibandronate (50 mg/day for up to 96 weeks) in breast cancer patients with bone metastases ($n = 564$), 10% of patients receiving ibandronate withdrew from the study because of adverse events [44].

Noncompliance can also adversely affect treatment outcome. If the dosing regimen for oral bisphosphonates is not followed and patients ingest food or beverages other than water within 30 minutes of taking a bisphosphonate, absorption will be further reduced resulting in decreased efficacy. In the case of oral ibandronate, patients must not ingest food for ≥1 hour after taking the drug to maintain efficacy. A study of oral ibandronate therapy for postmenopausal osteoporosis investigated the effects of a 30-minute versus 60-minute postdose fasting period [54]. That study demonstrated that oral ibandronate was approximately half as effective, based on measurements of lumbar spine bone mineral density (BMD), when patients ate within 30 minutes of taking the drug compared with the group that waited ≥1 hour before eating. However, the greater efficacy observed in the 60-minute fasting group was accompanied by a higher incidence of GI adverse events. In particular, the incidence of dyspepsia was more than twofold higher in the 60-minute fasting group (8.5% versus 3.7%).

Other studies assessing compliance with oral bisphosphonate therapy for osteoporosis have demonstrated that noncompliance can lead to reduced clinical efficacy and increases in the burden of disease. For example, the IMPACT study evaluated the effect of compliance on the efficacy of oral risedronate therapy in postmenopausal women with osteoporosis ($n = 2,302$) [55]. That study used bone resorption markers (urinary N-telopeptide and serum C-telopeptide) and changes in BMD to assess efficacy, and changes from baseline measurements were related to compliance using a proportional hazards model. The results showed a correlation between compliance with therapy and improvements in these clinical parameters. For example, at week 22 of treatment, C-telopeptide levels showed a reduction of >50% in 60% of compliant patients versus only approximately 20% of noncompliant patients. Therefore, noncompliance to oral bisphosphonate therapy can have significant effects on clinical outcomes.

Noncompliance with oral therapies can also have important health-economic implications. Although studies of the health-economic effects of noncompliance are limited, the available evidence suggests that noncompliance can result in increased morbidity and burden of disease, which increases health care costs. The increased health care costs stem from more frequent physician visits, diagnostic testing, hospital admissions, and longer hospital stays for patients who do not comply with their treatment regimen [47]. These increases in the economic burden of disease are unfortunate given that effective therapies exist, but patients are not receiving the full benefit of those available treatments. Noncompliance may also result in erroneous efficacy conclusions from clinical trials. An evaluation of the effect of noncompliance on efficacy and cost-effectiveness revealed that noncompliance always resulted in reduced efficacy, whereas the economic effects of noncompliance varied significantly among trials depending on the therapeutic agent and the disease being treated [56]. Among 22 clinical trials examined, the majority of the evaluations assumed that noncompliance with the dosing regimen altered the

effectiveness of the investigational drug. However, most studies did not include any measures of compliance. Therefore, it is not possible to assess the magnitude of the effect of noncompliance on efficacy conclusions. In the studies examined, noncompliance also clearly affected the cost of treating the disease; however, the impact on cost was variable.

Conclusions

Intravenous bisphosphonates are the standard of care for the treatment of HCM and the prevention of skeletal complications resulting from bone metastases. The i.v. administration of bisphosphonates is generally safe and well tolerated with long-term use, and the development of highly potent, new-generation bisphosphonates has greatly improved the safety and convenience of i.v. infusion. With these newer agents, the risk of decreased renal function is low when used at the recommended doses and infusion times, but serum creatinine monitoring is recommended. Oral bisphosphonates are also used for the treatment of bone metastases. Although oral bisphosphonates can be self-administered at home, the treatment regimens for these agents are complicated, and oral therapy can result in GI adverse events—one reason for patient noncompliance. The level of compliance with oral treatment regimens has not been extensively monitored in clinical trials; thus, it is difficult to fully evaluate the consequences of noncompliance. However, noncompliance has been shown to reduce clinical efficacy and may increase health care costs. In general, i.v. administration of bisphosphonates appears to be more effective in patients with HCM (i.e., more rapid onset of action) and for the prevention of skeletal complications. Furthermore, i.v. bisphosphonate therapy ensures full compliance, and monthly infusions—although they may require travel to an infusion center—may be more convenient than daily oral therapy for many patients. Moreover, home infusion of zoledronic acid by specialized care personnel is becoming increasingly popular in some European countries, making i.v. bisphosphonate therapy a favorable treatment option. For all these reasons, i.v. bisphosphonates should be the treatment of choice in patients with malignant bone disease.

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INTRAVENOUS ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

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ABSTRACT

Background Bisphosphonates are effective agents for the management of osteoporosis. Their low bioavailability and low potency necessitate frequent administration on an empty stomach, which may reduce compliance. Gastrointestinal intolerance limits maximal dosing. Although intermittent intravenous treatments have been used, the optimal doses and dosing interval have not been systematically explored.

Methods We studied the effects of five regimens of zoledronic acid, the most potent bisphosphonate, on bone turnover and density in 351 postmenopausal women with low bone mineral density in a one-year, randomized, double-blind, placebo-controlled trial. Women received placebo or intravenous zoledronic acid in doses of 0.25 mg, 0.5 mg, or 1 mg at three-month intervals. In addition, one group received a total annual dose of 4 mg as a single dose, and another received two doses of 2 mg each, six months apart. Lumbar-spine bone mineral density was the primary end point.

Results There were similar increases in bone mineral density in all the zoledronic acid groups to values for the spine that were 4.3 to 5.1 percent higher than those in the placebo group ($P<0.001$) and values for the femoral neck that were 3.1 to 3.5 percent higher than those in the placebo group ($P<0.001$). Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. Myalgia and pyrexia occurred more commonly in the zoledronic acid groups, but treatment-related dropout rates were similar to that in the placebo group.

Conclusions Zoledronic acid infusions given at intervals of up to one year produce effects on bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures, suggesting that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis. (N Engl J Med 2002;346:653-61.)

ORAL bisphosphonates are widely used for treating osteoporosis and have been shown to increase bone mineral density and decrease the rate of fracture.[1,2] However, they do have limitations related to long-term compliance, gastrointestinal intolerance, and poor and variable absorption from the gastrointestinal tract. Intermittent intravenous administration of bisphosphonates might address some of these problems and has been shown to be effective in the treatment of malignant hypercalcemia and Paget's disease and to reduce the rate of skeletal complications in patients with breast carcinoma or multiple myeloma. Evidence suggests that intravenous bisphosphonates increase bone mineral density in patients with osteoporosis, but most relevant studies have been small, unblinded, and short-term and have not systematically examined the effects of the dose and dosing interval on changes in bone mineral density and markers of bone turnover.[3-6]

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Zoledronic acid is the most potent bisphosphonate that has been studied in clinical trials to date.[7] It is superior to pamidronate in the treatment of cancer-related hypercalcemia.[8] Because it has high potency, only small doses are required for the inhibition of bone resorption, and long dosing intervals may be used. We undertook a phase 2 study to examine the effect of intravenous zoledronic acid on bone density and bone turnover in postmenopausal women with low bone density and to assess the effects of varying the total dose administered and the dosing interval.

METHODS

Study Subjects

A total of 351 postmenopausal women 45 to 80 years of age were studied at 24 centers in 10 countries. In all the women, menopause had occurred at least five years previously, either naturally or as the result of bilateral oophorectomy. All women had a bone mineral density at the lumbar spine (L1 to L4) that was at least 2.0 SD below the mean value for young adults (a T score lower than −2) and had no more than one vertebral fracture at screening. The date of onset of menopause was defined as the date of oophorectomy when applicable or as 12 months after the cessation of menses in women over 50 years of age and 18 months after the cessation of menses in women between 45 and 49 years of age. Major criteria for exclusion included systemic estrogen treatment within the previous three months, evidence of secondary osteoporosis, clinical or laboratory evidence of hepatic or renal disease, disorders of the parathyroid or thyroid glands, a serum 25-hydroxyvitamin D concentration of 15 ng per milliliter (37 nmol per liter) or less, a history of cancer, previous treatment with bisphosphonates or fluoride, and current therapy with any other drug known to affect the skeleton. The protocol was approved by the ethics committee at each center, and all the women gave written informed consent. Thirty-five women withdrew from the study, most commonly for personal reasons (in the case of 15 women) or because of adverse events (14 women). Thus, 316 women completed the study.

Treatment

All women received a calcium supplement (1 g per day). At study entry the women were randomly assigned to receive one of six treatment regimens in a double-blind fashion. Three groups received zoledronic acid by intravenous infusion every three months, one group at a dose of 0.25 mg, one at a dose of 0.5 mg, and one at a dose of 1 mg. Two other groups received a total dose of 4 mg of zoledronic acid — one group receiving a single 4-mg infusion at the beginning of the trial and the other group receiving two doses of 2 mg each, one at base line and the other at six months. Thus, there were three groups that received a total dose of 4 mg in one year. The sixth group received only placebo (saline). To maintain blinding, all women received an intravenous infusion of either zoledronic acid or placebo every three months. All infusions were 20 ml in volume and were infused over a period of five minutes. A dose of 4 mg given in this way produces a mean (±SD) peak serum concentration of zoledronic acid of 393±100 ng per milliliter. Infusions were prepared at each center by a pharmacist who had no contact with the patients and were labeled with the subject's study number and supplied to the study personnel.

Bone Density Measurement

The bone mineral density of the lumbar spine, the nondominant proximal femur and forearm, and the total body were measured by dual-energy x-ray absorptiometry at base line and at 6, 9, and 12 months with the use of Hologic QDR (Hologic, Waltham, Mass.) or Lunar (Madison, Wis.) instruments. Data were converted to Hologic-equivalent values by the method of Hui et al.[9] A central laboratory (Institut für Funktionsanalyse, Hamburg, Germany) was responsible for the supervision of quality control for these measurements and notified investigators if any patient had a decrease in bone density of more than 5 percent from the base-line values.

Markers of Bone Turnover

Measurement of biochemical markers was performed in a central laboratory with the use of established methods. For serum bone-specific alkaline phosphatase, the Tandem-MP Ostase assay was used (Hybritech, Liege, Belgium). Serum osteocalcin was measured with the N-MID one-step enzyme-linked immunosorbent assay (Osteometer, Herlev, Denmark). Urinary type I collagen cross-linked N-telopeptide was measured with the Osteomark assay (Ostex, Seattle). Serum type I collagen C-telopeptide was measured with the CrossLaps assay (Osteometer).

Statistical Analysis

The necessary sample size was calculated as the number of patients needed to detect a difference between the zoledronic acid groups and the placebo group of at least 4 percent in the degree of change in lumbar-spine bone mineral density from base line to 12 months. Bonferroni's correction was used to adjust for multiple comparisons in order to ensure an overall nominal significance level of 0.05. Given a noncentral t distribution with a type I error of 0.025, a power of 80 percent, a two-sided alternative, and a standard deviation of 5.7 percent, we calculated that 40 patients were needed in each treatment group in order to allow detection of a difference of 4 percent. To allow for a possible 15 percent dropout rate, a total sample size of 290 was selected.

All analyses were performed according to the intention-to-treat principle with the use of all available data from all patients who received study drug. Missing values were not imputed or replaced. Analysis of covariance was performed (with the Proc Mixed procedure of SAS software [SAS Institute, Cary, N.C.]) to estimate differences between the treatment groups. The statistical fixed-effects model considered center and treatment as main variables. In addition, the base-line values, if measured, were used as covariates. The analyses were repeated with the last observation carried forward and produced essentially the same results (data not shown).

For the primary variable, adjustment for multiple comparisons between placebo and the active doses of zoledronic acid was performed at a one-sided alpha level of 0.025, according to the method of Marcus et al.[10] For secondary variables, pairwise comparisons were investigated in the exploratory analysis (unadjusted for multiple comparisons). The pairwise comparisons were tested at a two-sided level of significance of 0.05. In addition to the P value for the comparisons between treatment groups, estimates of the differences and associated 95 percent confidence intervals were calculated.

The protocol was designed and developed by the sponsor and submitted to the investigators for comments and amendments. The final protocol was then accepted by the investigators and submitted to the ethics review committees of their institutions for approval. Data management and statistical analysis were performed by the sponsor. Interpretation of the data and preparation of the manuscript were performed by a publication committee that included three academic researchers who were investigators in the trial (Drs. Reid, Brown, and Burckhardt) and Dr. Trechsel, the author of the study protocol, as a representative of the sponsor. These authors had full and unfettered access to the data and take full responsibility for the completeness and accuracy of the reported data. The study sponsor placed no limits on statements made in the final paper.

RESULTS

Study Subjects

The base-line characteristics of the women who participated in the study are summarized in Table 1.

All but two women were white, and none had vertebral fractures at study entry.

Bone Mineral Density

Mean bone-mineral-density values in the lumbar spine corresponded to a T score of −2.9. All groups receiving zoledronic acid regimens had a progressive increase in bone mineral density in the lumbar spine throughout the 12-month study period, although the rate of increase tended to slow in the second half of the study (Fig. 1A). Throughout the study, the values for lumbar-spine bone mineral density achieved with all zoledronic acid regimens were significantly higher than those in the placebo group ($P<0.001$), and there were no significant differences among the zoledronic acid groups. At 12 months, the mean lumbar-spine bone mineral density in the groups receiving zoledronic acid was 4.3 to 5.1 percent higher than the mean value in the placebo group, which remained stable. The bone mineral density in the femoral neck also increased progressively throughout the study period; all zoledronic acid groups had similar increases to values that were significantly higher than those in the placebo group (differences of 3.1 to 3.5 percent at 12 months, $P<0.001$) (Fig. 1B). The femoral-neck bone mineral density declined by 0.4 percent in the placebo group.

Bone mineral density at the distal radius responded to zoledronic acid treatment to a lesser extent, resulting in differences from the placebo group of 0.8 to 1.6 percent at 12 months (data not shown); in the placebo group, distal radial bone mineral density decreased by 0.8 percent. All zoledronic acid regimens except the four doses of 0.25 mg each resulted in distal radial bone mineral density that was significantly greater than that in the placebo group ($P\leq0.05$ for all comparisons). The results for total-body bone mineral density were similar (data not shown). At 12 months, the differences in total-body bone mineral density between the zoledronic acid groups and the placebo group ranged from 0.9 percent to 1.3 percent and were significant ($P<0.03$ for all comparisons) for all regimens except the four doses of 0.5 mg each.

Markers of Bone Turnover

Markers of bone resorption reached a nadir at one month (median decreases of 65 to 83 percent in serum C-telopeptide and 50 to 69 percent in the urinary N-telopeptide:creatinine ratio), whereas there were no significant changes in the placebo group (Fig. 2). The decrease in markers of resorption tended to be dose-dependent, particularly at three months — a pattern that is consistent with previous reports that higher doses of bisphosphonates increase the duration of action of the drug.[11] We do not have full documentation of the immediate reductions in bone resorption after each infusion, because most samples were obtained only every three months. The suppression of

TABLE 1. BASE-LINE CHARACTERISTICS.*

CHARACTERISTIC	ZOLEDRONIC ACID GROUPS					PLACEBO GROUP (N=59)
	4×0.25 mg (N=60)	4×0.5 mg (N=58)	4×1 mg (N=53)	2×2 mg (N=61)	1×4 mg (N=60)	
No. of women completing the study	51	52	48	55	53	57
Age (yr)	64±6	64±7	65±7	63±7	65±7	64±6
Weight (kg)	60±10	62±10	61±9	63±13	62±11	63±10
Height (cm)	158±6	158±6	158±6	159±6	159±6	160±6
Urinary N-telopeptide:creatinine ratio†	48±32	56±43	45±21	46±27	48±24	45±26
Serum C-telopeptide (nmol/liter)	5.5±2.8	5.3±2.2	4.7±1.8	4.8±1.9	5.1±1.9	4.8±1.8
Serum bone-specific alkaline phosphatase (μg/liter)	17±8	18±6	15±5	15±5	15±6	16±7
Serum osteocalcin (μg/liter)	26±10	24±11	26±9	22±10	24±11	24±13
Bone mineral density (g/cm²)‡						
Lumbar spine	0.74±0.06	0.72±0.08	0.73±0.06	0.73±0.07	0.73±0.08	0.74±0.07
Femur	0.70±0.09	0.71±0.11	0.71±0.09	0.72±0.09	0.74±0.11	0.71±0.08
Radial	0.43±0.05	0.43±0.06	0.43±0.06	0.43±0.06	0.43±0.06	0.43±0.06
Total body	0.90±0.09	0.90±0.10	0.90±0.09	0.90±0.09	0.90±0.09	0.88±0.08

*Plus–minus values are means ±SD.

†N-telopeptide was measured in nanomoles, and creatinine in millimoles.

‡Data have been converted to Hologic-equivalent values.

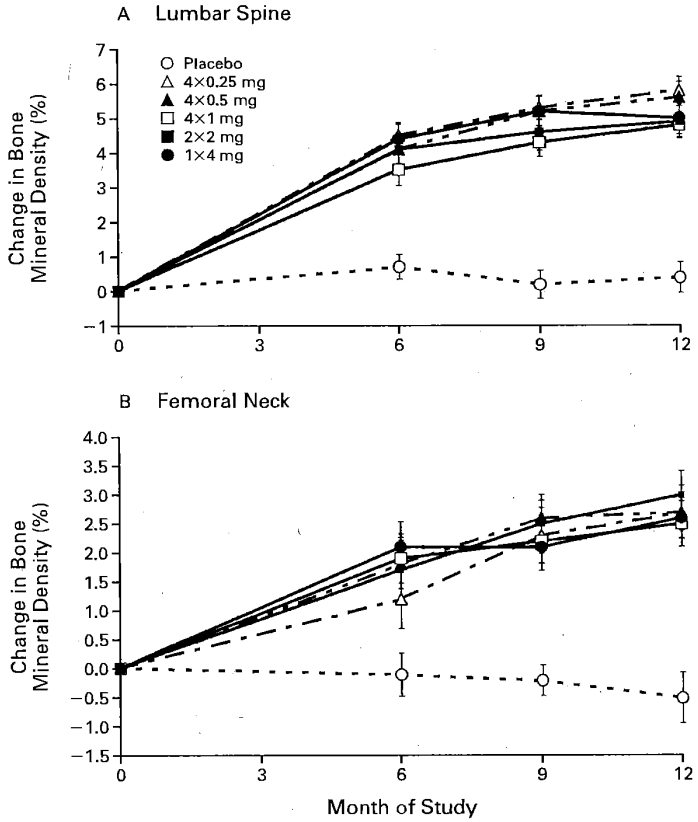

Figure 1. Effects of Various Regimens of Zoledronic Acid and Placebo on Bone Mineral Density in the Lumbar Spine (Panel A) and the Femoral Neck (Panel B) in Postmenopausal Women with Low Bone Mineral Density.

The curves show the mean changes from base line in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Achieved density with all regimens of zoledronic acid was significantly higher than that with placebo, and there were no significant differences among the zoledronic acid groups. T bars represent standard errors.

resorption was maintained at 12 months. At 12 months, the zoledronic acid regimens were associated with decreases of 49 to 52 percent in serum C-telopeptide (as compared with a decrease of 8 percent in the placebo group) and decreases of 54 to 65 percent in the ratio of urinary N-telopeptide to creatinine (as compared with an increase of 3 percent in the placebo group). All zoledronic acid groups had values for these markers of resorption that were significantly different from those in the placebo group ($P<0.01$ for all comparisons), but there were no significant differences among the zoledronic acid groups. Bone-specific alkaline phosphatase and osteocalcin, which are serum markers of bone formation, showed similar responses, but there was no sharp decrease apparent at one month (Fig. 3). Again, suppression persisted at 12 months with all doses ($P<0.001$).

Bone Biopsies

A 7.5-mm transiliac biopsy specimen was obtained from 43 women and double-labeled with tetracycline. Of these specimens, 27 were complete and suitable for histomorphometric analysis. The sections were undecalcified and stained with Goldner's trichrome, except for tetracycline measurements, which were made on unstained sections. Women treated with zoledronic

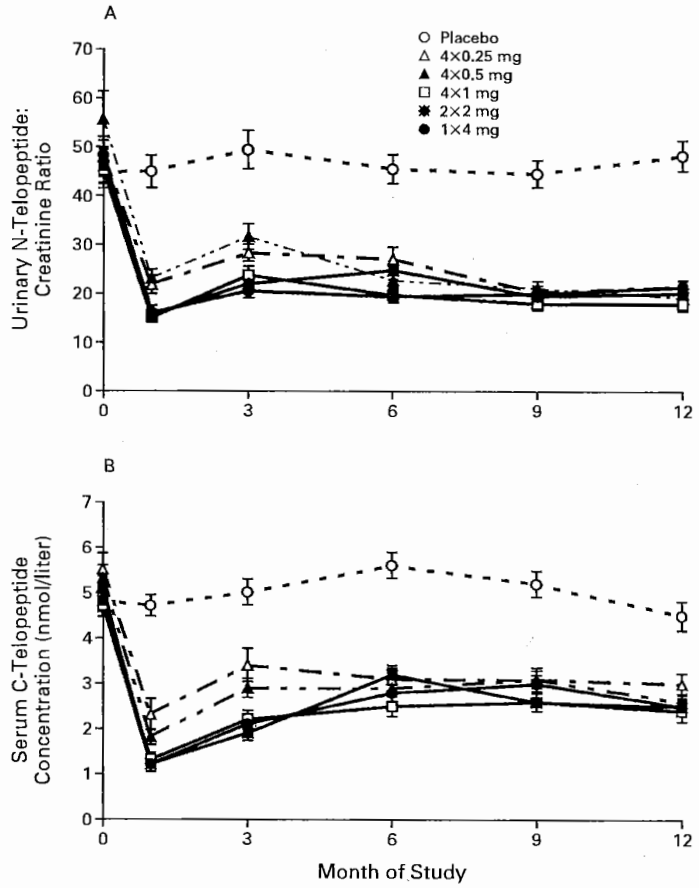

Figure 2. Effects of Various Regimens of Zoledronic Acid and Placebo on Biochemical Markers of Bone Resorption.

The ratio of N-telopeptide of type I collagen (in nanomoles) to creatinine (in millimoles) was measured in urine (Panel A). C-telopeptide was measured in serum (Panel B). The curves show the mean changes from base line in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Beginning at one month, the effects of all regimens were significantly different from those of placebo. The I bars represent standard errors.

acid at any dose had significantly lower proportions of mineralizing surfaces, rates of bone formation, adjusted mineral apposition rates, and activation frequencies than the women in the placebo group (differences of 71 percent to 84 percent, $P<0.05$); there were nonsignificant differences in the proportion of eroded surface (39 percent lower than that in the placebo group, $P<0.06$) and in eroded volume (48 percent lower, $P<0.07$). No change was noted in cortical bone thickness or porosity; cancellous bone volume; trabecular thickness, separation, or number; wall width of trabecular bone packets; number of nodes per volume of tissue; or osteoid maturation time. No dose effect was found with respect to any of these factors. No evidence of osteomalacia was found, either by qualitative assessment or on the basis of such quantitative measures as osteoid thickness and volume or the mineral apposition rate. No other qualitative abnormalities were apparent.

Fractures

Spinal radiographs at base line and one year showed no vertebral fractures during the study. No nonver-

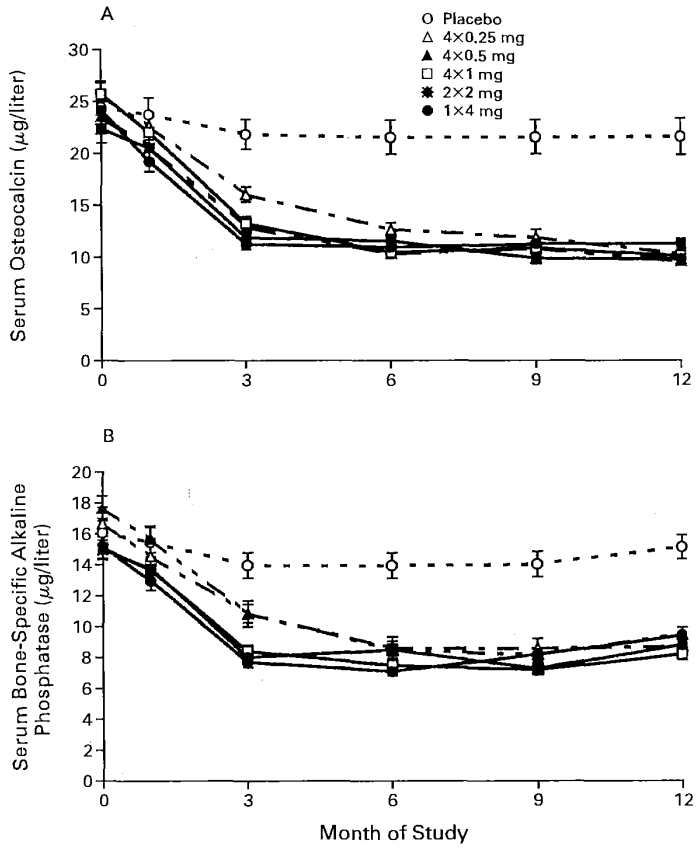

Figure 3. Effects of Various Regimens of Zoledronic Acid and Placebo on Serum Markers of Bone Formation.

The curves show the mean changes from base line in serum osteocalcin (Panel A) and serum bone-specific alkaline phosphatase (Panel B) in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Beginning at three months, the serum concentrations with all regimens of zoledronic acid were significantly lower than base-line values. The I bars represent standard errors.

tebral fractures occurred in the group receiving four doses of 0.25 mg of zoledronic acid; two nonvertebral fractures occurred in the group receiving four doses of 1 mg of zoledronic acid; and one nonvertebral fracture occurred in each of the other groups.

Safety

Mean serum calcium concentrations in the zoledronic acid groups declined significantly ($P<0.05$ for all comparisons), by approximately 0.08 mmol per liter, between base line and one month but were similar to those in the placebo group from three months onward. Serum phosphate concentrations in the zoledronic acid groups had decreased by 0.06 to 0.12 mmol per liter at one month and generally remained about 0.05 mmol per liter below those in the placebo group throughout the study period, although they did not differ significantly from those in the placebo group at one year. Intact parathyroid hormone was measured in serum at base line and 12 months. There were no significant differences among the groups at the 12-month follow-up, although the mean value was about 30 percent higher than the base-line value in the women in the group receiving four doses of 1 mg of zole-

dronic acid, possibly because sampling was performed only three months after the last dose had been administered in this group.

The rates of adverse events were similar in all the active-treatment groups (Table 2). However, treatment-related adverse events were significantly more common in the zoledronic acid groups than in the placebo group (rates of 45 to 67 percent vs. 27 percent; data not shown). In the zoledronic acid groups, most adverse events were instances of musculoskeletal pain, nausea, or fever, most of which were rated as mild. Most occurred the first time the drug was administered. Five women withdrew from the study because of drug-related adverse events, all of which were reactions after the first infusion of zoledronic acid. These withdrawals were not dose-related; two occurred in women who were receiving the lowest dose and two in women receiving the highest dose. There was no evidence of adverse effects on renal function with any of these regimens. Overall, the proportions of women who withdrew from the study because of adverse events were similar in all groups. Symptoms at the infusion site were uncommon in all groups (e.g., reported in no patients receiving a single 4-mg dose of zoledronic acid and in two patients receiving placebo). Iritis did not develop in any patients, and the occurrence of any eye disorder was uncommon (e.g., reported in two patients receiving a single 4-mg dose of zoledronic acid and in nine patients receiving placebo).

DISCUSSION

Intermittent intravenous administration of the potent bisphosphonate zoledronic acid results in changes in biochemical markers of bone turnover and in bone mineral density that are similar to those observed with daily oral bisphosphonate therapy. Thus, the reductions in markers at one year in the present study are similar to those seen with 5 mg of risedronate per day,[12] 2.5 to 5 mg of ibandronate per day,[13] and 10 mg of alendronate per day.[14-16] Zoledronic acid increases spinal bone mineral density at 12 months to 5 percent above values found in patients receiving placebo — an increase similar to that achieved with a daily 10-mg dose of alendronate (5 percent),[17] a daily 5-mg dose of risedronate (3 percent),[12] or a daily 150-mg dose of pamidronate (5 percent).[18] Intravenous zoledronic acid also produced results similar to those of the oral regimens at the femoral neck (alendronate, 3 percent increase in bone density; risedronate, 2 percent; pamidronate, 3 percent) and in the total body (alendronate, 1.5 percent increase; pamidronate, 1 percent).

Our study assessed longer intervals between doses than have been assessed by previous studies of intermittent bisphosphonate therapy. Etidronate has been used for many years in two-week oral courses administered at three-month intervals.[19,20] There is also evidence that intravenous pamidronate[3] or ibandronate,[4] given every three months, has beneficial effects on bone density in women with postmenopausal osteoporosis. The disappointing data on fractures from a recent study of intermittent ibandronate therapy (1 mg intravenously every three months)[21] has been interpreted as indicating that a dosing interval of three months is too long. However, this ibandronate regimen did not stably suppress markers of bone resorption; a substantial maximal suppression of C-telopeptide excretion (by 50 percent) was rapidly offset, so that the level before the next dose was only 10 to 20 percent below that in the placebo group.[4] As a result, the changes in bone density (increases of 2.9 percent

TABLE 2. ADVERSE EVENTS.*

VARIABLE	ZOLEDRONIC ACID GROUPS					PLACEBO GROUP (N=59)
	4×0.25 mg (N=60)	4×0.5 mg (N=58)	4×1 mg (N=53)	2×2 mg (N=61)	1×4 mg (N=60)	
Adverse events — no.	236	236	255	271	269	210
Women with an adverse event — no. (%)						
Any	52 (87)	50 (86)	50 (94)	56 (92)	54 (90)	45 (76)
Myalgia	12 (20)	6 (10)	7 (13)	10 (16)	6 (10)	1 (2)
Pyrexia	6 (10)	5 (9)	7 (13)	12 (20)	9 (15)	2 (3)
Arthralgia	9 (15)	8 (14)	9 (17)	15 (25)	5 (8)	9 (15)
Influenza-like illness	1 (2)	4 (7)	2 (4)	10 (16)	9 (15)	4 (7)
Nausea	3 (5)	4 (7)	5 (9)	6 (10)	8 (13)	3 (5)
Any leading to withdrawal from study	4 (7)	2 (3)	2 (4)	2 (3)	3 (5)	1 (2)
Any serious	4 (7)	4 (7)	7 (13)	5 (8)	6 (10)	3 (5)

*Data are for all adverse events in each category, not just those classified as drug-related.

in the spine at 12 months[4] or to 4 percent higher than the spinal bone mineral density in the placebo group at 3 years[21]) were smaller than those found in our study; this effect is consistent with the moderate effect of this dose of ibandronate on the incidence of vertebral fracture (a 26 percent reduction at 3 years). Our data indicate that much longer dosing intervals are compatible with efficacy (in terms of both suppression of bone turnover and increase in bone density) if the dose of bisphosphonate is sufficiently large. Indeed, the present study does not establish a maximal dosing interval, since turnover remained suppressed at 12 months. Thus, it is possible that a longer interval between doses could be effective, particularly if larger doses of zoledronic acid were used.

How a single infusion of zoledronic acid suppresses bone turnover for so long remains to be determined. Prolonged suppression is not the result of the persistence of the drug in the circulation, given that by 24 hours after administration, drug levels are less than 1 percent of the postadministration peak and 40 percent of the dose has been excreted in the urine. The balance of the dose is presumably bound to bone and is slowly released back into the circulation, giving rise to a 167-hour terminal half-life in plasma. It has been thought that bisphosphonates are located exclusively on osteoclastic surfaces[22] and that short-term exposure inhibits activity in a single generation of basic multicellular units in bone. The life span of the basic multicellular unit (about three months) then determines the duration of action of the drug. However, evidence suggests that bisphosphonates are also deposited on osteoblastic and resting bone surfaces and remain there for the long term.[23] The existence of such deposits would provide a possible explanation for our results, since residue from a single dose could interfere with the future development of basic multicellular units at these surfaces. It is also possible that direct effects on existing basic multicellular units and osteocytes[24,25] result in reduced formation of succeeding basic multicellular units.

Zoledronic acid was generally well tolerated, and the rate of retention of subjects in the study was high. The adverse events that were more common in women receiving zoledronic acid are those that have occurred previously in patients receiving intravenous aminobisphosphonates and are transient. Infrequent doses may increase tolerance of these side effects.

The inclusion of a placebo group in this study permits quantification of the size of the therapeutic effect and facilitates comparison of the present data with those from other studies. We believe this use of a placebo is ethical, since the bone density used as a criterion for entry (a T score of less than −2) is higher than that required at the participating centers for a diagnosis of osteoporosis and would certainly not be considered to be a threshold for therapeutic intervention at these centers. Thus, the study was conducted in a low-risk population — a characterization supported by the fact that no spinal fractures occurred during the study period. Only one sixth of these low-risk subjects received placebo, and they received it for a maximum of 12 months, after which all women received active therapy.

Osteoporosis has been regarded as requiring daily therapy, and maintaining compliance with daily regimens for a predominantly asymptomatic condition has been a major problem.[26,27] Administration of treatment at intervals of 6 to 12 months or more is likely to be much more acceptable to patients and could reduce costs. A greater proportion of the at-risk population might take advantage of prophylaxis against osteoporosis if an intermittent regimen were used, and the rate of fractures might therefore decrease. However, studies that demonstrate an effect on the rate of fractures are needed before any recommendation can be made.

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(54) **NOVEL ORAL FORMS OF A PHOSPHONIC ACID DERIVATIVE**

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(57) **ABSTRACT**

Novel solution complexes of zoledronic acid are described which give rise to improved properties of zoledronic acid. The invention includes aqueous solution and molecular complexes of zoledronic acid with and optical isomers of asparagine, histidine, arginine and proline as well as pharmaceutical complexes containing them and methods of treatment using them.

NOVEL ORAL FORMS OF A PHOSPHONIC ACID DERIVATIVE

CROSS REFERENCE TO RELATED APPLICATION

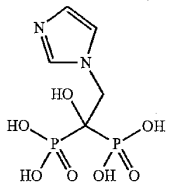
[0001] This application claims priority to PCT International Application No. PCT/US2010/043916, filed Jul. 30, 2010, and U.S. Application No. 61/230,234, filed Jul. 31, 2009, which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This disclosure pertains to new molecular complexes of zoledronic acid suitable for drug delivery as well as methods for their preparation and pharmaceutical compositions.

BACKGROUND OF THE INVENTION

[0003] Zoledronic acid is known as (1-hydroxy-2-imidazol-1-yl-1-phosphono-ethyl)phosphonic acid. Zoledronic acid is depicted by the following chemical structure:



Zoledronic acid is a third generation bisphosphonate which far exceeds the previous generations in terms of efficacy and is used predominately for indications of osteoporosis or tumor induced hypercalcemia (TIH). It was originally developed by Novartis and marketed in a monohydrate form under the Zometa® and Reclast® brand names. Zoledronic acid was first approved in 2000 for the treatment of TIH in Canada. It was later approved for use in the US in 2001 for indications of TIH and in 2007 for osteoporosis and Paget's disease. Clinical trials have also been conducted or are on-going exploring the use of zoledronic acid in neoadjuvant or adjuvant cancer therapy, Coleman, et al., British J Cancer 2010; 102(7):1099-1105, Gnant, et al., New England J. Medicine. 2009, 360 (17):679-691 and Davies, et al. J Clinical Oncology, 2010, 28(7s): Abstract 8021. Zoledronic acid is administered as an intravenous (IV) dose of 4 mg over 15 minutes for TIH and 5 mg over 15 minutes for osteoporosis.

[0004] Zoledronic acid is sparingly soluble in water and 0.1 N HCl solution but is freely soluble in 0.1 N NaOH. Zoledronic acid is practically insoluble in many organic solvents.

[0005] Various efforts have been taken to generate novel oral formulations of zoledronic acid through crystallization and metal salt formation to improve its aqueous solubility, permeability, and subsequent oral bioavailability. A crystalline trihydrate was disclosed in U.S. Patent application 2006/0178439 A1 and world patent application WO2007/032808. Seven hydrated forms, an amorphous form, three monosodium salts, and eleven disodium salts with varying degrees of hydration of zoledronic acid were also disclosed in the world patent application WO2005/005447 A2. Zoledronate metal salts including Na^+, Mg^{2+}, Zn^{2+} were reported in the monthly issued joumal Drugs of the Future (Sorbera et al, 25(3), *Drugs of the Future*, (2000)). Zoledronate, zoledronic, or zoledronic salt represents the ionic form of zoledronic acid. A recently filed patent application (WO2008/064849 A1) from Novartis disclosed additional metal salts including two Ca^{2+} salts, two Zn^{2+} salts, one Mg^{2+} salt, as well as a mono and trihydrate, an amorphous form, and an anhydrous form.

[0006] The low oral bioavailability of zoledronic acid, which is <1% of the oral dose, can be attributed to poor permeability in the gastrointestinal (GI) tract. It was also noted that insoluble metal complexes were formed in the upper intestines, most commonly with calcium. Zoledronic acid has also been shown to cause severe GI irritation both in the stomach and in the intestines. In some cases the irritation was so severe that medical treatment was required. Recent activity concerning the development of oral formulations has led to the use of medium chain fatty acids to enhance the drug's low permeability as disclosed in the US 2007/0134319 A1 and US 2007/0196464 patent applications. Modified amino acid carriers, but not pure proteinogenic amino acids, have also been employed to improve the absorption of the drug as shown in the WO 2007/093226 A1 application.

[0007] In general, sparingly water soluble, provides substantial challenges for drug development of parenteral formulations due to the amount of solvent needed to dissolve the drug which could render it more suitable for infusion. Typically, the greater the volume needed to be administered parenterally to a patient, the longer the infusion time, the higher the likelihood of a vehicle-related adverse effect, the more expensive the product, and the less likelihood that the formulation will be found acceptable by the patient. By improving the aqueous solubility of the drug the volume of solvent needed for reconstitution can therefore be dramatically reduced rendering it suitable for injection rather than infusion.

[0008] Due to the fact that zoledronic acid is only available as a parenteral dosage form (infusion over at least 15 minutes) there is a clear need to develop novel forms of zoledronic acid that can be included in an oral dosage form particularly as the use of orally administered drugs are becoming more wide spread in many therapeutic areas including the treatment of cancer. The upward trend in the use of oral drugs will continue especially in light of the goal to decrease the overall cost of healthcare. Thus, there is an opportunity to create oral dosage forms of IV drugs only where oral dosage forms do not yet exist due to their poor aqueous solubility and/or poor permeability providing a clear clinical benefit for patients. In addition, opportunity is also provided to improve the solubility of sparingly water soluble drugs by creating molecular complexes of such drugs with standard (proteinogenic) amino acids that can subsequently be incorporated in dosage forms for a variety of drug delivery systems.

[0009] The development of oral forms of zoledronic acid to enhance the aqueous solubility or permeability has thus far been problematic. However, by using the novel approach of generating molecular complexes of zoledronic acid with standard amino acids there is an opportunity provided to improve the solubility and/or permeability resulting in a new dosage form suitable administration to humans.

SUMMARY OF THE INVENTION

[0010] The present disclosure is directed towards generating new molecular complexes of zoledronic acid that have the therapeutic efficacy of zoledronic acid but also improved

aqueous solubility, rate of dissolution, and improved bioavailability. One aspect of the present disclosure relates to novel molecular complexes of zoledronic acid. In addition, the disclosure further includes methods for the preparation of such complexes. The disclosure further includes compositions of molecular complexes of zoledronic acid suitable for incorporation in a pharmaceutical dosage form. Specific molecular complexes pertaining to the disclosure include, but are not limited to, complexes of zoledronic acid with nicotinamide, adenine, glycine, and optical isomers of asparagine, histidine, argenine, and proline; D or L-asparagine, DL-asparagine, D or L-histidine, DL-histidine, D or L-arginine, DL-arginine, D or L-proline and DL-proline. Variants of the disclosed zoledronic acid forms in the text, including those described by the examples, will be readily apparent to the person of ordinary skill in the art having the present disclosure, and such variants are considered to be a part of the current invention.

[0011] The foregoing and other features and advantages of the disclosed technology will become more apparent from the following detailed description. Such description is meant to be illustrative, and not limiting, of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0012] In general, the active pharmaceutical ingredient (API) in pharmaceutical compositions can be prepared in a variety of different forms. Such compounds can be prepared so as to have a variety of different chemical forms including chemical derivatives, solvates, hydrates, cocrystal salts, etc. The API can also have different physical forms. For example, they may be amorphous or they may have different crystalline polymorphs or may exist in different solvated or hydrated states. The discovery of new forms of an API may provide the opportunity to improve the pharmacokinetic performance of a pharmaceutical product. Additionally, pharmaceutical cocrystallization can expand the array of resources available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics.

[0013] The physical form of the API has been shown to have a substantial impact upon its physicochemical properties. For example, crystalline polymorphs typically have different aqueous solubility from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. In addition to water solubility, pharmaceutical polymorphs can also differ in properties such as rate of dissolution, shelf-life, bioavailability, morphology, vapor pressure, density, color, and compressibility. Accordingly, it is desirable to enhance the properties of an API by forming molecular complexes with respect to aqueous solubility, rate of dissolution, bioavailability, Cmax, Tmax, physicochemical stability, down-stream processibility (e.g. flowability compressibility, degree of brittleness, particle size manipulation), crystallization of amorphous compounds, decrease in polymorphic form diversity, toxicity, taste, production costs, and manufacturing methods.

[0014] During the development of drugs for oral delivery, it is frequently advantageous to have novel forms of such drug materials that possess improved properties, including increased aqueous solubility and stability. It is also desirable in general to increase the dissolution rate of such solid forms, and potentially increase their bioavailability. This also applies to the development of novel forms of zoledronic acid which, when administered orally to a subject could achieve greater or similar bioavailabilities and pharmacokinetic (PK) profiles when compared to an IV or other formulations on a dose-for-dose basis.

[0015] Novel solution complexes of zoledronic acid in the present invention could give rise to improved properties of zoledronic acid. For example, a new form of zoledronic acid is particularly advantageous if it can improve the aqueous solubility and subsequent bioavailability of orally delivered zoledronic acid. A number of novel zoledronic acid forms have been synthesized, characterized, and disclosed herein. The aqueous solubility of zoledronic acid is low but has been dramatically increased in this invention up to greater than 350 mg/ml through creating new molecular complexes with cocrystal formers including such as nicotinamide, amino acids, and in particular with adenine, glycine, L-asparagine, DL-asparagine, L-histidine, DL-histidine, L-arginine, DL-arginine, L-proline, DL-proline. The techniques and approaches set forth in the present disclosure can further be used by the person of ordinary skill in the art to prepare obvious variants thereof, said variants are considered to be part of the inventive disclosure.

[0016] Accordingly, a first aspect of the present invention includes aqueous solution complexes of zoledronic acid with amino acids, including but not limited to adenine, glycine, and optical isomers of asparagine, histidine, argenine and proline. Preferred amino acids include but are not limited to nicotinamide, adenine, glycine, L-asparagine, DL-asparagine, L-histidine, DL-histidine, L-arginine, DL-arginine, L-proline, and DL-proline suitable for coformulation in an oral dosage form, as a solution, suspension, or a solution in capsules ether incorporated in a gel structure or polymer matrix. These pharmaceutical formulations contain a therapeutically effective amount of at least one solution complex of zoledronic acid according to the invention and at least one pharmaceutically acceptable carrier, (also known in the art as a pharmaceutically acceptable excipient). The novel molecular complexes of zoledronic acid are therapeutically useful for the treatment and/or prevention of disease states associated with osteoporosis, tumor induced hypercalcemia (TIH), or Paget's disease as discussed above. Accordingly, the invention also relates to methods of treatment using novel molecular complexes of zoledronic acid of the invention or a pharmaceutical formulation containing them. The pharmaceutical formulations generally contain about 1% to about 99% by weight of at least one novel molecular complex of zoledronic acid of the invention and 99% to 1% by weight of a suitable pharmaceutical excipient.

[0017] Another aspect of the invention includes improving the aqueous solubility of zoledronic acid to greater than 350 mg/ml, through creating new molecular complexes with L- and DL-histidine.

[0018] Another aspect of the invention includes improving the aqueous solubility of zoledronic acid to greater than 235 mg/ml, through creating new molecular complexes with L- and DL-arginine.

[0019] Another aspect of the invention includes improving the aqueous solubility of zoledronic acid to greater than 50 mg/ml, through creating new molecular complexes with L- and DL-asparagine.

[0020] Another aspect of the invention where the solution complexes of zoledronic acid with amino acids. Solution complexes of zoledronic acid and optical isomers of asparagine, histidine, arginine and proline; L-asparagine, DL-as-

paragine, L-histidine, DL-histidine, L-arginine, DL-arginine, L-proline, and DL-proline were physically stable and did not form any suspension or create precipitates when examined by the naked eye after being left standing at room temperature on the bench in screw cap vials for one year.

[0021] Another aspect of the invention provides complexes of zoledronic acid and optical isomers of asparagine, histidine, arginine and proline; L-asparagine, DL-asparagine, L-lysine, DL-lysine, nicotinamide, adenine, glycine, L-histidine, DL-histidine, L-arginine, DL-arginine, L-proline, and DL-proline suitable for a pharmaceutical formulation than can be delivered parenterally to the human body.

[0022] Another aspect of the invention provides a method for increasing the aqueous solubility of a bisphosphonic acid or bisphosphonates by dissolving a bisphosphonic acid or bisphosphonate in an aqueous solvent in the presence of an amino acid such as those discussed above. The bisphosphonic acid may be, for example, zoledronic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, residronic acid ibandronic acid or other bisphosphonic acids known in the art.

EXAMPLES

[0023] The following examples illustrate the invention without intending to limit the scope of the invention.

[0024] Zoledronic acid as a starting material used in all experiments in this disclosure was supplied by Farmkemi Limited (Wuhan Pharma Chemical Co.), China with purity of ca. 90% and was purified further via recrystallization from hot water. All other pure chemicals (Analytical Grade) were supplied by Sigma-Aldrich and used without further purification.

Example 1

Preparation of a Solution of Zoledronic Acid:L-Histidine

[0025] 7.8 mg of zoledronic acid and 9.5 mg of L-histidine were mixture and dissolved in 0.05 ml water. The solution containing the complex was stored in a screw cap vial.

Example 2

Preparation of a Solution of Zoledronic:DL-Histidine Complex

[0026] 17.8 mg of zoledronic acid and 9.5 mg of DL-histidine were mixed and dissolved in 0.05 ml water. The solution containing the complex was stored in a screw cap vial for subsequent analysis and use.

Example 3

Preparation of a Solution of Zoledronic:L-Arginine Complex

[0027] 5.6 mg of zoledronic acid and 21.4 mg of L-arginine were mixed and dissolved in 0.15 ml water. The solution containing the complex was stored in a screw cap vial for subsequent analysis and use.

Example 4

Preparation of a Solution of Zoledronic:DL-Arginine Complex

[0028] 35.6 mg of zoledronic acid and 21.4 mg of DL-arginine were mixed and dissolved in 0.15 ml water. The solution containing the complex was stored in a screw cap vial for subsequent analysis and use.

Example 5

Preparation of a Solution of Zoledronic:L-Asparagine Complex

[0029] 50 mg of zoledronic acid and 23 mg of L-asparagine were dissolved in 1 ml water. The solution containing the complex was stored in a screw cap vial for subsequent analysis and use.

Example 6

Preparation of a Solution of Zoledronic:DL-Asparagine Complex

[0030] 50 mg of zoledronic acid and 26 mg of DL-asparagine monohydrate were dissolved in 1 ml water. The solution containing the complex was stored in a screw cap vial for subsequent analysis and use.

Example 7

Preparation of a Solution of Zoledronic:L-Proline Complex

[0031] Approximately 11 mg of zoledronic acid and approximately 9 mg of L-proline were mixed and dissolved in 1 ml water. The solution containing the complex was stored in a screw cap vial for subsequent analysis and use.

Example 8

Preparation of a Solution of Zoledronic:DL-Proline Complex

[0032] Approximately 11 mg of zoledronic acid and approximately 9 mg of DL-proline were mixed and dissolved in 1 ml water. The solution containing the complex was stored in a screw cap vial for subsequent analysis and use.

1-17. (canceled)

18. A solution complex of a bisphosphonic acid or bisphosphonate comprising a bisphosphonic acid or bisphosphonate with a coformer to improve the aqueous solubility of the bisphosphonic acid or bisphosphonate.

19. A solution complex of claim **18** where the bisphosphonic acid is zoledronic acid.

20. A solution complex of claim **18** wherein the coformer is an amino acid.

21. A solution complex of claim **19** wherein the coformer is an amino acid is selected from the group consisting of glycine, adenine, asparagine, histidine, arginine and proline.

22. A solution complex of claim **20**, wherein the amino acid is selected from the group consisting of L-asparagine, DL-asparagine, L-histidine, DL-histidine, L-arginine, DL-arginine, L-proline, and DL-proline.

23. A solution complex of claim **21**, wherein the complex is:

- a solution complex of zoledronic acid and L-histidine having an aqueous solubility of zoledronic acid to greater than 350 mg/ml,
- a solution complex of zoledronic acid and DL-histidine having an aqueous solubility of zoledronic acid to greater than 350 mg/ml,
- a solution complex of zoledronic acid and L-arginine having an aqueous solubility of zoledronic acid to greater than 235 mg/ml,

a solution complex of zoledronic acid and DL-arginine having an aqueous solubility of zoledronic acid to greater than 235 mg/ml,

a solution complex of zoledronic acid and L-asparagine having an aqueous solubility of zoledronic acid to greater than 50 mg/ml, or

a solution complex of zoledronic acid and DL-asparagine having an aqueous solubility of zoledronic acid to greater than 50 mg/ml.

24. A molecular complex of zoledronic acid comprising zoledronic acid and an amino acid selected from the group consisting of asparagine, histidine, arginine and proline.

25. A molecular complex of claim **24**, wherein the amino acid is selected from the group consisting of L-asparagine, DL-asparagine, L-histidine, DL-histidine, L-arginine, DL-arginine, L-proline, and DL-proline.

26. A pharmaceutical composition comprising a complex of claim **18** and a pharmaceutically acceptable carrier.

27. A pharmaceutical composition of claim **24**, wherein the composition is a parenteral composition.

28. A pharmaceutical composition of claim **24**, wherein the composition is an oral dosage form.

29. A method for the treatment and/or prevention of disease states associated with osteoporosis, tumor induced hypercalcemia (TIH), or Paget's disease comprising the step of administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim **26**.

30. A method for the treatment and/or prevention of disease states associated with osteoporosis, tumor induced hypercalcemia (TIH), or Paget's disease, adjuvant or neoadjuvant cancer therapies comprising the step of administering to a patient in need thereof a therapeutically effective amount of a complex according to claim **18**.

31. A method for increasing the aqueous solubility of zoledronic acid comprising the step of:

dissolving zoledronic acid in an aqueous solvent in the presence of an amino acid.

32. A method of claim **31**, wherein the amino acid is selected from the group consisting of glycine, adenine, asparagine, histidine, arginine and proline.

33. A method of claim **32**, wherein the amino acid is selected from the group consisting of L-asparagine, DL-asparagine, L-histidine, DL-histidine, L-arginine, DL-arginine, L-proline, and DL-proline and wherein the amino acid forms a solution complex with the zoledronic acid.

34. A method of claim **31**, wherein the aqueous solvent is water.

35. A method for increasing the aqueous solubility of a bisphosphonic acid or bisphosphonate comprising the step of:

dissolving a bisphosphonic acid or bisphosphonate in an aqueous solvent in the presence of an amino acid.

36. A pharmaceutical composition comprising a complex of claim **23** and a pharmaceutically acceptable carrier.

37. A method for the treatment and/or prevention of disease states associated with osteoporosis, tumor induced hypercalcemia (TIH), or Paget's disease, adjuvant or neoadjuvant cancer therapies comprising the step of administering to a patient in need thereof a therapeutically effective amount of a complex according to claim **23**.

38. A method of claim **32**, wherein the aqueous solvent is water.

* * * * *

18. Johann D. Ringe, *Development of Clinical Utility of Zoledronic Acid and Patient Considerations in the Treatment of Osteoporosis*, 4 J. PATIENT PREFERENCE & ADHERENCE 231 (2010) ("Ringe").

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REVIEW

Development of clinical utility of zoledronic acid and patient considerations in the treatment of osteoporosis

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Abstract: Osteoporosis is a major health concern, which results in the increased risk of fractures. There is a high risk for the first or consecutive fractures leading to considerable morbidity and debilitating consequences if osteoporosis is untreated. Currently, bisphosphonates are the mainstay of treatment for osteoporosis though long-term persistence and adherence to bisphosphonates, especially those taken orally, remain low. This medication noncompliance has serious consequences on osteoporotic patients as it is associated with a significantly higher fracture risk. Intravenous (IV) zoledronic acid (ZOL), developed to increase compliance by overcoming the frequent and burdensome dosing requirements of oral bisphosphonates, is the first and the only once-yearly bisphosphonate globally approved for use in the treatment of up to 6 indications of osteoporosis. Several clinical studies have documented that a single infusion of IV ZOL resulted in decreased bone turnover and improved bone density for at least 12 months post infusion. This article traces the development of ZOL's clinical utility and evaluates its patient preference by collating data from all major clinical trials, studying the efficacy and safety of ZOL in the treatment of osteoporosis and other benign bone disorders.

Keywords: bisphosphonates, patient preference, efficacy, safety, Paget's disease

Introduction

Osteoporosis

Osteoporosis, a chronic disease that affects an estimated 200 million people worldwide, is characterized by decreased bone mass, as well as weakened bones, with an increased risk of fractures. Often diagnosed late and subsequent to a fracture, it leads to significant morbidity and mortality.[1,2] Osteoporosis can be classified into 2 forms: primary and secondary. Primary osteoporosis results from cumulative bone loss as people age and go through changes in their sex hormones. Secondary osteoporosis results from a variety of medical conditions, diseases, or use of certain medications that adversely affect skeletal health.[3] The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) with a T-score of ≥ 2.5 standard deviations below the gender-specific young adult mean (ie, T-score ≤ -2.5), as measured by dual energy X-ray absorptiometry (DXA).[4] However, total fracture risk reflects both BMD-dependent and BMD-independent risk factors, and the new WHO absolute fracture risk algorithm takes into account BMD, age, smoking, alcohol intake, personal or parental history of fracture, body mass index, corticosteroid use, and rheumatoid arthritis to predict individual patients 10-year probability of sustaining osteoporotic fractures.[5,6]

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Bisphosphonates

Bisphosphonates, which inhibit osteoclastic activity, are the most commonly used medications for the treatment of osteoporosis.[7,8] Several formulations of bisphosphonates are currently available. Alendronate (ALN), risedronate (RIS), and ibandronate are oral bisphosphonates that have been widely used for the treatment of postmenopausal osteoporosis (PMO). These bisphosphonates were originally approved as a once-daily formulation. However, low adherence to daily therapy coupled with recognition of the long skeletal retention of these bisphosphonates led to the evolution of less-frequently-dosed but bioequivalent formulations.[9,10] Current bisphosphonate regimens include once-weekly ALN or RIS, once- or twice-monthly ibandronate and RIS, quarterly intravenous (IV) ibandronate, and once-yearly IV ZOL.[8]

Zoledronic acid

Zoledronic acid (ZOL) (Aclasta®/Reclast®; Novartis Pharma AG, Basel, Switzerland), a third-generation bisphosphonate available as an IV formulation (5 mg given once-yearly, recommended with daily supplementation of 500–1,200 mg elemental calcium plus 400–800 U of vitamin D), is approved globally for up to 6 indications.

i. Treatment of PMO in women to reduce the incidence of hip, vertebral, and nonvertebral fractures and to increase BMD
ii. Prevention of clinical fractures after hip fracture in men and women
iii. Treatment of osteoporosis in men
iv. Treatment and prevention of glucocorticoid-induced osteoporosis (GIO)
v. Prevention of PMO (in the United States)
vi. Treatment of Paget's disease of bone

In May 2009, ZOL was approved by the US Food and Drug Administration for use, once every 2 years to prevent osteoporosis in postmenopausal women with osteopenia in the United States.[11] ZOL (Zometa®; Novartis Pharma AG, Basel, Switzerland) is also approved for the treatment of hypercalcemia of malignancy (HCM) and advanced malignancies involving bone.[12]

This article traces the development of ZOL's clinical utility by collating data from all major clinical trials, studying the efficacy and safety of ZOL in the treatment of primary and secondary osteoporosis and other benign bone disorders. This article also reviews the patient preferences for different osteoporosis medications with a special focus on ZOL. The pharmacology and mechanism of action of ZOL are not reviewed in this article as both have been extensively reviewed previously.[13–24]

Studies evaluating the therapeutic utility of ZOL

Clinical studies

Treatment of PMO

The clinical utility of ZOL in the treatment of PMO was evaluated in 3 randomized and 2 open-label trials.

Early studies of ZOL

The potential of IV ZOL in the treatment of PMO was initially assessed by Reid et al[25] in a placebo-controlled, dose-ranging, 1-year study. This phase II study randomized 351 postmenopausal women aged 45–80 years to receive placebo or one of the following 5 ZOL regimens: 0.25 mg, 0.5 mg, or 1 mg at 3-month intervals; a single 4-mg dose; or 2 doses of 2 mg administered 6 months apart. Mean lumbar spine and femoral neck BMD was, on average, 4.3%–5.1% ($P < 0.001$) and 3.1%–3.5% ($P < 0.001$), respectively, higher in all the ZOL treatment groups vs the placebo group at the end of the study period. Significant decreases in bone turn over markers (BTMs) were also observed at the end of the study (49%–52% decrease in serum type I collagen C telopeptide [CTx] with ZOL vs 8% decrease in CTx with placebo; $P < 0.01$). These results indicated that ZOL infusions given even at intervals of up to 1 year produce similar effects on bone turnover and bone density as those achieved with daily oral dosing with bisphosphonates of proven efficacy against fractures.

The above 1-year trial had 2 consecutive, open-label, 2-year extension phases. The objective of these extension studies was to assess the long-term efficacy and safety of prolonged use of ZOL for a further 4 years. A total of 119 women who completed the 1-year core study entered the next phase. Majority of the patients who entered the first extension study received 1 mg ZOL every 3 months (total annual dose, 4 mg), and others with 0.5 mg ZOL every 3 months (total annual dose, 2 mg). Patients who entered the second extension study received either calcium only or ZOL 4 mg. All patients entering the active treatment arm of the second extension had previously received ZOL 4 mg per year during core and extension 1 studies. Patients received treatment for 2, 3, or 5 years. Study results showed that BMD increased in all 3 subgroups by the end of the 5-year study period in lumbar spine (6.4%–9%), proximal femur (4.9%–5.5%), distal radius (2.2%–3%), and total body

(3.6%–5%), whereas BTMs decreased. However, there was an insufficient reduction in BTMs and moreover levels of alkaline phosphatase and CTx increased from month 24 onwards in patients treated for up to 5 years.[26]

The long duration of the study allowed trends to be identified regarding the degree of reduction in bone modeling achieved by ZOL and suitability of 4 mg as a total annual dose. The results showed that ZOL 4 mg once-yearly increased BMD and was effective in reducing BTMs over 5 years. However, detailed analysis of BTM changes suggested that the 4-mg dose caused insufficient reduction in remodeling activity and may not suffice to maintain the suppression of bone resorption.[26] This upward trend in BTMs, leading to insufficient reduction of bone turnover to keep stable reduction in remodeling activity, was similar to a previous trial in which an IV bisphosphonate (ibandronate) was underdosed.[27] Therefore, the authors concluded that the same mechanism could also play a role in this study and to achieve a more pronounced suppression of bone turnover, a higher IV dose of ZOL might be required.[26]

The health outcomes and reduced incidence with zoledronic acid once yearly-pivotal fracture trial

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) was a large, international, multicenter, randomized, double-blind, placebo-controlled trial of 3 years duration in which 7,765 patients with PMO were randomized to receive either a 15-minute IV infusion of ZOL (5 mg) or placebo.[28] This study showed that ZOL significantly reduced morphometric vertebral, clinical vertebral, hip, and nonvertebral fractures by 70%, 77%, 41%, and 25%, respectively (Table 1). The 3-year risk reduction (70%) in the incidence of the vertebral fractures with ZOL exceeded the reduction previously observed for oral bisphosphonates and other therapeutic interventions.[28–35] Assessment of bone structure and microarchitecture was also performed in a subgroup of patients. Overall, the findings from the study indicated preservation of trabecular bone structure in the ZOL group at 3 years.[36]

First head-to-head study of ZOL vs ALN

The first head-to-head study involving ZOL and ALN was conducted by McClung et al.[37] This noninferiority 12-month trial included postmenopausal women (age, 45–79 years) treated with ALN for at least 1 year prior to randomization. A total of 225 patients were randomized (1:1) to receive either a single IV infusion of ZOL 5 mg plus oral placebo or a weekly 70 mg ALN plus a single IV infusion of placebo. The study showed that single-infusion ZOL maintained BMD for 12 months, following the switch from oral ALN in women with osteoporosis (Table 1). At the end of the study period, the ZOL group experienced a 0.12% (standard error [SE] = 0.273) increase from baseline in lumbar spine BMD compared with the ALN group that had a 0.828% (standard error [SE] = 0.288) increase from baseline (95% confidence interval [CI], −1.491 to 0.075). The authors concluded that patients can be switched from oral ALN to ZOL infusion with maintenance of therapeutic effect for at least 12 months.

Effect on bone resorption markers

Saag et al[38] investigated the onset of action and effects on bone resorption markers of a single-infusion ZOL vs weekly oral ALN. The 24-week trial randomized (1:1) 128 postmenopausal women aged 45–79 years to receive either a single IV infusion of ZOL 5 mg plus oral placebo or a weekly oral 70 mg ALN plus a single IV infusion of placebo. The primary end point was the change in N-telopeptide of type I collagen (NTx) at week 1 from baseline. A significantly lower mean urine NTx value was seen in the ZOL group compared with the ALN group at week 1 (15.2 nmol BCE [bone collagen equivalents]/mmol creatinine and 35.5 nmol BCE/mmol creatinine, respectively; $P < 0.0001$). Overall, ZOL caused a greater and more rapid reduction in BTMs compared with weekly ALN (Table 1). Moreover, results from this study also showed that the majority of patients were more satisfied with the annual ZOL infusion (59.8%), were more willing to take it for a long period of time (68.0%), and felt that the annual infusion was more convenient than once-weekly therapy (66.4%).

Prevention of PMO

ZOL is also approved for the prevention of PMO. The recommended regimen is a 5-mg IV infusion once every 2 years over no less than 15 minutes. Data from a 2-year, randomized, multicenter, double-blind clinical study (n = 581) showed that ZOL significantly increased BMD at lumbar spine and total hip compared with placebo at month 24 for osteopenic women in early and late menopause.[39]

In another 2-year study in a volunteer sample of 50 postmenopausal women with osteopenia treated with

ZOL or placebo,[40] ZOL decreased mean levels of each of 4 BTMs by at least 38% (range, 38%–45%) for the duration of the study ($P < 0.0001$). After 2 years, BMD was higher in the ZOL group than in the placebo group at an average of 5.7% (95% CI, 4.0–7.4) at the lumbar spine, 3.9% (2.2–5.7) at the proximal femur, and 1.7% (0.8–2.5) at the total body ($P < 0.0001$ for each skeletal site). Moreover, between-group differences in BTM and BMD were similar at 12 and 24 months.[40]

Hip fractures

Hip fractures are associated with increased morbidity, functional decline, and death in older adults.[41] Mortality is increased with reported rates of 15%–25% in the year following hip fracture.[41,42] The clinical efficacy of ZOL in patients with a recent, low-trauma hip fracture was investigated in a large, randomized, double-blind, placebo-controlled, multicenter 5-year study known as the HORIZON-Recurrent Fracture Trial (HORIZON-RFT) (n = 2127), which is the only trial ever conducted to study the risk of fracture incidence in patients who have already sustained a hip fracture, in which the median duration of follow-up was 1.9 years.[43] Patients included in the HORIZON-RFT study were men or women aged ≥50 years, who had a low-trauma hip fracture surgically repaired within the previous 90 days.[43] Patients were randomized (1:1) to receive IV infusions of ZOL 5 mg or placebo once-yearly. The primary measure of efficacy was new clinical fracture (excluding toe, finger, and facial bone fractures, and those occurring in abnormal bone) over the duration of the study. Secondary efficacy measures included new hip fracture, nonvertebral fracture, and vertebral fracture and the change in BMD in the nonfractured hip (measured annually with DXA); and prespecified safety end points, including death.

Data from the study showed that once-yearly ZOL 5 mg IV was effective in reducing the risk of fractures developing in patients who recently had a low-trauma hip fracture (Table 1).[43] ZOL significantly ($P = 0.001$) reduced the risk of any new clinical fracture by 35% relative to placebo, with 8.6% of ZOL and 13.9% of placebo recipients experiencing such fractures at 2 years. ZOL also reduced the risk of most secondary end point fractures. After 2 years of treatment, the risk of nonvertebral (7.6% ZOL vs 10.7% placebo recipients) and vertebral fractures (1.7% ZOL vs 3.8% placebo recipients) were also significantly reduced ($P < 0.05$) by 27% and 46% with ZOL relative to placebo, although the treatment groups did not significantly differ in terms of hip fracture risk (2.0% ZOL vs 3.5% placebo recipients).[43]

BMD at both the total hip and the femoral neck improved significantly ($P < 0.001$) with ZOL relative to placebo after 12, 24, and 36 months of treatment. Moreover, clinically relevant losses of BMD (based on prespecified measures of bone safety) were observed in 2.4% ZOL vs 11.9% placebo recipients.[43]

A significant reduction in all-cause mortality in patients treated with ZOL was also observed: 9.6% patients in the ZOL group and 13.3% patients in the placebo group died, a 28% reduction in deaths from any cause in the ZOL group ($P = 0.01$).[43]

Post hoc analysis of the HORIZON-RFT study to examine whether the timing of the first infusion had any relationship to fracture and mortality benefit showed that patients infused 2–12 weeks after hip fracture, showed significant reduction in clinical vertebral fractures, nonvertebral fractures, and hip fractures, as well as all-cause mortality (first trial ever to show a significant reduction in mortality after using an antiosteoporosis medication).[44]

Male osteoporosis

Male osteoporosis is an important public health issue and remains largely undertreated in general practice. Moreover, even though men experience fewer osteoporotic fractures than women, they have higher mortality after fracture.[45] Two analyses provide evidence for the efficacy of ZOL in the treatment of osteoporosis in men, and based on these studies, ZOL was approved in the European Union (EU).

Data analyzed from the male subpopulation of the 3-year HORIZON-RFT trial[43] showed that ZOL was significantly more effective than placebo in increasing total hip BMD in men at 12, 24, and 36 months and in increasing femoral neck BMD at 24 and 36 months.[46] Though the study was not powered to show a reduction in clinical fractures in men, the 2-year cumulative clinical fracture event rates were 7.45% and 8.7% for ZOL and placebo, respectively (Kaplan–Meier estimates).[46] Moreover, the study showed that men experienced greater absolute mortality benefit than women (6.4% vs 2.8%), although they had a similar reduction in the risk of death.[47]

A 2-year study randomizing 302 hypogonadal men to annual ZOL 5 mg IV or weekly oral ALN 70 mg demonstrated that the ZOL group had 6.1% increase in lumbar spine BMD compared with the ALN group that had 6.2% increase at 24 months. At month 12 relative to baseline ZOL and ALN reduced serum CTx by 52% and 57%, urine NTx by 54% and 59%, serum N-terminal propeptide of type I collagen (P1NP)

by 51% and 56%, serum bone-specific alkaline phosphatase (BSAP) by 22% and 25%, respectively (Table1). The majority of subjects preferred once-yearly IV infusion of ZOL 5 mg over once-a-week oral 70 mg ALN.[48]

Pediatric osteoporosis

The use of bisphosphonates in children with osteogenesis imperfecta is well established. Most of the reports in children are almost exclusively on IV pamidronate,[49] although successful treatment with the oral bisphosphonates, such as ALN,[50,51] has also been reported.

In a recently published study in children with osteogenesis imperfecta, patients were switched to ZOL (0.04–0.05 mg/kg every 4 months) for a mean of 3.4 years after pamidronate therapy (1 mg/kg per dose every 2 months) for a mean of 3.75 years. Results from the study showed that ZOL appeared to be similarly effective as pamidronate in improving vertebral BMD and in reducing fracture rates implying that ZOL may be considered a potential alternative to pamidronate infusions in this patient group.[52]

Geriatric osteoporosis

Osteoporosis is for the most part a disease of the aged. Intravenous bisphosphonates are an option in the elderly who cannot tolerate or may have difficulty adhering to oral bisphosphonate therapy. Once-yearly infusion of ZOL may significantly improve adherence, especially in a geriatric population. Post hoc analysis of pooled data from HORIZON-PFT[28] and HORIZON-RFT[43] determining the efficacy of ZOL in osteoporotic postmenopausal women aged ≥75 years has shown that once-yearly ZOL treatment over 3 years significantly reduced the risk of any clinical fracture, clinical vertebral and nonvertebral fractures (Table1). These findings provide evidence of the efficacy of once-yearly ZOL 5 mg IV in osteoporosis patients of advanced age.[53]

Glucocorticoid-induced osteoporosis

Persistent use of glucocorticoids is a major cause for secondary osteoporosis, leading to bone loss and increased fracture risk.[54–58] This increased risk is apparent in some patients within 3 months of starting glucocorticoids.[56] Prevention and treatment of GIO has been established with bisphosphonates.[58] Recently once-yearly ZOL 5 mg has been approved for the prevention and treatment of osteoporosis caused by long-term use of glucocorticoids.

The approval for the GIO indication for men and women is based on the study showing that annual ZOL 5 mg IV is more effective in treating bone loss than daily oral RIS in patients with GIO. The study investigated both the prevention and the treatment of GIO in 833 men and women (288 prevention vs 545 treatment subgroups).[59] Over 1 year, ZOL produced significantly greater increases in BMD of the lumbar spine, femoral neck, trochanter, and total hip than RIS. The increase in BMD with ZOL was evident at 6 months, and ZOL was better than RIS at 12 months (Table1).[59]

Thalassemia-induced osteoporosis

Osteoporosis is an important cause of morbidity in beta-thalassemia patients. In a study by Otrock et al,[60] 18 thalassemia patients with osteoporosis were given ZOL 4 mg IV every 3 months over a period of 12 months. Patients on ZOL had a significant increase in their lumbar spine, femoral neck, trochanter, and total hip BMD measurements over the 12-month period. Patients in the control group did not have any significant change in BMD measurements. There was a significant change in the levels of osteocalcin and bone alkaline phosphatase (BAP) and also a significant decrease in the number of painful sites (bone pain) experienced by the patients.[60,61]

In another study, 66 thalassemia patients with osteoporosis were randomized (1:1:1) to receive ZOL 4 mg IV, every 6 or 3 months, or to receive placebo every 3 months, for a period of 1 year. BMD of the lumbar spine, femoral neck, and wrist was determined before and 12 months after treatment. Patients treated with ZOL 4 mg IV every 6 months had no change in BMD; however, there was an increase in BMD with ZOL 4 mg IV given every 3 months. Both regimens of ZOL reduced pain.[62] BMD remained higher than baseline after 24 months of stopping ZOL treatment.[63]

Overall, the data from the above studies suggest that ZOL may be an effective option for the treatment of osteoporosis in thalassemia patients.[60–63]

Localized transient osteoporosis

Localized transient osteoporosis (LTO; bone marrow edema) is an increasingly diagnosed condition characterized by acute onset of disabling bone pain, which typically occurs at a single skeletal site. Although its etiology is unknown, LTO has been linked to pregnancy and prolonged periods of exercise but with absence of previous trauma or surgical history, as in algodystrophy. Current treatment options are limited in number and provide inadequate efficacy except recent positive experience with IV bisphosphonates.

A study by Ringe et al[64] in 8 patients with LTO showed that ZOL was highly effective in reducing pain, measured by visual analog scale (VAS 1–10). Pain scores decreased from 9.4 (at baseline) to 0.4. BMD was restored with an average increase in the lumbar spine of 4.1% after 6 months of treatment and in the affected and unaffected hip area by 9.4% and 3.0%, respectively (difference 6.4%, $P < 0.01$), improving mobility and quality of life (QoL) in patients with LTO of the hip.

Paget's disease

Paget's disease of bone is characterized by a dramatic increase in bone turnover (both formation and resorption) at one or more skeletal sites.[65] The bone pain, skeletal deformity, pathologic fractures, secondary arthritis, neurologic complications, and deafness that may accompany this disease contribute to its substantial morbidity. Bisphosphonate therapy is the most commonly used treatment for Paget's disease.[65]

In 2005, Reid and colleagues[65] published results of a pivotal study comparing ZOL with RIS in patients with Paget's disease. The paper combined 2 identical, double-blinded, randomized controlled trials, comparing ZOL with RIS. In the 6-month trial, patients received either a single IV infusion of ZOL 5 mg (177 patients) or a daily 30 mg RIS for 2 months (172 patients). The primary end point was normalization or a 75% reduction of serum alkaline phosphatase (SAP) levels in 6 months. A pain scale, gait, and QoL measures were assessed as well. At the completion of this study, a greater number of patients treated with ZOL (96%) achieved the primary end point compared to those treated with RIS (74%, $P < 0.001$). Further, ZOL provided patients with a significantly shorter median time to first therapeutic response (64 days ZOL vs 89 days RIS, $P < 0.001$).

In patients with Paget's disease of bone, normalization of SAP correlates with a longer duration of biochemical remission. SAP levels were normalized in more patients in the ZOL-treated group (88.6%) than in the RIS-treated group (57.9%), $P < 0.001$. Bone turnover markers, including serum NTx and serum β-CTx, measuring osteoblast function (bone formation) and urinary α-CTx measuring osteoclast function (bone resorption) were all suppressed into the normal range earlier and more consistently in patients treated with ZOL, $P < 0.001$ (Table 1).

At a median of 190 days following the formal trial, only 0.9% of patients on ZOL showed evidence of recurrent disease activity by biochemical markers compared with 25.6% of patients on RIS, $P < 0.001$. Although the study was designed to demonstrate the noninferiority of ZOL compared to RIS in the treatment of Paget's disease, the authors concluded that "ZOL appeared to be superior in terms of the degree of disease suppression, the rate of onset of effect and (on the basis of preliminary data) the persistence of these effects beyond the six-month trial period." In addition, there was a trend toward improved QoL in patients treated with ZOL.

In a follow-up extension trial of the above study published by Hosking et al,[66] 152 patients who had been treated with ZOL and 115 patients who had been treated with RIS were followed for 18 months to determine the length of remission and durability of bone suppression. A sustained therapeutic response was noted in 98% of those treated with ZOL vs 57% of those treated with RIS (Table 1).

ZOL in oncology

Skeletal complications contribute substantially to the burden of disease in patients with bone metastases from solid tumors and in patients with multiple myeloma. Bone metastases are the most common cause of cancer-related pain and often require palliative therapy. ZOL is widely used as palliative therapy in patients with bone metastases secondary to a wide range of solid tumors, including prostate cancer, lung cancer, and renal cell carcinoma.[67]

ZOL received approval for the treatment of bone metastases secondary to all solid tumor types and bone lesions from multiple myeloma based on the results of 3 large, randomized, phase III clinical trials enrolling more than 3,000 patients.

These trials demonstrated that ZOL (4 mg via 15-minute IV infusion, every 3–4 weeks) effectively reduced the incidence of skeletal complications associated with malignant bone disease for patients with breast cancer, multiple myeloma, prostate cancer, or solid tumors other than breast or prostate cancer.[68–71] The primary efficacy end point in all 3 trials was the proportion of patients who experienced at least 1 skeletal-related event (SRE), defined as a pathologic fracture, spinal cord compression, radiotherapy to bone, or surgery to bone. Change in antineoplastic therapy to palliate bone pain was also included as an SRE only in the trial evaluating patients with prostate cancer. HCM was included as an SRE in the analysis of secondary end points. The results of these 3 international trials demonstrate that ZOL has significant and durable clinical benefit in reducing skeletal complications for patients with malignant bone involvement from multiple myeloma and a variety of solid tumors, including breast, prostate, and lung cancers.[68–71] ZOL is also being studied for the prevention of aromatase inhibitor-associated bone loss in women receiving adjuvant

hormonal therapy for early-stage breast cancer and also for the prevention of bone loss during androgen-deprivation therapy.[72,73]

Safety and tolerability of ZOL in osteoporosis and Paget's disease

Data from several clinical trials have demonstrated that IV ZOL is generally well tolerated in patients with osteoporosis[28,37] and Paget's disease.[65,66] In the present section, clinically significant adverse events (AEs) associated with the use of ZOL in osteoporosis are discussed. Tolerability data of ZOL vs placebo, ALN, and RIS is also evaluated.

Clinically significant AEs associated with ZOL

Acute-phase reactions

The most common AEs observed with ZOL are acute-phase reactions, usually characterized by flu-like symptoms, headache, pyrexia, arthralgia, and myalgia. Most of these symptoms occur within the first 3 days after infusion and tend to resolve within several days after administration (Table 2).[28,74]

Hypocalcemia

The incidence of hypocalcemia (a serum calcium level <2.075 mmol/L) with ZOL has been reported in some studies, although in most cases it was asymptomatic and transient.[28,38,43,65] However, in patients with low normal calcium at onset, it is recommend to start with the regular calcium/vitamin D supplementation before the infusion of ZOL.

Renal function

Evaluation of the renal safety of once-yearly ZOL 5 mg in several studies has shown that administration of ZOL was not associated with any long-term detrimental effects on renal function. Generally, the renal effects were short term, mild, and transient.[28,43,59] A minimal infusion time of ZOL of 15 minutes, however, is mandatory to avoid an impairment of renal function.

Cardiovascular: atrial fibrillation

Individual studies of ZOL have found an increased incidence of atrial fibrillation (AF); however, larger epidemiological studies have found no increased risk of AF in patients receiving bisphosphonate treatment.

The only study in the HORIZON clinical trial program where AF was significantly increased as serious AE (SAE) was the HORIZON-PFT study; AF, as SAE, was found to be more frequent in patients who received ZOL compared with placebo (1.3% ZOL vs 0.5% placebo; $P < 0.001$).[28] Of the 50 events that occurred in patients receiving ZOL, 47 (94%) occurred >30 days after infusion, when ZOL was no longer detectable in systemic circulation. Furthermore, electrocardiograms performed on a subset of 559 patients before and 9–11 days after treatment found no differences between the treatment groups.

In the HORIZON-RFT study, which included an older patient population with more comorbidities compared with other osteoporosis trials, the incidence of serious AF was similar with ZOL and placebo (1.0% ZOL vs 1.2% placebo).[43] When ZOL was compared with RIS in patients with GIO, no serious AF was reported in either of the treatment arms.[59]

Osteonecrosis of the jaw

In patients receiving high cumulative doses of IV bisphosphonates to prevent SRE associated with bone metastases or HCM, cases of osteonecrosis of the jaw (ONJ) have been reported. As most of these patients were also receiving cytotoxic chemotherapy or corticosteroids, it is difficult to determine the true impact of bisphosphonate treatment on risk of ONJ. In patients receiving lower cumulative doses of bisphosphonates for treatment of osteoporosis, very rare cases of ONJ have been reported.

The safety data from the HORIZON-PFT study showed that of the 7,714 patients in the study, there were only 2 cases of possible ONJ: one in a patient receiving ZOL and other in a patient receiving placebo. Both patients experienced delayed healing associated with infection, and both conditions were resolved after antibiotic therapy or debridement. In several other studies with ZOL for the treatment of osteoporosis and Paget's disease, no cases of ONJ were reported.[43,59,66]

Overall, the incidence of ONJ in osteoporotic patients receiving ZOL is very low, and this can be managed with no special treatment beyond routine dental care.[75]

Tolerability

ZOL vs placebo

Data from the HORIZON trials show that ZOL was generally well tolerated, and there was no significant difference between the ZOL and placebo groups in terms of number of patients who had SAEs, or discontinued follow-up due to an AE. In the HORIZON-PFT study, the number of patients with AEs was significantly higher in the ZOL group (95.5% ZOL vs

Table 1 Summary of key efficacy data for ZOL in the treatment of osteoporosis and Paget's disease

Study	No. of patients, N	Study design	Intervention	Key efficacy results
Black et al[28] (HORIZON-PFT)	7,765	3-year, randomized, double-blind, placebo-controlled clinical trial in postmenopausal osteoporosis patients	ZOL 5 mg; placebo	• 70% reduction in morphometric vertebral fractures over 3 years • 41% reduction in hip fractures over 3 years • 25% reduction in nonvertebral fractures over 3 years
Lyles et al[43] (HORIZON-RFT)	2,127	Multicenter, randomized, double-blind, placebo-controlled, parallel-group 5-year trial in patients who had already sustained hip fracture; median follow-up was 1.9 years	ZOL 5 mg; placebo	• 28% reduction in mortality after hip fracture • 35% risk reduction of all new clinical fractures • 46% risk reduction of all new clinical vertebral fractures and 27% risk reduction in new nonvertebral fractures • ZOL improved BMD at total hip and femoral neck • ZOL demonstrated fracture prevention across all patients, even those at highest risk of fracture
McClung et al[37]	225	1-year, double-blind, double-dummy study in postmenopausal osteoporosis patients	ZOL 5 mg; ALN 70 mg	• Lumbar spine BMD remained stable with both treatments at 12 months • 78.7% of patients preferred a once-a-year infusion to weekly oral therapy at the end of study
Saag et al[38]	128	24-week, multicenter, randomized, double-blind, double-dummy, active-controlled trial in postmenopausal osteoporosis patients	ZOL 5 mg; ALN 70 mg	• Significantly greater relative change in urine NTx values at week 1 with ZOL vs ALN • ZOL group had significantly lower mean urine NTx values throughout the 24-week study vs the ALN group • ZOL caused greater and more rapid reduction in BTMs compared with weekly ALN
Reid et al[59] (GIO trial)	833	1-year, multinational, multicenter, randomized, double-blind, double-dummy, stratified, active-controlled clinical trial in the prevention and in the treatment of GIO	ZOL 5 mg; RIS 30 mg	• ZOL demonstrated superior BMD increase at 12 months compared with oral daily RIS in both subpopulations • ZOL significantly decreased levels of β-CTx and PINP compared with oral daily RIS in both the prevention and the treatment subpopulations • 84% of all patients preferred annual IV over daily oral pills
Reid et al[65] (Paget's disease-core studies)	357	2 identical, 6-month, randomized, double-blind, active-controlled trials in patients with Paget's disease	ZOL 5 mg; RIS 30 mg	• 96% of patients achieved therapeutic response[a] with ZOL vs 74% with RIS at 6 months • 88.6% of patients achieved normal alkaline phosphatase with ZOL vs 57.9% with RIS • ZOL produced significantly greater reductions in alkaline phosphatase than RIS
Hosking et al[66] (Paget's disease-extension study)	267	Eligible patients from both core studies reexamined 24 months after treatment	ZOL 5 mg; RIS 30 mg	• 98% of those given ZOL maintained therapeutic response[a] vs 57% of those given RIS at 24 months

(Continued)

Table 1 *(Continued)*

Study	No. of patients, N	Study design	Intervention	Key efficacy results
Boonen et al[53] (geriatric osteoporosis)	3,887	A post hoc subgroup analysis of pooled data from the HORIZON-PFT and HORIZON-RFT.	ZOL 5 mg; placebo	• At 3 years, incidence of any clinical, vertebral and non-vertebral fracture was significantly lower in ZOL group compared with placebo group (10.8% vs 16.6%, 1.1% vs 3.7%, and 9.9% vs 13.7%, respectively).
Orwoll et al[48] (male osteoporosis)	302	Multicenter, double-blind, active-controlled, parallel-group study for 24 months in hypogonadal men	ZOL 5 mg; ALN 70 mg	• ZOL increased BMD at lumbar spine, total hip, femoral neck, and trochanter and was noninferior to ALN at 24 months. • At month 12, the median changes from the baseline of markers for bone resorption β-CTx, urine NTx and PINP formation, serum BSAP were comparable between ZOL and ALN groups.

Note: *Therapeutic response defined as normalization of alkaline phosphate or ≥75% decrease in excess alkaline phosphatase.
Abbreviations: ZOL, zoledronic acid; HORIZON-PFT, The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial; HORIZON-RFT, HORIZON-Recurrent Fracture Trial; BMD: bone mineral density; ALN, alendronate; NTx, N-telopeptide of type I collagen; BTM, bone turnover markers; GIO, glucocorticoid-induced osteoporosis; β-CTx, beta-serum type I collagen C telopeptide; PINP, serum N-terminal propeptide of type I collagen; RIS, risedronate; BSAP, bone-specific alkaline phosphatase.

93.9% placebo; $P = 0.002$), driven primarily by larger number of AEs associated with postdose symptoms.[28] However, in the HORIZON-RFT study, the difference in the number of AEs between both groups was not significant (82.3% ZOL vs 80.6% placebo).[43]

The incidence of death was significantly lower in ZOL than that in placebo recipients in the HORIZON-RFT study (9.6% ZOL vs 13.3% placebo; $P = 0.01$), but not in the HORIZON-PFT study (3.4% ZOL vs 2.9% placebo).[28,43]

The tolerability profile of ZOL was generally similar to that of placebo with regard to most cardiovascular-related AEs, and no long-term renal toxicity was associated with ZOL in patients from either the HORIZON-PFT or the HORIZON-RFT study.[28,43]

ZOL vs ALN

The overall incidence of AEs in recipients of ZOL 5 mg IV (once-yearly) was generally similar to that seen in recipients of oral ALN 70 mg once-weekly in a comparative trial of 1-year duration (86.7% vs 80.4%).[37] No patient died during the course of the study. Treatment-emergent SAEs were reported in 10.6% of ZOL recipients compared with 9.8% of ALN recipients; no SAEs were considered to be study drug related. Only 3.5% ZOL recipients and 0.9% ALN recipients discontinued treatment because of AEs. Within the first 3 days of initial drug administration, treatment-emergent AEs occurred in 36.3% of ZOL recipients compared with 21.4% of ALN recipients (Table 2). Three or more days after initial administration, the incidence of treatment-emergent AEs was broadly similar in ZOL and ALN recipients (77.9% vs 73.2% of patients).[37]

Safety results from a study by Saag et al[38] showed that a comparable proportion of patients reported AEs in each treatment group (ZOL 5 mg, 91.3%; ALN 70 mg, 86.4%). Transient, flu-like symptoms were the most common AEs in the ZOL group and resulted in a higher frequency of AEs in the group during the first 3 days of treatment (Table 2). After 3 days, AE rates were similar in both groups (79.7% ZOL vs 78.0% ALN). There were no deaths during this study. SAEs occurred in 2 patients in the ZOL group (osteoarthritis, chest pain) and 3 patients in the ALN group (1 patella fracture, 2 osteoarthritis). None were considered related to the treatment.

ZOL vs RIS

Safety data from a comparative trial of 1-year duration that tested the effectiveness of once-yearly IV ZOL 5 mg vs daily oralRIS 30 mg, for the prevention and treatment of GIO, showed that the overall incidence of SAEs was similar between the ZOL and RIS groups, but AEs were more common with ZOL than with RIS largely as a result of transient, flu-like symptoms during the first 3 days after infusion (Table 2).[59]

In the treatment subgroup, the most frequently reported SAE for patients tested with ZOL and RIS was worsening rheumatoid arthritis, which was judged to be severe in 2% of patients in each drug group.

In the prevention subgroup, the most frequently reported SAE was pyrexia, which was judged to be severe in 1% of patients in each drug group. No signifcant

differences were recorded between the drug groups in either the treatment or the prevention subgroups within the cardiac disorders.[59] In the treatment subgroup, the incidence of death was comparable between ZOL and RIS, (1% ZOL vs 1% RIS). However, in the prevention subgroup, it was slightly higher in the ZOL vs RIS groups (1% ZOL vs 0% RIS).

In a study by Reid et al[65] comparing ZOL with RIS in patients with Paget's disease, the number of patients with AEs (146 ZOL vs 133 RIS; Table 2) and SAEs (9 ZOL vs 11 RIS) were similar in the 2 groups. In the first 3 days, the ZOL group had twice the number of AEs as compared to the RIS group ($P < 0.001$), and these were principally the flu-like symptoms, known to occur in association with the IV use of nitrogen-containing bisphosphonates (Table 2). Subsequently, the rates of AEs were similar in the 2 groups. The frequencies of gastrointestinal and renal or urinary disorders were similar in the 2 groups. An 18-month extension of the study showed that death rates and SAEs were similar between ZOL and RIS.[66]

Patient considerations and treatment preference

Several large clinical trials have shown the efficacy of bisphosphonates in the treatment of osteoporosis. However, the long-term treatment with bisphosphonates is required for optimal and sustained benefit. Therefore, compliance and adherence to prescribed medication are needed for an evaluable therapeutic benefit to patients.[76]

In the treatment of osteoporosis, nonadherence to bisphosphonate therapy correlates with reduced gains in BMD and lower reductions in the levels of BTMs.[77,78] In addition, nonadherence leads to an increased incidence of secondary complications associated with fractures, such as pain,

Table 2 Summary of five most frequently reported AEs after first infusion of ZOL in the treatment of osteoporosis and Paget's disease compared with placebo, ALN and RIS

Study	Intervention	N	Any AE, n (%)	Five typical AEs within 3 days of initial dosing[a]				
				Pyrexia, n (%)	Myalgia, n (%)	Influenza-like symptoms, n (%)	Headache, n (%)	Arthralgia, n (%)
ZOL vs placebo								
Reid et al[25]	ZOL							
	4 × 0.25 mg	60	52 (87)	6 (10)	12 (20)	1 (2)	Not reported	9 (15)
	4 × 0.5 mg	58	50 (86)	5 (9)	6 (10)	4 (7)		8 (14)
	4 × 1 mg	53	50 (94)	7 (13)	7 (13)	2 (4)		9 (17)
	2 × 2 mg	61	56 (92)	12 (20)	10 (16)	10 (16)		15 (25)
	1 × 4 mg	60	54 (90)	9 (15)	6 (10)	9 (15)		5 (8)
	Placebo	59	45 (76)	2 (3)	1 (2)	4 (7)	Not reported	9 (15)
Black et al[28]	ZOL 5 mg	3862	3688 (95.5)	621 (16.1)	365 (9.5)	301 (7.8)	273 (7.1)	245 (6.3)
(HORIZON-PFT)	Placebo	3852	3616 (93.9)	79 (2.1)	66 (1.7)	61 (1.6)	90 (2.3)	76 (2.0)
Lyles et al[43]	ZOL 5 mg	1054	867 (82.3)	73 (6.9)	33 (3.1)	6 (0.6)	16 (1.5)	33 (3.1)
(HORIZON-RFT)	Placebo	1057	852 (80.6)	9 (0.9)	9 (0.9)	3 (0.3)	9 (0.9)	23 (2.2)
ZOL vs ALN								
McClung et al[37]	ZOL 5 mg	113	98 (86.7)	Not reported	Not reported	Not reported	14 (12.4)	6 (5.3)
	ALN 70 mg	112	90 (80.4)	Not reported	Not reported	Not reported	7 (6.3)	1 (0.9)
Saag et al[38]	ZOL	69	63 (91.3)	4(5.8)	8 (11.6)	13 (18.8)	5 (7.2)	5 (7.2)
	ALN 70 mg	59	51 (86.4)	1 (1.7)	1 (1.7)	3 (5.1)	7 (11.9)	4 (6.8)
ZOL vs RIS								
Reid et al[65]	ZOL 5 mg	177	146 (82.5)	13 (7.3)	13 (7.3)	17 (9.6)	12 (6.8)	Not reported
	RIS 30 mg	172	133 (77.3)	1 (0.6)	6 (3.5)	7 (4.1)	7 (4.1)	Not reported
Reid et al[59]	ZOL 5 mg	272	211 (78)	32 (12)	29 (11)	15 (6)	13 (5)	32 (12)
(Treatment group)	RIS 30 mg	273	186 (68)	12 (4)	6 (2)	3 (1)	5 (2)	21 (8)
Reid et al[59]	ZOL 5 mg	144	111 (77)	21 (15)	9 (6)	10 (7)	9 (6)	9 (6)
(Prevention group)	RIS 30 mg	144	93 (65)	3 (2)	8 (6)	1(1)	5 (3)	10 (7)

Note: [a]The 5 symptoms listed were the most frequently cited in Black et al[28] and other studies.

Abbreviations: AE, adverse event; ZOL, zoledronic acid; ALN, alendronate; RIS, risedronate; N, number of patients; HORIZON-PFT, The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial; HORIZON-RFT, HORIZON-Recurrent Fracture Trial.

nosocomial infections, and pulmonary thromboembolism, and hence to a decreased QoL.[78–81]

Reasons for the suboptimal adherence to earlier developed bisphosphonates

The main reasons patients cite for not continuing to take their osteoporosis medication are the stringent dosing schedule, AEs, not feeling that treatment is working, and not believing that they have a disease that needs to be treated.[76] The commonest reasons were the strict dosing requirements for oral bisphosphonates (fasting overnight or for at least 6 hours prior to taking the medication and 30–60 min after administration) and posture (staying upright for 30–60 minutes after taking the medication), which can be inconvenient and often not feasible in the daily routine. The second most common reason for discontinuation of therapy is side effects. The main complaints with oral bisphosphonates are upper gastrointestinal irritation, dyspepsia, nausea, upper abdominal pain, vomiting, and gastroesophageal reflux. Finally, as patients often have no symptoms until they suffer a fracture, they do not feel that treatment is worth taking or do not believe they have a disease that needs treatment. They may consider the pill a burden and the inconvenience of the dosing requirements to be unnecessary.[76]

Evolution of dosing regimens to overcome nonadherence

Initially, all the studies for oral bisphosphonates (ALN, RIS, and ibandronate), which showed antifracture efficacy, were conducted using a daily regimen.[29–31,33,82] However, the burdensome dosing requirements needed for gastrointestinal protection with daily oral bisphosphonates led to the development of less-frequent oral regimens. As the half-life of bone-bound bisphosphonates is long, weekly dosing of bisphosphonates is possible; moreover, they remain at resorption sites longer than the 2-week lifespan of individual osteoclasts.[83] Weekly oral ALN and RIS achieved approval based on comparisons with the respective daily regimens.[84,85] Weekly oral ibandronate has also shown noninferior efficacy to the daily regimen[86] but has not been marketed. Bisphosphonate pharmacology also makes possible monthly, intermittent, quarterly, or yearly dosing. To improve adherence and persistence, these extended interval regimens were developed. Monthly oral ibandronate, the first approved monthly bisphosphonate regimen, was supported by comparison trials with the daily regimen and is in use since 2005.[34,87] An intermittent oral RIS regimen (2 consecutive days monthly) was approved in April 2007,[88] and a once-monthly RIS dosing regimen was approved in April 2008.[89]

Intravenous bisphosphonate regimens do not require stringent dosing requirements as oral bisphosphonates, and therefore, it provides alternative options for osteoporosis patients unable to take oral bisphosphonates. Quarterly IV ibandronate injection (3 mg/3 months) became, in 2006, the first IV bisphosphonate to be approved for PMO in the United States and in the EU. Quarterly IV ibandronate has shown efficacy in PMO with a similar safety profile to the monthly oral regimen.[90] This was followed by once-yearly ZOL 5 mg IV, which is approved globally for up to 6 indications in osteoporosis. It provides the greatest extended dosing interval and reduces concerns about oral administration, gastrointestinal intolerance, and bioavailability. The efficacy and safety of ZOL have been demonstrated from several large randomized trials.[28,37,38,43]

Patient preference for once-yearly ZOL dosing

A once-yearly IV ZOL has been preferred by a majority of trial outpatients in 2 separate trials, who switched to ZOL from weekly oral ALN.[37,38] McClung et al[37] reported that 79% of patients preferred an annual infusion of ZOL vs weekly oral ALN. Similarly, Saag et al[38] reported that a majority of patients (66%) preferred for annual ZOL vs weekly ALN. Moreover, patients who cannot tolerate or do not prefer oral dosing may opt for yearly IV infusion of ZOL.[28] Intravenous regimens may also be particularly advantageous for elderly patients residing in long-term care facilities or those with impairments affecting self-management of medication.[91]

Optimizing the dosing interval for ZOL

Optimizing the dosing interval for ZOL is important. It is likely that even less frequent administration of ZOL will become more acceptable to patients and hence associated with greater adherence to long-term therapy. It has been demonstrated that the duration of antiresorptive action of a single 5-mg dose of ZOL exceeds 12 months, and it would be worth evaluating the antifracture efficacy of ZOL with a dosing interval of more than 12 months.[92]

Place of ZOL in the treatment of osteoporosis

In randomized clinical trials, ZOL 5 mg has been proven to be effective in reducing the risk of vertebral, nonvertebral and hip fractures, and to be generally well tolerated in PMO.[28] ZOL is the only bisphosphonate to have demonstrated significant risk reduction at all major osteoporotic fracture sites. The 70% relative risk reduction in vertebral fracture at 3 years demonstrated by once-yearly ZOL 5 mg[28] is numerically greater than the relative risk reductions shown by ALN (44%)[82] or RIS (49%).[93] ZOL 5 mg has also been shown to be effective in the prevention of clinical fracture in patients (male and female) who have previously experienced a low-trauma hip fracture.[43] ZOL 5 mg is the only agent with demonstrated efficacy in this indication. ZOL is also significantly more effective than RIS in preventing and treating GIO.[59] Most recently, the efficacy of ZOL in treating osteoporosis in men has also been demonstrated.[47,48] The formulation and administration regimen of ZOL 5 mg ensures year-long effectiveness. Thus, it presents an attractive alternative to other daily, weekly, or monthly bisphosphonate therapies. Moreover, several studies are underway to determine the efficacy of ZOL compared with other bisphosphonates, ie, ZOL is being compared with pamidronate in heart- and lung-transplant-related osteopenia and osteoporosis, with ALN in heart and liver transplantations and with ALN in kidney and kidney/pancreas transplantations.[94]

Conclusions

The main aim of treatment in osteoporosis is to reduce the risk of fractures, thereby reducing fracture-associated morbidity and mortality. A once-yearly administration of ZOL 5 mg has the potential to help meet this main clinical need of patients with osteoporosis because clinical evidence suggests that it is more effective than oral bisphosphonates in reducing the risk of vertebral and hip fractures, and it improves compliance through provision of medication over the entire 1-year period in a formulation that is well tolerated.

Review criteria

Searches were performed using PubMed to find material published in English between 2000 and 2009. We used the search terms *zoledronic acid*, *bisphosphonates*, *osteoporosis*, *secondary osteoporosis*, *clinical utility*, *adherence*, *patient preference*, and *Paget's disease* to find full-text articles and abstracts. Reference lists from various articles were also searched for further sources.

Abbreviations

AE, adverse event; AF, atrial fibrillation; ALN, alendronate; BAP, bone alkaline phosphatase; BCE, bone collagen equivalents; BMD, bone mineral density; BSAP, bone specific alkaline phosphatase; BTMs, bone turn over markers; CTx, Serum type I collagen C telopeptide; DXA, dual energy X-ray absorptiometry; EU, European Union; GIO, glucocorticoid-induced osteoporosis; HCM, hypercalcemia of malignancy; HORIZON-PFT, The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial; HORIZON-RFT, The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Recurrent Fracture Trial; IV, intravenous; LTO, localized transient osteoporosis; NTx, N-telopeptide of type I collagen; ONJ, osteonecrosis of the jaw; P1NP, serum N-terminal propeptide of type I collagen; PMO, postmenopausal osteoporosis; QoL, quality of life; RIS, risedronate; SAE, serious adverse event; SAP, serum alkaline phosphatase; SE, standard error; SRE, skeletal-related event; US, United States of America; VAS, visual analog scale; WHO, World Health Organization; ZOL, zoledronic acid.

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19. Orange Book listings from "OB_Rx" table for query on "zoledronic acid" performed on Feb. 28, 2014.

FDA Home[3] Drug Databases[4] Orange Book[5]

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Active Ingredient Search Results from "OB_Rx" table for query on "zoledronic acid."

Displaying records 1 to 19 of 19

Download data

Appl No	TE Code[7]	RLD[8]	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N203231	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/100ML	ZOLEDRONIC ACID	ACS DOBFAR INFO SA
A202828	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	ACS DOBFAR INFO SA
A202472	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	ACTAVIS INC
A202650	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	AGILA SPECLTS
A091186	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	DR REDDYS LABS LTD
A091363	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	DR REDDYS LABS LTD
A201783	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	EMCURE PHARMS LTD
A201801	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	EMCURE PHARMS LTD
A202930	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	GLAND PHARMA LTD
A202182	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	HIKMA FARMACEUTICA
A202837	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	HOSPIRA INC
N021223	AP	Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/100ML	ZOMETA	NOVARTIS
N021223	AP	Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOMETA	NOVARTIS
N021817	AP	Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	RECLAST	NOVARTIS
A091170	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	PHARMACEUTICS
A202163	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	PHARMACEUTICS
A202571	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	PHARMS
A202746	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	SUN PHARMA GLOBAL
A090018		Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/VIAL	ZOLEDRONIC ACID	SUN PHARMA GLOBAL

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20. Orange Book Preface.

Drugs

Orange Book Preface

Food and Drug Administration
Center for Drug Evaluation and Research
Approved Drug Products with Therapeutic Equivalence Evaluations
32nd Edition

PREFACE

The publication, ***Approved Drug Products with Therapeutic Equivalence Evaluations*** (the List, commonly known as the Orange Book), identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act). Drugs on the market approved only on the basis of safety (covered by the ongoing Drug Efficacy Study Implementation [DESI] review [e.g., Donnatal® Tablets and Librax® Capsules] or pre-1938 drugs [e.g., Phenobarbital Tablets]) are not included in this publication. The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products on the List is independent of any current regulatory action through administrative or judicial means against a drug product. In addition, the List contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. Therapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the Act.

Background of the Publication. To contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products. These state laws generally require either that substitution be limited to drugs on a specific list (the positive formulary approach) or that it be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). Because of the number of requests in the late 1970s for FDA assistance in preparing both positive and negative formularies, it became apparent that FDA could not serve the needs of each state on an individual basis. The Agency also recognized that providing a single list based on common criteria would be preferable to evaluating drug products on the basis of differing definitions and criteria in various state laws. As a result, on May 31, 1978, the Commissioner of the Food and Drug Administration sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

The List was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through new drug applications (NDAs) and abbreviated new drug applications (ANDAs) under the provisions of Section 505 of the Act.

The therapeutic equivalence evaluations in the List reflect FDA's application of specific criteria to the multisource prescription drug products on the List approved under Section 505 of the Act. These evaluations are presented in the form of code letters that indicate the basis for the evaluation made. An explanation of the code appears in the Introduction.

A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the *Federal Register* on January 12, 1979 (44 FR 2932). The final rule, which includes FDA's responses to the public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 FR 72582). The first publication, October 1980, of the final version of the List incorporated appropriate corrections and additions. Each subsequent edition has included the new approvals and made appropriate changes in data.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act (1984 Amendments). The 1984 Amendments require that FDA, among other things, make publicly available a list of approved drug products with monthly supplements. The ***Approved Drug Products with Therapeutic Equivalence Evaluations*** publication and its monthly Cumulative Supplements satisfy this requirement. The *Addendum*[1] to this publication identifies drugs that qualify under the 1984 Amendments for periods of exclusivity (during which ANDAs or applications described in Section 505(b)(2) of the Act for those drugs may not be submitted for a specified period of time and, if allowed to be submitted, would be tentatively approved) and provides patent information concerning the listed drugs which also may delay the approval of ANDAs or Section 505(b)(2) applications. The *Addendum*[2] also provides additional information that may be helpful to those submitting a new drug application to the Agency.

The Agency intends to use this publication to further its objective of obtaining input and comment on the publication itself and related Agency procedures. Therefore, if you have comments on how the publication can be improved, please send them to the Director, Division of Labeling and Program Support HFD-610, Office of Generic Drugs, Center for Drug and Evaluation and Research, 7620 Standish Place, Rockville, MD 20855. Comments received are publicly available to the extent allowable under the Freedom of Information regulations.

INTRODUCTION

Content and Exclusion

The List is composed of four parts: (1) approved prescription drug products with therapeutic equivalence evaluations; (2) approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs; (3) drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research; and (4) a cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. [Note: Newly approved products are added to parts 1, 2, or 3 of the List, depending on the dispensing requirements (prescription or OTC) or approval authority, unless the Orange Book staff is otherwise notified before publication.]

This publication also includes indices of prescription and OTC drug products by trade or established name (if no trade name exists) and by applicant name (holder of the approved application). All established names for active ingredients generally conform to official compendial names or *United States Adopted Names* (USAN) as prescribed in (21 CFR 299.4(e)). The latter list includes applicants' names as abbreviated in this publication; in addition, a list of uniform terms is provided. An *Addendum*[3] contains drug patent and exclusivity information for the Prescription, OTC, Discontinued Drug Product Lists, and for the Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research. The publication may include additional information that the Agency deems appropriate to disseminate.

Prior to the 6th Edition, the publication had excluded OTC drug products and drug products with approval under Section 505 of the Act administered by the Center fo Biologics Evaluation and Research because the main purpose of the publication was to provide information to states regarding FDA's recommendation as to which generic prescription drug products were acceptable candidates for drug product selection. The 1984 Amendments required the Agency to begin publishing an upâ€toâ€date list of all marketed drug products, OTC as well as prescription, that have been approved for safety and efficacy and for which new drug applications are required.

Under the 1984 Amendments, some drug products are given tentative approvals. The Agency will not include drug products with tentative approval in the List; however, they are available at ANDA Approvals[4]. When the tentative approval becomes a full approval through a subsequent action letter to the application holder, the Agency will list the drug product and the final approval date in the appropriate approved drug product list.

Distributors or repackagers of products on the List are not identified. Because distributors or repackagers are not required to notify FDA when they shift their source of supply from one approved manufacturer to another, it is not possible to maintain complete information linking product approval with the distributor or repackager handling the products.

Therapeutic Equivalence-Related Terms

Pharmaceutical Equivalents. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutical Alternatives. Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Data are generally not available for FDA to make the determination of tablet to capsule bioequivalence. Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.

Therapeutic Equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. *The concept of therapeutic equivalence, as used to develop the List, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., ibuprofen vs. naproxen for the treatment of pain).* Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications.

FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

Bioavailability. This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Bioequivalent Drug Products. This term describes pharmaceutical equivalent or alternative products that display comparable bioavailability when studied under similar experimental conditions. Section 505 (j)(8)(B) of the Act describes one set of conditions under which a test and reference listed drug[5] shall be considered bioequivalent:

the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be appropriate.

Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

Statistical Criteria for Bioequivalence

Under the Drug Price Competition and Patent Term Restoration Act of 1984, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the drug product is bioequivalent to the pioneer (innovator) drug product. A major premise underlying the 1984 law is that bioequivalent drug products[6] are therapeutically equivalent and, therefore, interchangeable.

Bioavailability refers to the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action (Federal Food, Drug and Cosmetic Act, section 505(j)(8)). Bioequivalence refers to equivalent release of the same drug substance from two or more drug products or formulations. This leads to an equivalent rate and extent of absorption from these formulations. Underlying the concept of bioequivalence is the thesis that, if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product. Methods used to define bioequivalence can be found in 21 CFR 320.24, and include (1) pharmacokinetic (PK) studies, (2) pharmacodynamic (PD) studies, (3) comparative clinical trials, and (4) in-vitro studies. The choice of study used is based on the site of action of the drug and the ability of the study design to compare drug delivered to that site by the two products.

The standard bioequivalence (PK) study is conducted using a two-treatment crossover study design in a limited number of volunteers, usually 24 to 36 adults. Alternately, a four-period, replicate design crossover study may also be used. Single doses of the test and reference drug products are administered and blood or plasma levels of the drug are measured over time. Pharmacokinetic parameters characterizing rate and extent of drug absorption are evaluated statistically. The PK parameters of interest are the resulting area under the plasma concentration-time curve (AUC), calculated to the last measured concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-inf)), for extent of absorption; and the maximum or peak drug concentrations (Cmax), for rate of absorption. Crossover studies may not be practical in drugs with a long half-life in the body, and a parallel study design may be used instead. Alternate study methods, such as in-vitro studies or equivalence studies with clinical or pharmacodynamic endpoints, are used for drug products where plasma concentrations are not useful to determine delivery of the drug substance to the site of activity (such as inhalers, nasal sprays and topical products applied to the skin).

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided-test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20% for each of the above tests was determined to be significant, and therefore, undesirable for all drug products. Numerically, this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

For statistical reasons, all data is log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90% confidence interval for each pharmacokinetic parameter (Cmax and AUC). The confidence interval for both pharmacokinetic parameters, AUC and Cmax, must be entirely within the 80% to 125% boundaries cited above. Because the mean of the study data lies in the center of the 90% confidence interval, the mean of the data is usually close to 100% (a test/reference ratio of 1). Different statistical criteria are sometimes used when bioequivalence is demonstrated through comparative clinical trials pharmacodynamic studies, or comparative in-vitro methodology.

The bioequivalence methodology and criteria described above simultaneously control for both, differences in the average response between test and reference as well as the precision with which the average response in the population is estimated. This precision depends on the within-subject (normal volunteer or patient) variability in the pharmacokinetic parameters (AUC and Cmax) of the two products and on the number of subjects in the study. The width of the 90% confidence interval is a reflection in part of the within-subject variability of the test and reference products in the bioequivalence study. A test product with no differences in the average response when compared to the reference might still fail to pass the bioequivalence criteria if the variability of one or both products is high and the bioequivalence study has insufficient statistical power (i.e., insufficient number of subjects). Likewise, a test product with low variability may pass the bioequivalence criteria, when there are somewhat larger differences in the average response.

This system of assessing bioequivalence of generic products assures that these substitutable products do not deviate substantially in in-vivo performance from the reference product. The Office of Generic Drugs has conducted two surveys to quantify the differences between generic and brand name products. The first survey included 224 bioequivalence studies submitted in approved applications during 1985 and 1986. The observed average differences between reference and generic products for AUC was 3.5% (JAMA, Sept. 4, 1987, Vol. 258, No. 9). The second survey included 127 bioequivalence studies submitted to the agency in 273 ANDAs approved in 1997. The three measures reviewed include AUC(0-t), AUC(0-inf), and Cmax. The observed average differences between reference and generic products were + 3.47% (SD 2.84) for AUC(0-t), + 3.25% (SD 2.97) for AUC(0-inf), and + 4.29% (SD 3.72) for Cmax (JAMA, Dec. 1, 1999, Vol. 282, No. 21).

The primary concern from the regulatory point of view is the protection of the patient against approval of products that are not bioequivalent. The current practice o carrying out two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent t the reference will be approved.

Reference Listed Drug (RLD)

A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

FDA has identified in the Prescription Drug Product and OTC Drug Product Lists those reference listed drugs to which the *in vivo* bioequivalence (reference standard) and, in some instances, the *in vitro* bioequivalence of the applicant's product is compared. By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs. However, in some instances when listed drugs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition. A firm wishing to market a generic version of a listed drug that is not designated as the reference listed drug may petition the Agency through the Citizen Petition procedure (see 21 CFR 10.25(a) and CFR 10.30). When the Citizen Petition is approved, the second listed drug will be designated as an additional reference listed drug and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug. *Therapeutic Equivalence Evaluations Codes*[7] *Products meeting necessary bioequivalence requirements* explains the ***AB, AB1, AB2, AB3***coding system for multisource drug products listed under the same heading with two reference listed drugs.

In addition, there are two situations in which two listed drugs that have been shown to be bioequivalent to each other may both be designated as reference listed drugs. The first situation occurs when the in vivo determination of bioequivalence is self-evident and a waiver of the *in vitro* methodology. The reference listed drug is identified by the symbol "+" in the Prescription and Over-the-Counter (OTC) Drug Product Lists. These identified reference listed drugs represent the best judgment of the Division of Bioequivalence at this time. The Prescription and OTC Drug Product Lists identify reference drugs for oral dosage forms, injectables, ophthalmics, otics, and topical products. It is recommended that a firm planning to conduct an *in vivo* waiver of bioequivalence will be requested, contact the Division of Bioequivalence, Office of Generic Drugs, to confirm the appropriate reference listed drug.

General Policies and Legal Status

The List contains public information and advice. It does not mandate the drug products which may be purchased, prescribed, dispensed, or substituted for one another, nor does it, conversely, mandate the products that should be avoided. To the extent that the List sets forth FDA's evaluations of the therapeutic equivalenc of drug products that have been approved, it contains FDA's advice to the public, to practitioners and to the states regarding drug product selection. These evaluations do not constitute determinations that any product is in violation of the Act or that any product is preferable to any other. Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, intended to reduce the cost of drugs to consumers. To the extent that the List identifies drug products approved under Section 505 of the Act, it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act. Exclusion of a drug product from the List does not necessarily mean that the drug product is either in violation of Section 505 of the Act, or that such a product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products. Rather, the exclusion is based on the fact that FDA has not evaluated the safety, effectiveness, and quality of the drug product.

Practitioner/User Responsibilities

Professional care and judgment should be exercised in using the List. Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling. If products with such differences are substituted for each other, there is a potential for patient confusion due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. There may also be better stability of one product over another under adverse storage conditions, or allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.

FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate. Pharmacists must also be familiar with the expiration dates/times and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised when one product is substituted for another.

Multisource and single-source drug products. FDA has evaluated for therapeutic equivalence only multisource prescription drug products approved under Section 505 of the Act, which in most instances means those pharmaceutical equivalents available from more than one manufacturer. For such products, a therapeutic equivalence code is included and, in addition, product information is highlighted in bold face and underlined. Those products with approved applications that are single-source (i.e., there is only one approved product available for that active ingredient, dosage form, route of administration, and strength) are also included on the List, but no therapeutic equivalence code is included with such products. Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, although not identified in the List, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. The details of these codes and the policies underlying them are discussed in *Therapeutic Equivalence Evaluations Codes*[8].

Products on the List are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product. The applicant may have had its product manufactured by a contract manufacturer and may simply be distributing the product for which it has obtained approval. In most instances, however, the manufacturer of the product is also the applicant. The name of the manufacturer is permitted by regulation to appear on the label, even when the manufacturer is not the marketer.

Although the products on the List are identified by the names of the applicants, circumstances, such as changing corporate ownership, have sometimes made identification of the applicant difficult. The Agency believes, based on continuing document review and communication with firms, that the applicant designations on the List are, in most cases, correct.

To relate firm name information on a product label to that on the List, the following should be noted: the applicant's name always appears on the List. This applies whether the applicant (firm name on the Form FDA 356h in the application) is the marketer (firm name in largest letters on the label) or not. However, the applicant's name may not always appear on the label of the product.

If the applicant is the marketer, its name appears on the List and on the label; if the applicant is not the marketer, and the Agency is aware of a corporate relationship (e.g., parent and subsidiary) between the applicant and the marketer, the name of the applicant appears on the List and both firm names may appear or the label. Firms with known corporate relationships are displayed in Appendix B. If there is no known corporate relationship between the applicant and the marketer, the applicant's name appears on the List; however, unless the applicant is the manufacturer, packager, or distributor, the applicant's name may not appear on the label. In this case, the practitioner, from labeling alone, will not be able to relate the marketed product to an applicant cited in the List, and hence to a specific approved drug product. In such cases, to assure that the product in question is the subject of an approved application, the firm named on the label should be contacted.

To relate trade name (proprietary name) information on a product label to that on the List, the following should be noted: if the applicant is the marketer, its name appears on the List and on the label; if the Agency is aware of a corporate relationship between the applicant and the marketer, the trade name (proprietary name) of the drug product (established drug name if no trade name exists) appears on the List. If a corporate relationship exists between an application holder and a marketer and both firms are distributing the drug product, the FDA reserves the right to select the trade name of either the marketer or the application holder to appear on the List. If there is no known corporate relationship between the applicant and the marketer, the established drug name appears on the List.

Every product on the List is subject at all times to regulatory action. From time to time, approved products may be found in violation of one or more provisions of the Act. In such circumstances, the Agency will commence appropriate enforcement action to correct the violation, if necessary, by securing removal of the product from the market by voluntary recall, seizure, or other enforcement actions. Such regulatory actions are, however, independent of the inclusion of a product on the List. The main criterion for inclusion of a product is that it has an application with an effective approval that has not been withdrawn for safety or efficacy reasons. FDA believes that retention of a violative product on the List will not have any significant adverse health consequences, because other legal mechanisms are available to the Agency to prevent the product's actual marketing. FDA may however, change a product's therapeutic equivalence rating if the circumstances giving rise to the violation change or otherwise call into question the data upon which the Agency's assessment of whether a product meets the criteria for therapeutic equivalence was made.

Therapeutic Equivalence Evaluations Codes

The coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the Agency has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). With few exceptions, the therapeutic equivalence evaluation date is the same as the approval date.

The two basic categories into which multisource drugs have been placed are indicated by the first letter as follows:

A Drug products that FDA considers to be therapeutically equivalent[9] to other pharmaceutically equivalent products, i.e., drug products for which:

(1) there are no known or suspected bioequivalence problems. These are designated **AA, AN, AO, AP,** or **AT**, depending on the dosage form; or

(2) actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. These are designated **AB**.

B Drug products that FDA at this time, considers NOT to be therapeutically equivalent to other pharmaceutically equivalent products, i.e.,

drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients. These are designated **BC, BD, BE, BN, BP, BR, BS, BT, BX,** or **B***.

Individual drug products have been evaluated as therapeutically equivalent to the reference product in accordance with the definitions and policies outlined below:

"A" CODES

Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products.

"**A**" products are those for which actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. Drug products designated with an "**A**" code fall under one of two main policies:

(1) for those active ingredients or dosage forms for which no *in vivo* bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions or satisfied for solid oral dosage forms by a showing that an acceptable *in vitro* dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated **AA, AN, AO, AP,** or **AT,** depending on the dosage form, as described below); or

(2) for those DESI drug products containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems, and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected reference product (these products are designated as **AB**).

There are some general principles that may affect the substitution of pharmaceutically equivalent products in specific cases. Prescribers and dispensers of drugs should be alert to these principles so as to deal appropriately with situations that require professional judgment and discretion.

There may be labeling differences among pharmaceutically equivalent products that require attention on the part of the health professional. For example, pharmaceutically equivalent powders to be reconstituted for administration as oral or injectable liquids may vary with respect to their expiration time or storage conditions after reconstitution. An FDA evaluation that such products are therapeutically equivalent is applicable only when each product is reconstituted, stored, and used under the conditions specified in the labeling of that product.

The Agency will use notes in this publication to point out special situations such as potential differences between two drug products that have been evaluated as bioequivalent and otherwise therapeutically equivalent, when they should be brought to the attention of health professionals. These notes are contained in *Description of Special Situations*[10].

For example, in rare instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note will be added to *Description of Special Situations*[11].

Also, occasionally a situation may arise in which changes in a listed drug product after its approval (for example, a change in dosing interval) may have an impact on the substitutability of already approved generic versions of that product that were rated by the Agency as therapeutically equivalent to the listed product. When such changes in the listed drug product are considered by the Agency to have a significant impact on therapeutic equivalence, the Agency will change the therapeutic equivalence ratings for other versions of the drug product unless the manufacturers of those other versions of the product provide additional information to assure equivalence under the changed conditions. Pending receipt of the additional data, the Agency may add a note to *Description of Special Situations*[12], or, in rare cases may even change the therapeutic equivalence rating.

In some cases (e.g., Isolyte® S w/ Dextrose 5% in Plastic Container and Plasma-Lyte® 148 and Dextrose 5% in Plastic Container), closely related products are listed as containing the same active ingredients, but in somewhat different amounts. In determining which of these products are pharmaceutically equivalent, the Agency has considered products to be pharmaceutically equivalent with labeled strengths of an ingredient that do not vary by more than 1%.

Different salts and esters of the same therapeutic moiety are regarded as pharmaceutical alternatives. For the purpose of this publication, such products are not considered to be therapeutically equivalent. There are no instances in this List where pharmaceutical alternatives are evaluated or coded with regard to therapeutic equivalence. Anhydrous and hydrated entities, as well as different polymorphs, are considered pharmaceutical equivalents and must meet the same standards and, where necessary, as in the case of ampicillin/ampicillin trihydrate, their equivalence is supported by appropriate bioavailability/bioequivalence studies.

The codes in this book are not intended to preclude health care professionals from converting pharmaceutically different concentrations into pharmaceutical equivalents using accepted professional practice.

Where package size variations have therapeutic implications, products so packaged have not been considered pharmaceutically equivalent. For example, some oral contraceptives are supplied in 21-tablet and 28-tablet packets; the 28-tablet packets contain 7 placebo or iron tablets. These two packaging configurations are not regarded as pharmaceutically equivalent; thus, they are not designated as therapeutically equivalent.

Preservatives may differ among some therapeutically equivalent drug products. Differences in preservatives and other inactive ingredients do not affect FDA's evaluation of therapeutic equivalence except in cases where these components may influence bioequivalence or routes of administration.

The specific sub-codes for those drugs evaluated as therapeutically equivalent and the policies underlying these sub-codes follow:

AA Products in conventional dosage forms not presenting bioequivalence problems

Products coded as **AA** contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. However, all oral dosage forms must, nonetheless, meet an appropriate *in vitro* bioequivalence standard that is acceptable to the Agency in order to be approved.

AB, AB1, AB2, AB3... Products meeting necessary bioequivalence requirements

Multisource drug products listed under the same heading (i.e., identical active ingredients(s), dosage form, and route(s) of administration) and having the same strength (see *Therapeutic Equivalence-Related Terms, Pharmaceutical Equivalents*[13]) generally will be coded **AB** if a study is submitted demonstrating bioequivalence. In certain instances, a number is added to the end of the **AB** code to make a three character code (i.e., **AB1, AB2, AB3, etc.**). Three-character codes are assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. Two or more reference listed drugs are generally selected only when there are at least two potential reference drug products which are not bioequivalent to each other. If a study is submitted that demonstrates bioequivalence to a specific listed drug product, the generic product will be given the same three-character code as the reference listed drug it was compared against. For example, Adalat® CC (Miles) and Procardia XL® (Pfizer), extended-release tablets, are listed under the active ingredient nifedipine. These drug products, listed under the same heading, are not bioequivalent to each other. Generic drug products deemed by FDA to be bioequivalent to Adalat® CC and Procardia XL® have been approved, Adalat® CC and Procardia XL® have been assigned ratings of **AB1** and **AB2,** respectively. The generic drug products bioequivalent to Adalat® CC would be assigned a rating of **AB1** and those bioequivalent to Procardia XL® would be assigned a rating of **AB2**. (The assignment of an **AB1** or **AB2** rating to a specific product does not imply product preference.) Even though drug products of distributors and/or repackagers are not included in the List, they are considered therapeutically equivalent to the application holder's drug product if the application holder's drug product is rated either with an **AB** or three-character code or is single source in the List. Drugs coded as **AB** under a heading are considered therapeutically equivalent only to other drugs coded as **AB** under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

AN Solutions and powders for aerosolization

Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded **AN**. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded **BN**, unless they have met an appropriate bioequivalence standard. Solutions or suspensions in a specific delivery system will be coded **AN** if the bioequivalence standard is based upon *in vitro* methodology, if bioequivalence needs to be demonstrated by *in vivo* methodology then the drug products will be code **AB**.

AO Injectable oil solutions

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

AP Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, *Injectable; Injection*. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s of administration stated in the labeling.

Certain commonly used large volume intravenous products in glass containers are not included on the List (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.

The strength of parenteral drugs products is defined as the total drug content of the container. Until recently the strength of liquid parenteral drug products in the Orange Book have not been displayed. The concentration of the liquid parenteral drug product in the Orange Book has been shown as xmg/ml. The amount of dry powder or freeze dried powder in a container has always been identified as the strength.

With the finalization of the Waxman-Hatch amendments that characterized each strength of a drug product as a listed drug it became evident that the format of the Orange Book should be changed to reflect each strength of a parenteral solution. To this end the OGD has started to display the strength of all new approvals of parenteral solutions. Previously we would have displayed only the concentration of an approved parenteral solution, e.g. 50mg/ml. If this drug product had a 20 ml and 60 ml container approved the two products would be shown as 1Gm / 20ml (50mg/ml) and 3Gm / 60ml (50mg/ml).

AT Topical products

There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including creams, gels, lotions, oils, ointments, pastes, solutions, sprays and suppositories. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and OESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of *in vivo* bioequivalence has been granted and for which chemistry and manufacturing processes are adequate to demonstrate bioequivalence, are considered therapeutically equivalent and coded **AT**. Pharmaceutically equivalent topical products that raise questions of bioequivalence, including all post-1962 non-solution topical drug products, are coded **AB** when supported by adequate bioequivalence data, and **BT** in the absence of such data.

"B" CODES

Drug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.

"**B**" products, for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, often have a problem with specific dosage forms rather than with the active ingredients. Drug products designated with a "**B**" code fall under one of three main policies:

(1) the drug products contain active ingredients or are manufactured in dosage forms that have been identified by the Agency as having documented bioequivalence problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or

(2) the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or

(3) the drug products are under regulatory review.

The specific coding definitions and policies for the "**B**" sub-codes are as follows:

B* Drug products requiring further FDA investigation and review to determine therapeutic equivalence

The code **B*** is assigned to products previously assigned an **A** or **B** code when FDA receives new information that raises a significant question regarding therapeutic equivalence that can be resolved only through further Agency investigation and/or review of data and information submitted by the applicant. The **B*** code signifies that the Agency will take no position regarding the therapeutic equivalence of the product until the Agency completes its investigation and review.

BC Extended-release dosage forms (capsules, injectables and tablets)

Extended-release tablets are formulated in such a manner as to make the contained medicament available over an extended period of time following ingestion.

Although bioavailability studies have been conducted on these dosage forms, they may be subject to bioavailability differences, primarily because firms developing extended-release products for the same active ingredient rarely employ the same formulation approach. FDA, therefore, does not consider different extended-release dosage forms containing the same active ingredient in equal strength to be therapeutically equivalent unless equivalence between individual products in both rate and extent has been specifically demonstrated through appropriate bioequivalence studies. Extended-release products for which such bioequivalence data have not been submitted are coded **BC**, while those for which such data are available have been coded **AB**.

BD Active ingredients and dosage forms with documented bioequivalence problems

The **BD** code denotes products containing active ingredients with known bioequivalence problems and for which adequate studies have not been submitted to FDA demonstrating bioequivalence. Where studies showing bioequivalence have been submitted, the product has been coded **AB**.

BE Delayed-release oral dosage forms

Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. Drug products in delayed-release dosage forms containing the same active ingredients are subject to significant differences in absorption. Unless otherwise specifically noted, the Agency considers different delayed release products containing the same active ingredients as presenting a potential bioequivalence problem and codes these products **BE** in the absence of *in vivo* studies showing bioequivalence. If adequate *in vivo* studies have demonstrated the bioequivalence of specific delayed-release products, such products are coded **AB**

BN Products in aerosol-nebulizer drug delivery systems

This code applies to drug solutions or powders that are marketed only as a component of, or as compatible with, a specific drug delivery system. There may, for example, be significant differences in the dose of drug and particle size delivered by different products of this type. Therefore, the Agency does not consider differen metered aerosol dosage forms containing the same active ingredient(s) in equal strengths to be therapeutically equivalent unless the drug products meet an appropriate bioequivalence standard, such products are coded **AB**.

BP Active ingredients and dosage forms with potential bioequivalence problems

FDA's bioequivalence regulations (21 CFR 320.33) contain criteria and procedures for determining whether a specific active ingredient in a specific dosage form has a potential for causing a bioequivalence problem. It is FDA's policy to consider an ingredient meeting these criteria as having a potential bioequivalence problem even in the absence of positive data demonstrating inequivalence. Pharmaceutically equivalent products containing these ingredients in oral dosage forms are coded **BP** until adequate *in vivo* bioequivalence data are submitted, such products are coded **AB**. Injectable suspensions containing an active ingredient suspended in an aqueous or oleaginous vehicle have also been coded **BP**. Injectable suspensions are subject to bioequivalence problems because differences in particle size,

polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption. FDA does not consider pharmaceutical equivalents of these products bioequivalent without adequate evidence of bioequivalence, such products would be coded **AB**.

BR Suppositories or enemas that deliver drugs for systemic absorption

The absorption of active ingredients from suppositories or enemas that are intended to have a systemic effect (as distinct from suppositories administered for local effect) can vary significantly from product to product. Therefore, FDA considers pharmaceutically equivalent systemic suppositories or enemas bioequivalent only if *in vivo* evidence of bioequivalence is available. In those cases where *in vivo* evidence is available, the product is coded **AB**. If such evidence is not available, the products are coded **BR**.

BS Products having drug standard deficiencies

If the drug standards for an active ingredient in a particular dosage form are found by FDA to be deficient so as to prevent an FDA evaluation of either pharmaceutical or therapeutic equivalence, all drug products containing that active ingredient in that dosage form are coded **BS**. For example, if the standards permit a wide variation in pharmacologically active components of the active ingredient such that pharmaceutical equivalence is in question, all products containing that active ingredient in that dosage form are coded **BS**.

BT Topical products with bioequivalence issues

This code applies mainly to post-1962 dermatologic, ophthalmic, otic, rectal, and vaginal products for topical administration, including creams, ointments, gels, lotions, pastes, and sprays, as well as suppositories not intended for systemic drug absorption. Topical products evaluated as having acceptable clinical performance but that are not bioequivalent to other pharmaceutically equivalent products or that lack sufficient evidence of bioequivalence, will be coded **BT**.

BX Drug products for which the data are insufficient to determine therapeutic equivalence

The code **BX** is assigned to specific drug products for which the data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence under the policies stated in this document. In these situations, the drug products are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.

Description of Special Situations

Certain drugs listed in the Orange Book present special situations that merit further discussion. Following is a description of those special situations:

Amino Acid and Protein Hydrolysate Injections. These products differ in the amount and kinds of amino acids they contain and, therefore, are not considered pharmaceutical equivalents. For this reason, these products are not considered therapeutically equivalent. At the same time, the Agency believes that it is appropriate to point out that where nitrogen balance is the sole therapeutic objective and individual amino acid content is not a consideration, pharmaceutical alternatives with the same total amount of nitrogen content may be considered therapeutically equivalent.

Follitropin Alfa and Beta. Based on available data derived from physico-chemical tests and bioassay, follitropin alfa and follitropin beta are indistinguishable.

Gaviscon®. Gaviscon® is an OTC product which has been marketed since September 1970. The active ingredients in this product, aluminum hydroxide and magnesium trisilicate, were reviewed by the Agency's OTC Antacid Panel and were considered to be safe and effective ingredients (Category I) by that Panel. However, the tablet failed to pass the antacid test which is required of all antacid products. The Agency, therefore, placed the tablet in Category III for lack of effectiveness. A full NDA with clinical studies was submitted by Marion Laboratories, Inc., and approved by FDA on December 9, 1983. Gaviscon® 's activity in treating reflux acidity is made possible by the physical-chemical properties of the inactive ingredients, sodium bicarbonate and alginic acid. Therefore, *all ANDAs which cite Gaviscon® tablets as the listed drug must contain the inactive ingredients sodium bicarbonate and alginic acid.* A full NDA will be required to support the effectiveness of the drug product if different inactive ingredients are to be substituted for sodium bicarbonate or alginic acid or if different proportions of these ingredients are to be used.

Levothyroxine Sodium. Because there are multiple reference listed drugs of levothyroxine sodium tablets and some reference listed drugs' sponsors have conducted studies to establish their drugs' therapeutic equivalence to other reference listed drugs, FDA has determined that its usual practice of assigning two or three character TE codes may be potentially confusing and inadequate for these drug products. Accordingly, FDA provides the following explanation and chart of therapeutic equivalence evaluations for levothyroxine sodium drug products.

Levothyroxine Sodium (Mylan ANDA 76187), tablets have been determined to be therapeutically equivalent to corresponding strengths of Unithroid (Jerome Stevens NDA 021210) tablets.

Levo-T (Alara NDA 021342), Levothyroxine Sodium (Mylan ANDA 76187), Unithroid (Jerome Stevens NDA 021210) and Levothyroxine Sodium (Merck KGAA ANDA 76752)tablets have been determined to be therapeutically equivalent to corresponding strengths of Synthroid (Abbott NDA 021402) tablets.

Levo-T (Alara NDA 021342), Unithroid (Jerome Stevens NDA 021210), Levothyroxine Sodium (Mylan ANDA 076187) and Levothyroxine Sodium (Merck KGAA ANDA 76752) tablets have been determined to be therapeutically equivalent to corresponding strengths of Levoxyl (King Pharms NDA 021301) tablets.

Levothyroxine Sodium (Mylan ANDA 76187) tablets have been determined to be therapeutically equivalent to corresponding strengths of Levothroid (Lloyd NDA 021116) tablets.

The chart outlines TE codes for all 0.025mg products. Other product strenghts may be similar. Therapeutic equivalence has been established between products that have the same AB+number TE code. More than one TE code may apply to some products. One common TE code indicates therapeutic equivalence between products.

Trade Name	Applicant	Patency	TE Code	Appl No	Product No
UNITHROID	STEVENS J	0.025MG	AB1	21210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB1	76187	001
LEVOXYL	KING PHARMS	0.025MG	AB1	21301	001
SYNTHROID	ABBOTT	0.025MG	AB1	21402	001
LEVO-T	ALARA PHARM	0.025MG	AB1	21342	001
SYNTHROID	ABBOTT	0.025MG	AB2	21402	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB2	76187	001
LEVO-T	ALARA PHARM	0.025MG	AB2	21342	001
UNITHROID	STEVENS J	0.025MG	AB2	21210	001
LEVOTHYROXINE SODIUM	MERCK KGAA	0.025MG	AB2	76752	001
LEVOXYL	KING PHARMS	0.025MG	AB3	21301	001
LEVO-T	ALARA PHARM	0.025MG	AB3	21342	001
UNITHROID	STEVENS J	0.025MG	AB3	21210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB3	76187	001
LEVOTHYROXINE SODIUM	MERCK KGAA	0.025MG	AB3	76752	001
LEVOTHROID	LLOYD	0.025MG	AB4	21116	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB4	76187	001

Patent Certification(s) Reference Listed Drug based upon a suitability petition. An abbreviated new drug application that refers to a Reference Listed Drug (RLD) approved pursuant to a suitability petition must demonstrate that the proposed product is bioequivalent to the RLD, and it must include appropriate patent certification(s) and an exclusivity statement with respect to the listed drug which served as the basis for the approved suitability petition. This concept also applies to an ANDA applicant that cites a RLD that was based upon an NDA that is still covered by patent (s) and/or exclusivity, e.g. a second RLD that was selected when the in vivo determination of bioequivalence of the original RLD is self evident and the waiver of the in vivo determination of bioequivalence may be granted.

Waived exclusivity. If a new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (Act) qualifies for exclusivity under sections 505(c)(3)(D) and 505(j)(5)(D), the exclusivity is listed in the Patent and Exclusivity Section of the Orange Book. If a drug product has received this exclusivity, the FDA will delay the approval of a 505(b)(2) application or an abbreviated new drug application (ANDA) under section 505(j) of the Act until the expiration of the exclusivity. If the listed drug is also protected by one or more patents, the approval date for the 505(b)(2) application or ANDA will be determined by the latest expiring patent or exclusivity listed in the Orange Book. However, the holder of the NDA may waiver its exclusivity as to any or all 505(b)(2) and ANDA applications referencing the protected drug product. If an NDA sponsor waivers its right to the exclusivity protection, qualified 505(b)(2) or ANDA applications may be approved without regard to the NDA holder's exclusivity. An NDA for which the holder has waived its exclusivity as to all 505(b)(2) and ANDA applications will be coded with a W in the Patent and Exclusivity Section of the Orange Book and be referred to this section. The applicant referencing this listed drug should indicate in the exclusivity statement that the holder of the listed drug has waived its exclusivity.

Therapeutic Equivalence Code Change for a Drug Entity

The Agency will use the following procedures when, in response to a petition or on its own initiative, it is considering a change in the therapeutic equivalence code for approved multi-source drug products. Such changes will generally occur when the Agency becomes aware of new scientific information affecting the therapeutic equivalence of an entire category of drug products in the List (e.g., information concerning the active ingredient or the dosage form), rather than information concerning a single drug product within the category. These procedures will be used when a change in therapeutic equivalence code is under consideration for all drug products found in the Prescription Drug Product List under a specific drug entity and dosage form. The change may be from the code signifying that the drug does not present a bioequivalence problem (e.g., **AA**) to a code signifying a bioequivalence problem (e.g., **BP**), or vice versa. This procedure does not apply to a change of a particular product code (e.g., a change from **BP** to **AB** or from **AB** to **BX**).

Before making a change in a therapeutic equivalence code for an entire category of drugs, the Agency will announce in the *Introduction* that it is considering the change, and will invite comment. Comments, along with scientific data, may be sent to the Director, Division of Bioequivalence, Office of Generic Drugs, Center for Drug Evaluation and Research, (MPN-2) HFD-650, 7620 Standish Place, Rockville, MD 20855. The comment period will generally be 60 days in length, and the closing date for comments will be listed in the description of the proposed change for each drug entity.

The most useful type of scientific data submission is an *in vivo* bioavailability/bioequivalence study conducted on batches of the subject drug products. These submissions should present a full description of the analytical procedures and equipment used, a validation of the analytical methodology, including the standard curve, a description of the method of calculating results, and a description of the pharmacokinetic and statistical models used in analyzing the data. Anecdotal or testimonial information is the least useful to the Agency, and such submissions are discouraged. Copies of supporting reports published in the scientific literature or unpublished material, however, are welcome.

Change of the Therapeutic Equivalence Evaluation for a Single Product

The aforementioned procedure does not apply to a change in a single drug product code. For example, a change in a single drug product's code from **BP** to **AB** as a result of the submission of a bioequivalence study ordinarily will not be the subject of notice and comment. Likewise, a change in a single drug product's code from **AB** to **BX** (e.g., as a result of new information raising a significant question as to bioequivalence) does not require notice and comment. The Agency's responsibility to provide the public with the Agency's most current information related to therapeutic equivalence may require a change in a drug product's code prior to any formal notice and opportunity for the applicant to be heard. The publication in the *Federal Register* of a proposal to withdraw approval of a drug product will ordinarily result in a change in a product's code from **AB** to **BX** if this action has not already been taken.

Discontinued Section

Those drug products in the Discontinued Section of the Orange Book in which a determination has already been made that the products were not withdrawn for safety or efficacy reasons have "**Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**" following the product strength. Those drug products are only reflective of citizen petitions approved since 1995. The identification of these drug products in the Discontinued Section of the Orange Book should avoid the submission of multiple citizen petitions for the same drug product. FR notices no longer applicable are removed from the Annual Edition (i.e., there is a currently marketed Reference Listed Drug and no applicable patent or exclusivity). Safety or Effectiveness Determinations List[14] lists products that have current and removed notices. The list is updated periodically throughout the year. Notices issued during the year are added to the Electronic Orange Book Query[15] in the month they become effective.

Generally, approved products are added to the Discontinued Section of the Orange Book when the applicant holder notifies the Orange Book staff of the products' not marketed status. Products may also be added if annual reports indicate the product is no longer marketed or other Agency administrative action (e.g., Withdrawal of an Application). Changes to the Orange Book are not affected by the drug registration and listing requirements of Section 510 of the Act.

Changes to the Orange Book

Every effort is made to ensure the Annual Edition is current and accurate. Applicant holders are requested to inform the FDA Orange Book Staff (OBS) of any changes or corrections. Please inform the OBS when products are no longer marketed. Notification of the Orange Book staff to include the newly approved product in the Discontinued Drug Product List rather than parts 1, 2 or 3 of the List (as discussed in Section 1.1) must occur by the end of the month in which the product is approved to ensure that the product is not included in the "active" portions of the next published Orange Book update

We can be contacted by email at drugproducts@cder.fda.gov. Send Changes by FAX: 240-276-8974; mail to:

FDA/CDER Orange Book Staff
Office of Generic Drugs, HFD-610
7620 Standish Place
Rockville , MD 20855-2773

Availability of the Edition

Commencing with the 25th edition, the Annual Edition and current monthly Cumulative Supplements are available in a Portable Document Format (PDF) at the EOB home page, http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm[16], by clicking on the Publications[17]. The PDF annual format duplicates previous paper versions except for the Orphan Products Designations and Approvals List. An annual subscription of the PDF format may be obtained from the U.S. Government Printing Office, 866-512-1800.

HOW TO USE THE DRUG PRODUCT LISTS

Key Sections for Using the Drug Product Lists

This publication contains illustrations, along with Drug Product Lists, indices, and lists of abbreviations and terms which facilitate their use.

Illustrations. The annotated Drug Product Illustration, see Section 2.2, and the Therapeutic Equivalence Evaluations Illustration, see Section 2.3, are offered to provide further clarification. These depict the format found in the Prescription Drug Product List (the only list in which therapeutic equivalence evaluation codes are displayed).

Drug Product Lists. Drug Product Lists. The Prescription and OTC Drug Product Lists, arranged alphabetically by active ingredient(s), contain product identification information (active ingredients, dosage forms, routes of administration, product names, application holders, strengths) for single and multiple ingredient drug products. Also shown are the application number and drug product number (FDA internal computer data use only) and approval dates for those drug products approved on or after January 1, 1982 . The application number preceded by "N" is a New Drug Application (NDA) or commonly the innovator). The application number preceded by an "A" is an Abbreviated New Drug Application (ANDA or commonly the generic).

The Discontinued Product List, arranged alphabetically by active ingredient(s), contain product identification information (dosage form, product name, strength, and application number).

If a prescription drug product is available from more than one source (multisource), a therapeutic equivalence code will appear in front of the applicant's name. If a product is therapeutically equivalent to one or more products or to an appropriate reference, it will be designated with a code beginning with "A" and the entry will be underlined and printed in bold font for emphasis.

Active ingredient headings for multiple ingredient (combination) drug products are arranged alphabetically. For purposes of this publication, this alphabetical sort takes precedence over United States Pharmacopeia official monograph order (i.e., Reserpine, Hydralazine Hydrochloride, Hydrochlorothiazide). For example, product information labeled as Reserpine, Hydrochlorothiazide and Hydralazine Hydrochloride appears under the active ingredient heading Hydralazine Hydrochloride; Hydrochlorothiazide; Reserpine. A cross-reference to the product information (for prescription and OTC products) appears for each additional active ingredient in the product. For combination drug products, the ingredient strengths are separated by semicolons and appear in the same relative sequence as the ingredients in the heading. Available strengths of the dosage form from an applicant appear on separate lines.

To use the Drug Product Lists, determine by alphabetical order the ingredient under which the product information is listed, using the Product Name Index, if necessary. Then, find the ingredient in the applicable Drug Product List. Proceed to the dosage form and route of administration and compare products within that ingredient heading only. Therapeutic equivalence or inequivalence for prescription products is determined on the basis of the therapeutic equivalence codes provided within that specific dosage form and route heading. The OTC Drug Product List, Discontinued Drug Product List, and Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research List have their data arranged similarly.

The Discontinued Drug Product List contains approved products that have never been marketed, have been discontinued from marketing, are for military use, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. All products having a "@" in the 12th Cumulative Supplement of the 31st Edition List have been added to the Discontinued Drug Product List appearing in the 32nd Edition. In addition, approved drug products that are not in the commercial distribution channel e.g., approved drug products in applications for export only are also listed in the Discontinued Section of the Orange Book.

PATENT AND EXCLUSIVITY INFORMATION ADDENDUM

This *Addendum* identifies drugs that qualify under the Drug Price Competition and Patent Term Restoration Act (1984 Amendments) for periods of exclusivity, during which abbreviated new drug applications (ANDAs) and applications described in Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for those drug products may, in some instances, not be submitted or made effective as described below, and provides patent information concerning the listed drug products. Those drugs that have qualified for Orphan Drug Exclusivity pursuant to Section 527 of the Act and those drugs that have qualified for Pediatric Exclusivity pursuant to Section 505A are also included in this *Addendum*. This section is arranged in alphabetical order by active ingredient name followed the trade name. Active ingredient headings for multiple ingredient (combination) drug products are arranged alphabetically. For an explanation of the codes used in the *Addendum*, see the *Patent and Exclusivity Terms* Section. Exclusivity prevents the submission or effective approval of ANDAs or applications described in Section 505(b)(2) of the Act. It does not prevent the submission or approval of a second 505(b)(1) application except in the case of Orphan Drug exclusivity. Applications qualifying for periods of exclusivity are:

(1) A new drug application approved after September 24, 1984, for a drug product all active ingredients (including any ester or salt of the active ingredient) of which had never been approved in any other new drug application under Section 505 (b) of the Act. No subsequent ANDA or application described in Section 505(b)(2) of the Act for the same drug may be *submitted* for a period of *five years* from the date of approval of the original application, except that such an application may be *submitted* after *four years* if it contains a certification that a patent claiming the drug is invalid or will not be infringed by the product for which approval is sought.

(2) A new drug application approved after September 24, 1984, for a drug product containing an active ingredient (including any ester or salt of that active ingredient) that has been approved in an earlier new drug application and that includes reports of new clinical investigations (other than bioavailability studies). Such investigations must have been conducted or sponsored by the applicant and must have been essential to approval of the application. If these requirements are met, the approval of a subsequent ANDA or an application described in Section 505(b)(2) of the Act may not be *made effective* for the same drug or use, if for a new indication, before the expiration of *three years* from the date of approval of the original application. If an applicant has exclusivity for a new application or 505(b)(2) application for the drug product with indications or use, this does not preclude the approval of an ANDA or 505(b)(2) application not covered by the exclusivity.

(3) A supplement to a new drug application for a drug containing a previously approved active ingredient including (any ester or salt of the active ingredient) approved after September 24, 1984, that contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the applicant. The approval of a subsequent ANDA or 505(b)(2) application for a change approved in the supplement may not be *made effective* for *three years* from the date of approval of the original supplement.

The Act requires that patent information be filed with all newly submitted Section 505(b) drug applications. No NDA may be approved after September 24, 1984, without the submission of patent information to the Agency. Effective August 18, 2003, this information must be filed using FDA Form 3524a "Patent Information Submitted with the Filing of an NDA, Amendment or Supplement".

Effective August 18, 2003, upon approval of an application, patent information for purposes of listing in the Orange Book must be submitted to the agency within 30 days of approval on FDA Form 3542 "Patent Information Submitted Upon and After Approval of an NDA or Supplement". Patent information on unapproved applications or on patents beyond the scope of the Act (i.e., process or manufacturing patents) will not be published. FDA form 3542 will be the only form used for the purposes of this publication.

The patents that FDA regards as covered by the statutory provisions for submission of patent information are: patents that claim the active ingredient(s); drug product patents which include formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents as detailed on FDA Form 3542. This information, as provided by the sponsor on FDA form 3542, will be published as described above.

A requirement for submission of patent information to FDA for certain old antibiotics became effective October 7, 2008 under section 4(b)(1) of the Q1 Act. A guidance for industry on this subject is available[18]. Upon approval, patent numbers and expiration dates, in addition to certain other information on appropriate patents claiming drug products that are the subject of approved applications, will be published on a daily basis in the Electronic Orange Book, http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm[19]. The Addendum lists patent and exclusivity information up to January of the Edition year. The monthly Cumulative Supplements to the annual edition list patent and exclusivity information changes since the Annual Edition Addendum. Since all parts of this publication are subject to changes, additions, or deletions, the Electronic Orange Book, updated daily, should be consulted for the most recent patent and exclusivity information.

Search the Orange Book[20]

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#patent_addendum
2. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#patent_addendum
3. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#patent_addendum
4. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugAppro
5. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Reference%20Listed%20Drug
6. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Bioequivalent%20Drug%20Products
7. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Therapeutic%20Equivalence%20Evaluations%20Codes
8. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Section%201.7,%20Therapeutic%20Equivalence%20Evaluations%20Codes
9. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Therapeutic%20Equivalents
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20. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

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(19) **United States**

(12) **Patent Application Publication**

HANNA et al.

(10) **Pub. No.: US 2011/0028435 A1**

(43) **Pub. Date: Feb. 3, 2011**

(54) **CRYSTALLIZATION METHOD AND BIOAVAILABILITY**

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(21) Appl. No.: **12/847,568**

(22) Filed: **Jul. 30, 2010**

Related U.S. Application Data

(60) Provisional application No. 61/230,222, filed on Jul. 31, 2009, provisional application No. 61/288,036, filed on Dec. 18, 2009, provisional application No. 61/302,110, filed on Feb. 6, 2010, provisional application No. 61/312,879, filed on Mar. 11, 2010, provisional application No. 61/318,503, filed on Mar. 29, 2010, provisional application No. 61/359,544, filed on Jun. 29, 2010.

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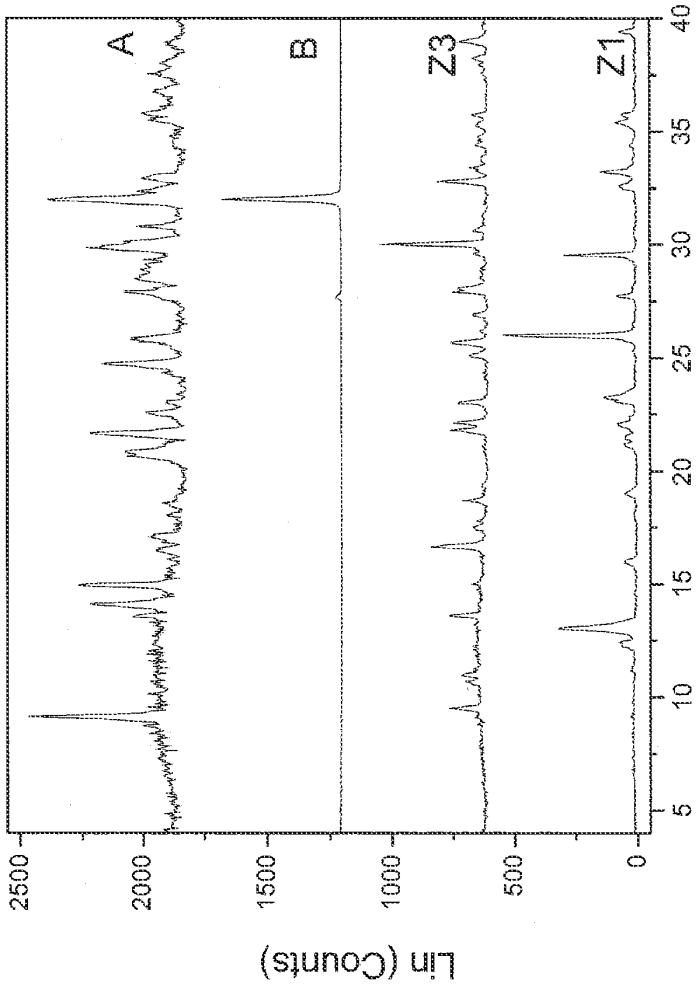
A61P 3/14	(2006.01)
A61P 35/04	(2006.01)
A61P 19/08	(2006.01)

(52) **U.S. Cl.** **514/89**; 548/112; 514/94

(57) **ABSTRACT**

Preparation, in-vitro and in vivo characterization of novel forms of (1-hydroxy-2-imidazol-1-yl-1-phosphono-ethyl) phosphonic acid, suitable for pharmaceutical compositions in drug delivery systems for humans.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B
Z3
Z1
Lin (Counts)
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1500
1000
500
0
5
10
15
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25
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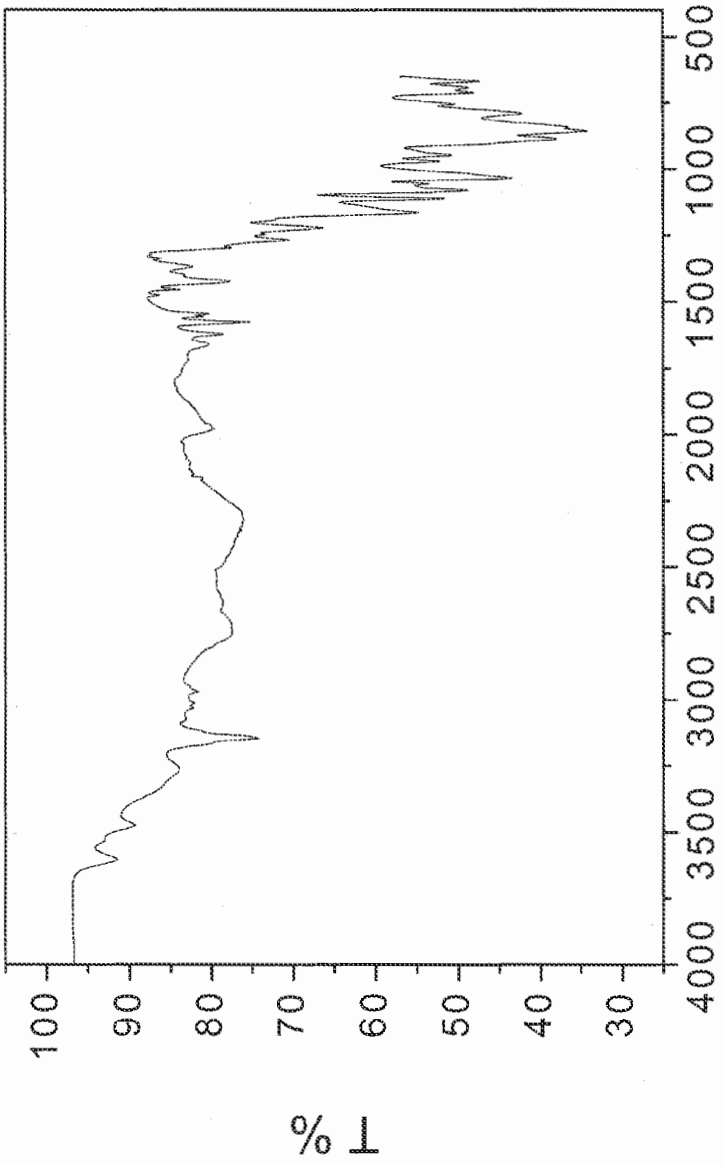
35
40
2-Theta - Scale

FIG. 1


100
90
80
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40
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T %
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3500
3000
2500
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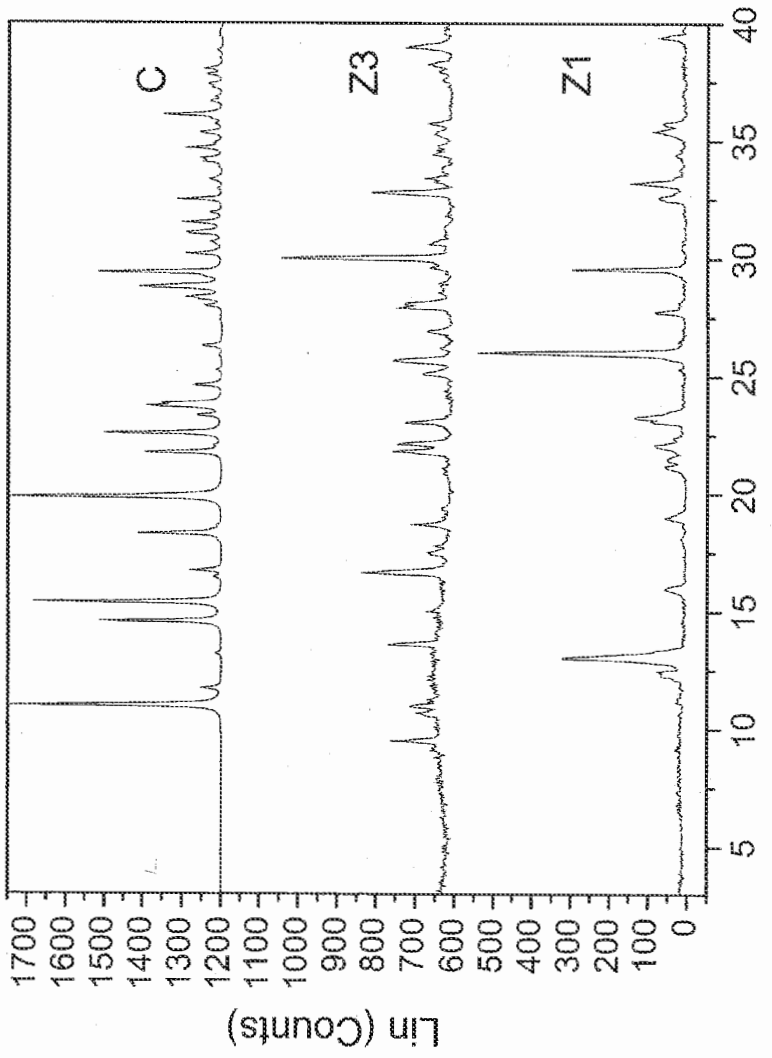
cm -1

FIG. 2


C
Z3
Z1
Lin (Counts)
2-Theta - Scale
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100
200
300
400
500
600
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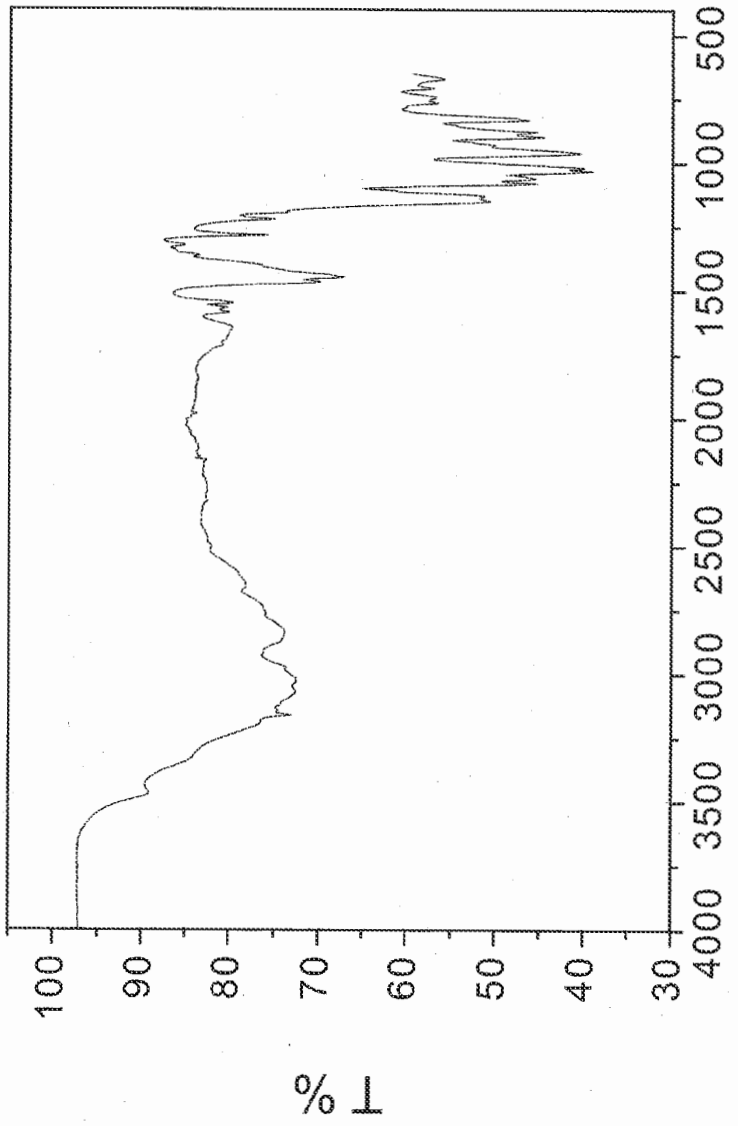
FIG. 3


T %
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90
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70
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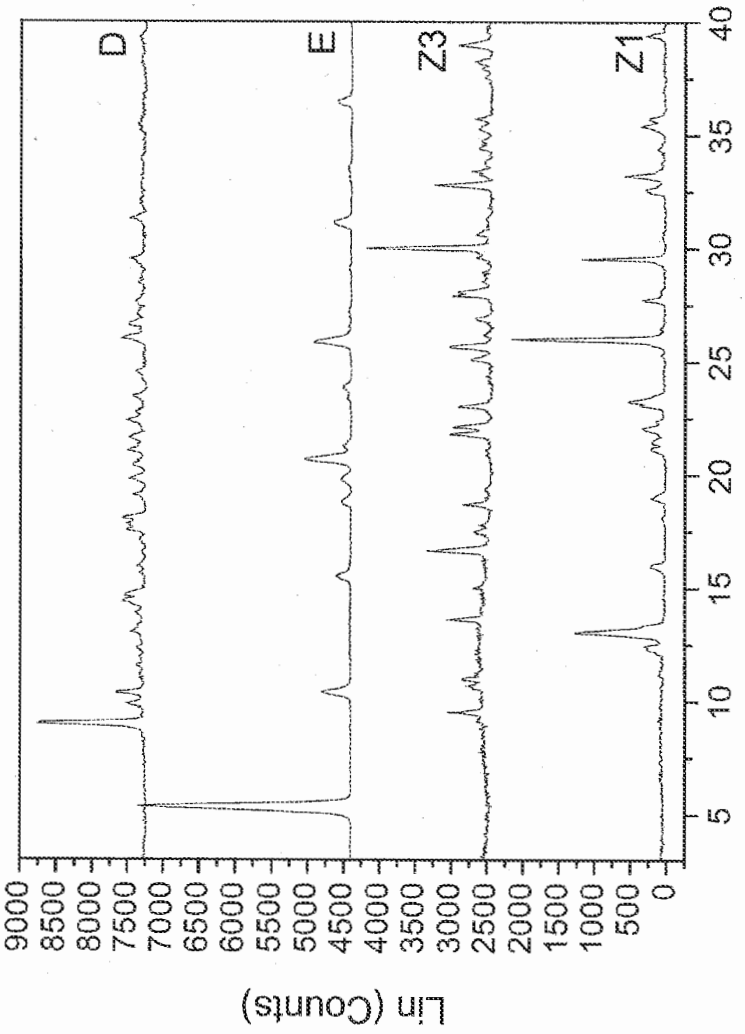
cm -1

FIG. 4


D
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8000
7500
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2-Theta-Scale

FIG. 5

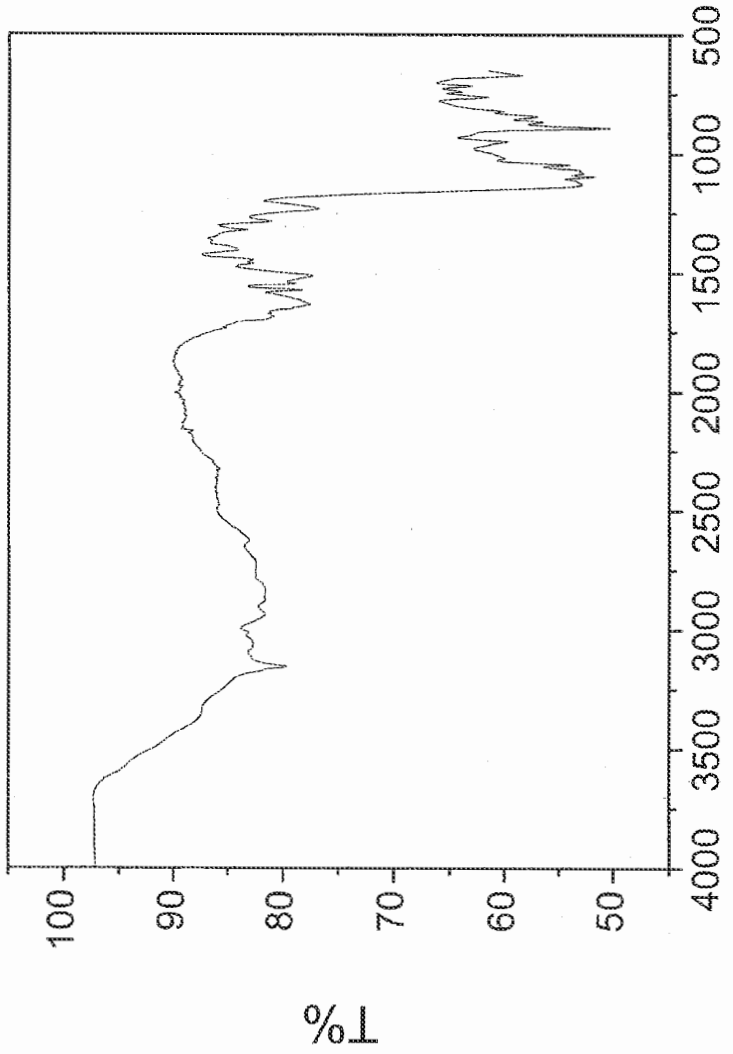
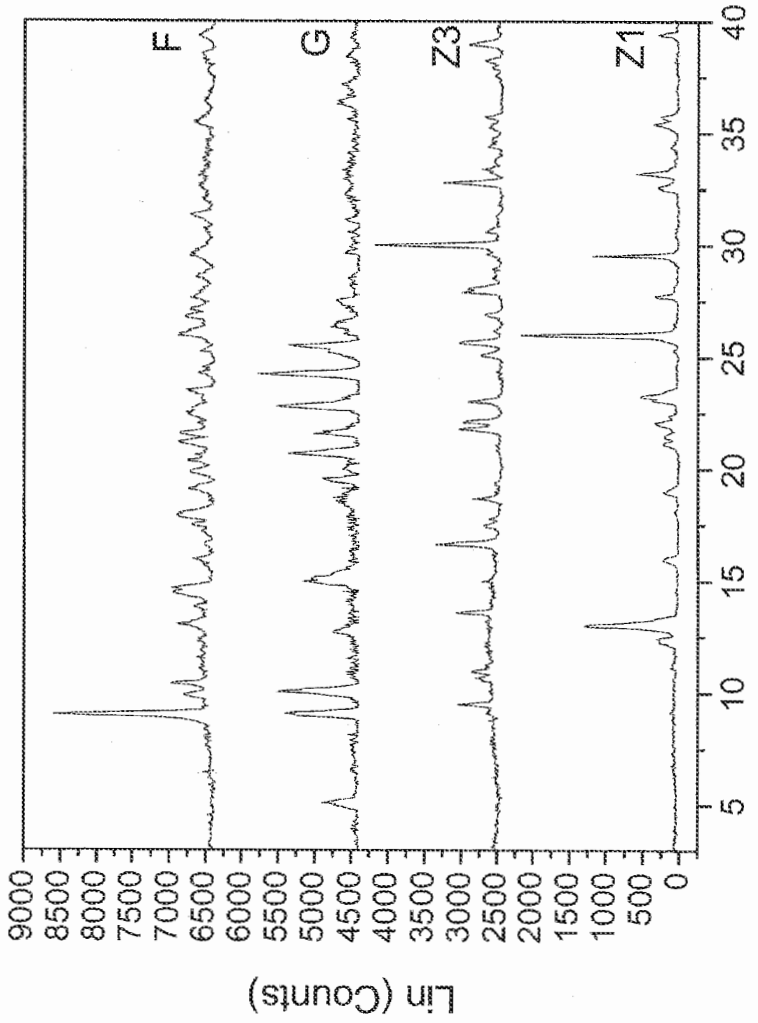


FIG. 6


F
G
Z3
Z1
Lin (Counts)
2-Theta-Scale
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1000
1500
2000
2500
3000
3500
4000
4500
5000
5500
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7500
8000
8500
9000
5
10
15
20
25
30
35
40

FIG. 7

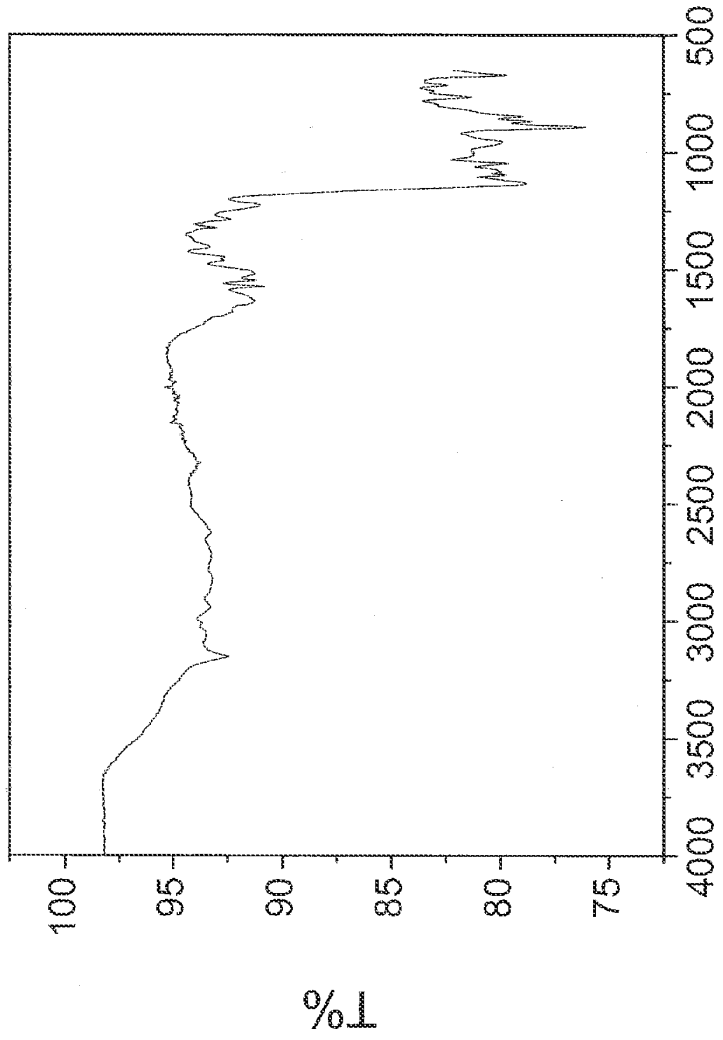


FIG. 8

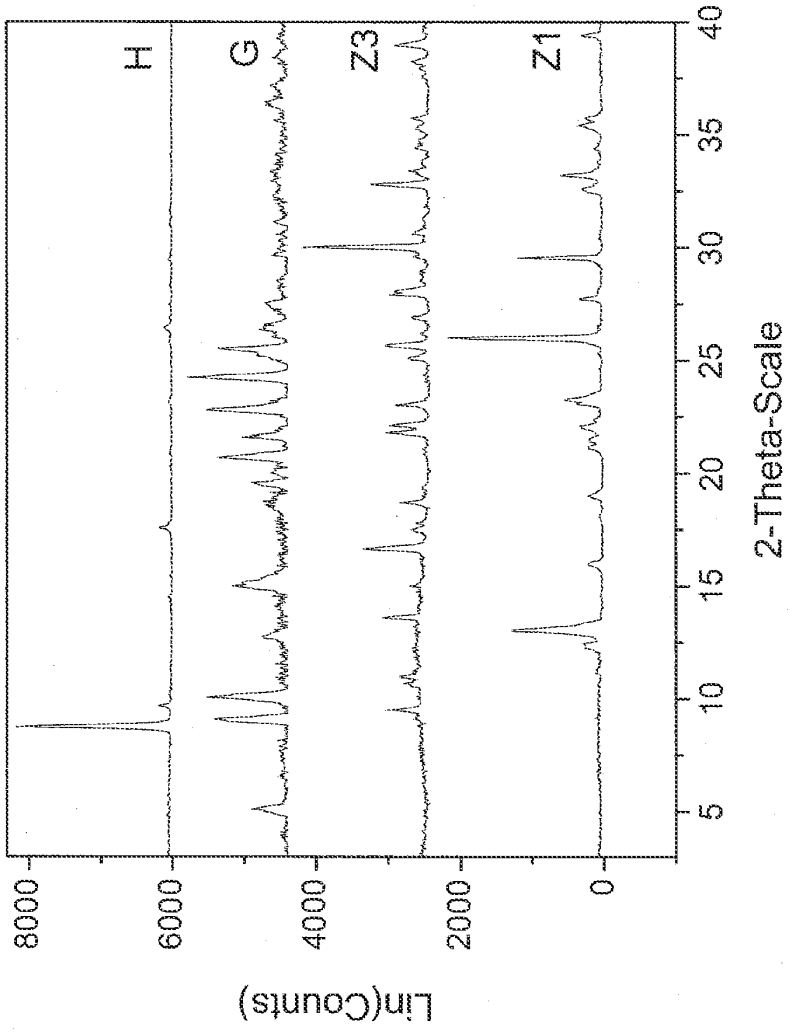

H
G
Z3
Z1
8000
6000
4000
2000
0
Lin(Counts)
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 9

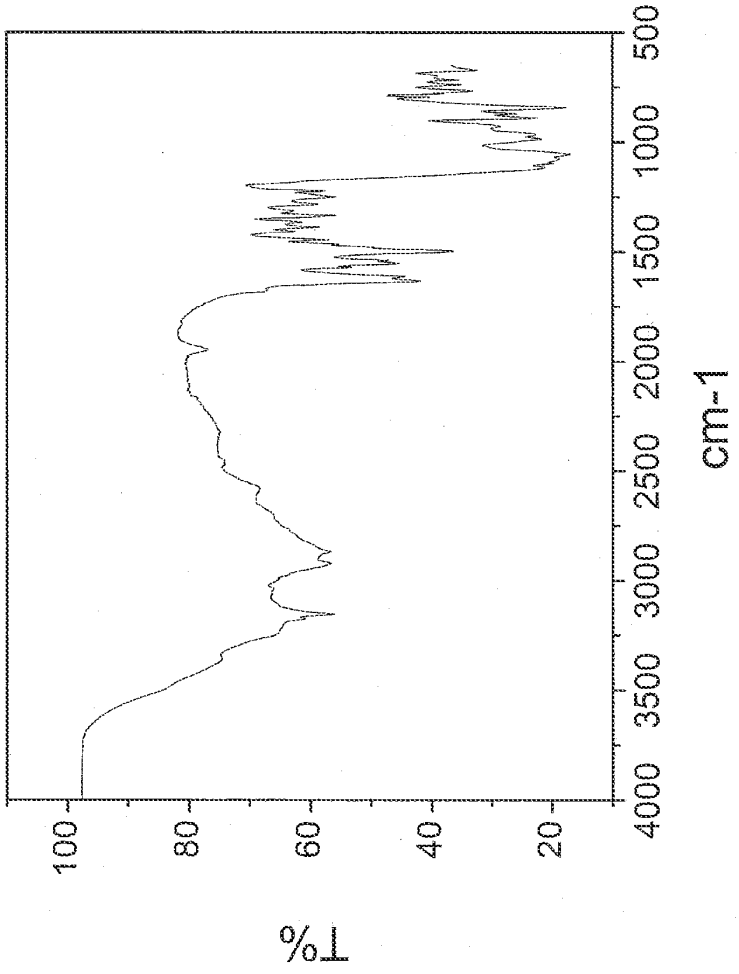


FIG. 10

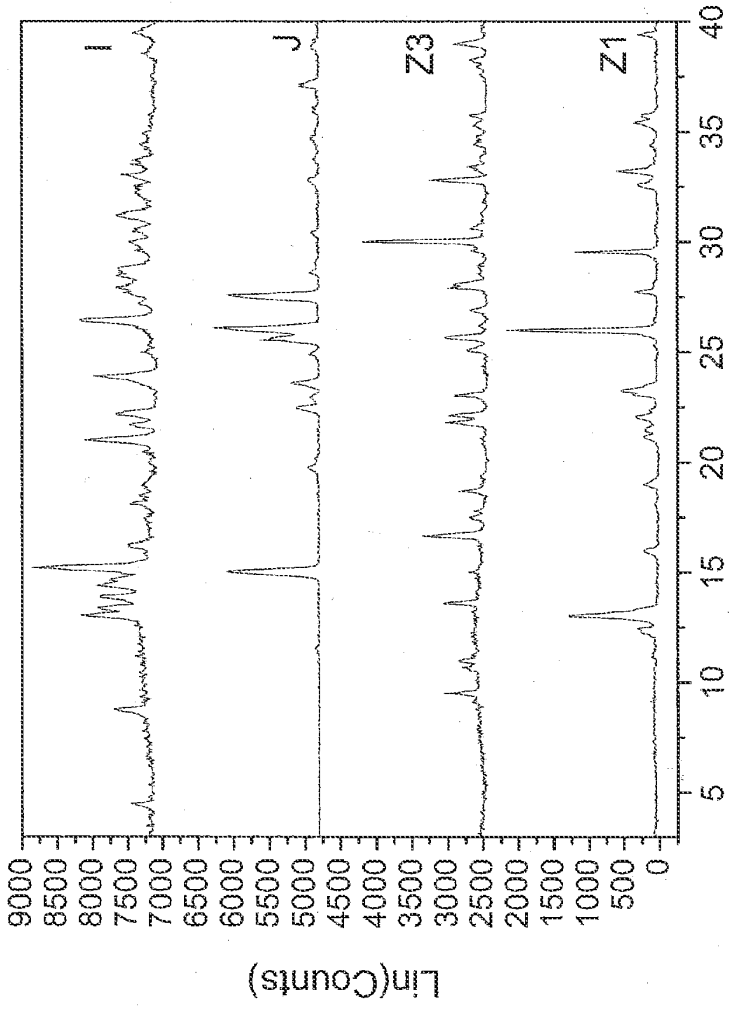

I
J
Z3
Z1
Lin(Counts)
2-Theta-Scale
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40

FIG. 11

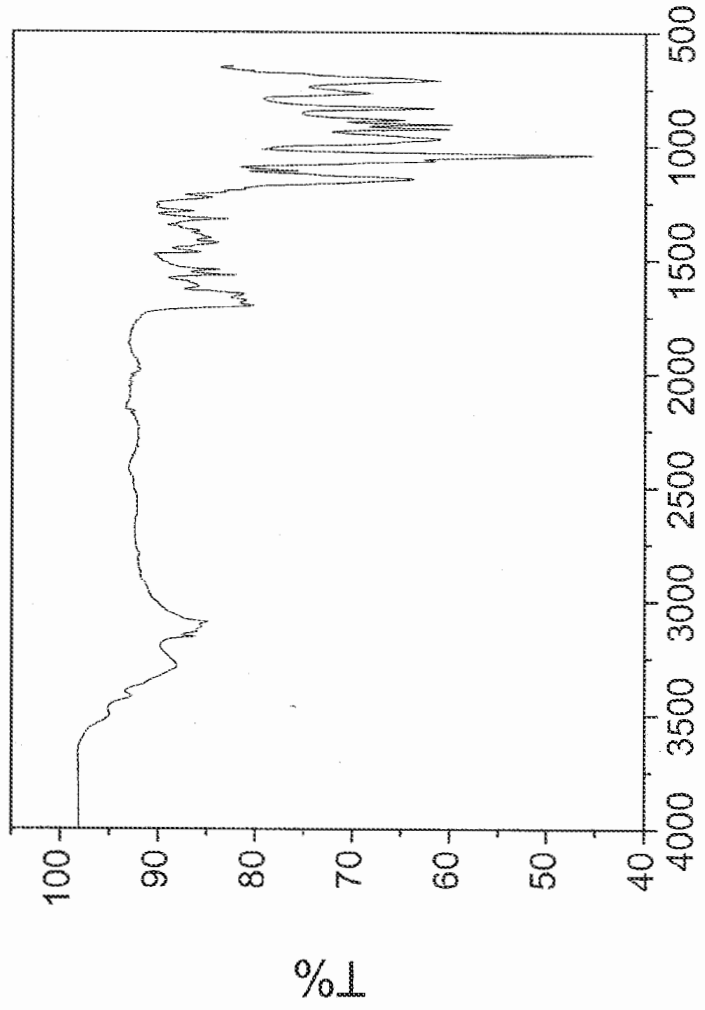

T%
100
90
80
70
60
50
40
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 12

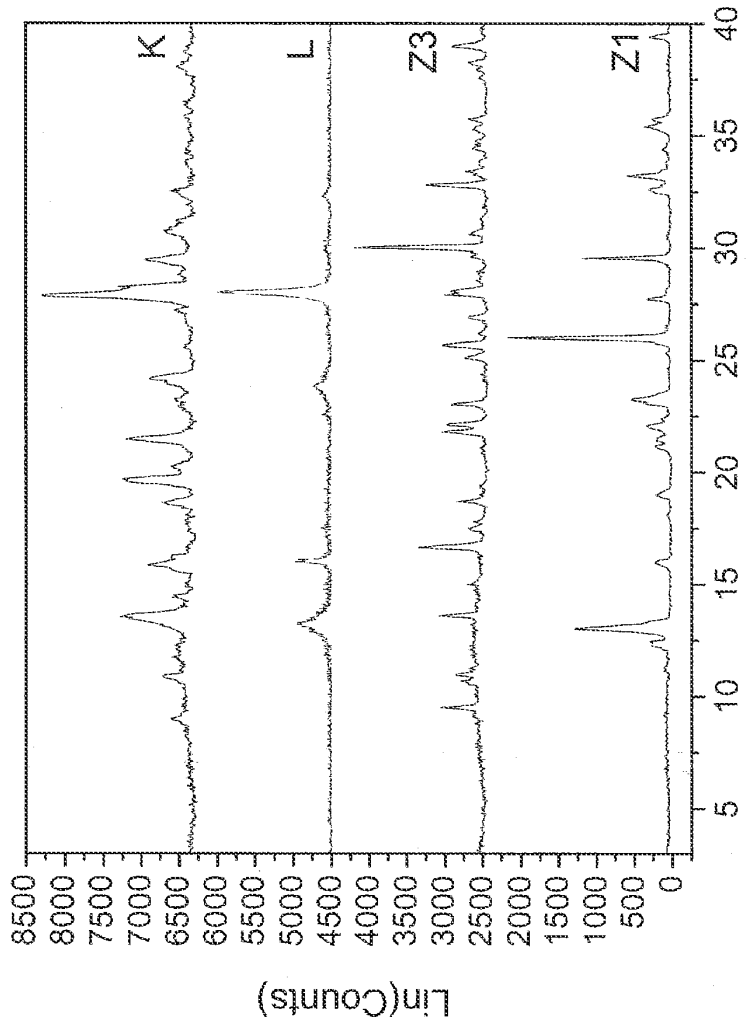

K
L
Z3
Z1
Lin(Counts)
2-Theta-Scale
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40

FIG. 13

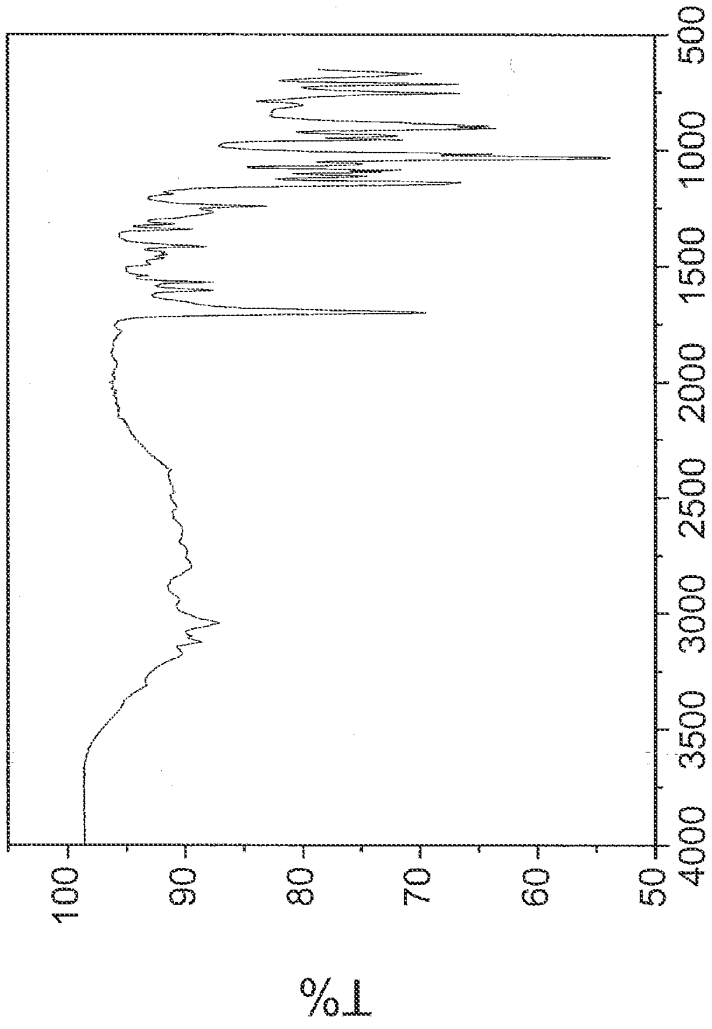


FIG. 14

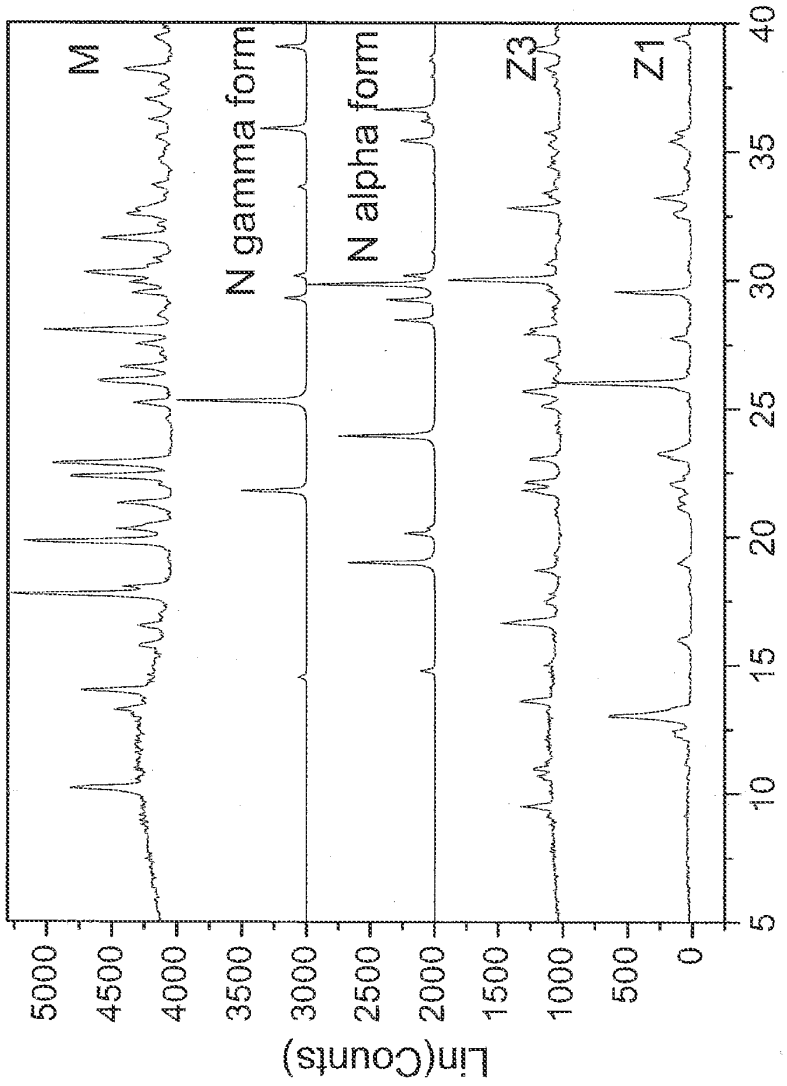

M
N gamma form
N alpha form
Z3
Z1
Lin(Counts)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
2-theta

FIG. 15

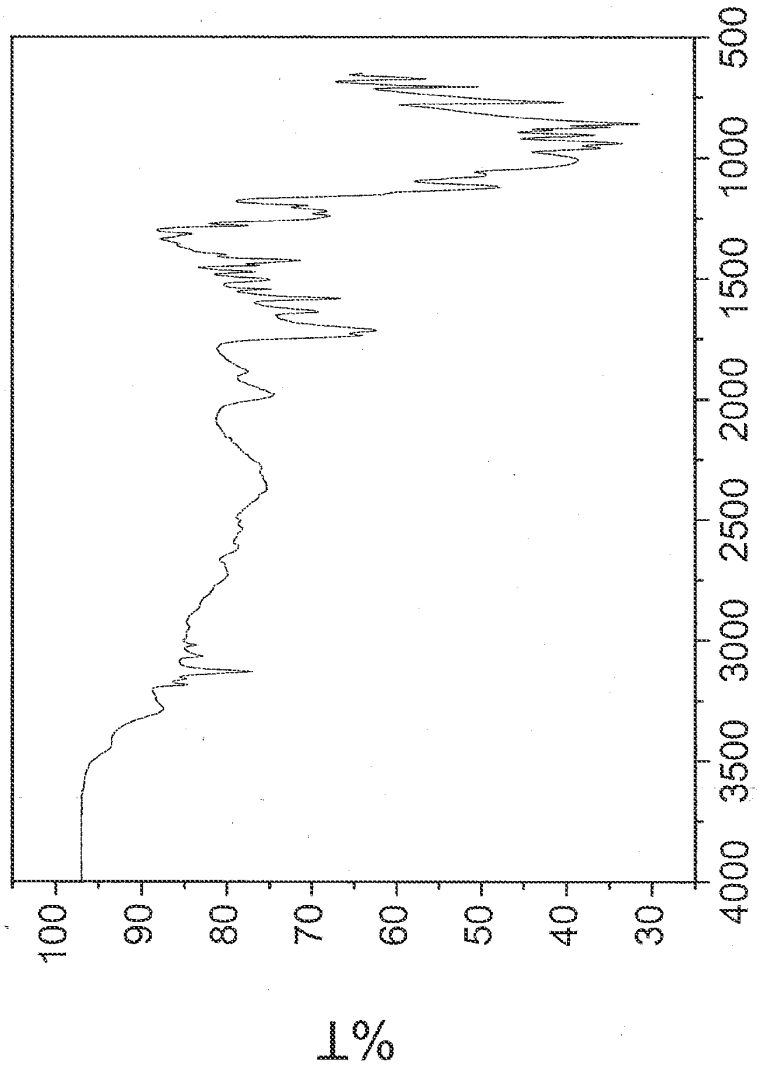

100
90
80
70
60
50
40
30
%T
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 16

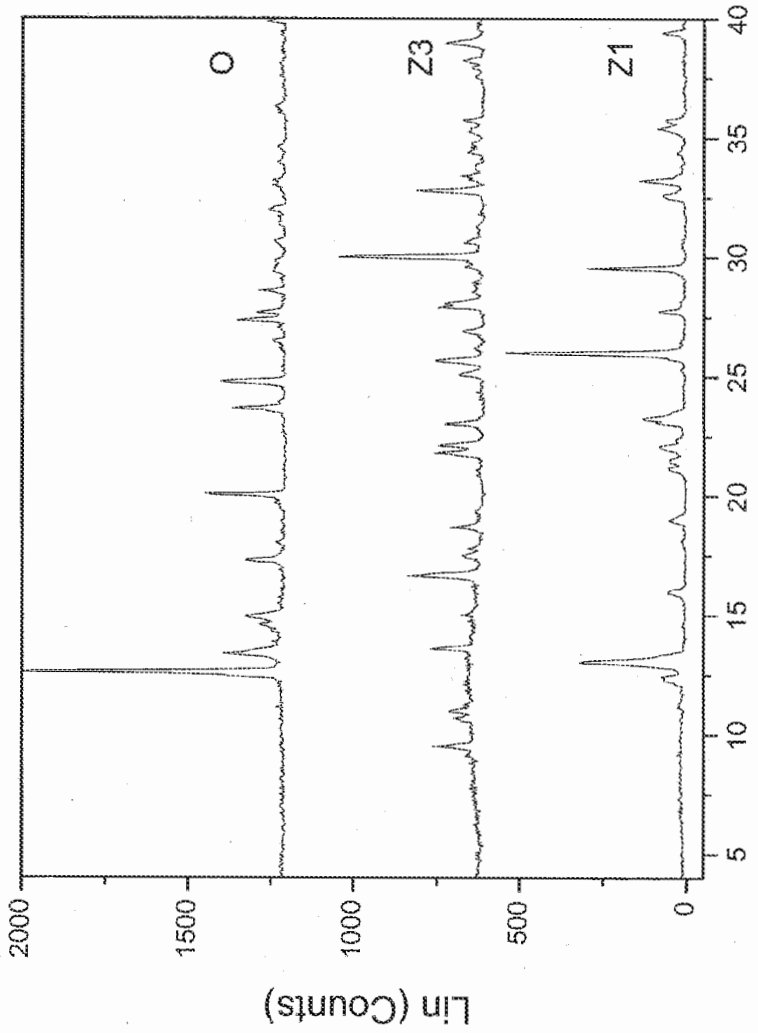

O
Z3
Z1
Lin (Counts)
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
2-Theta - Scale

FIG. 17

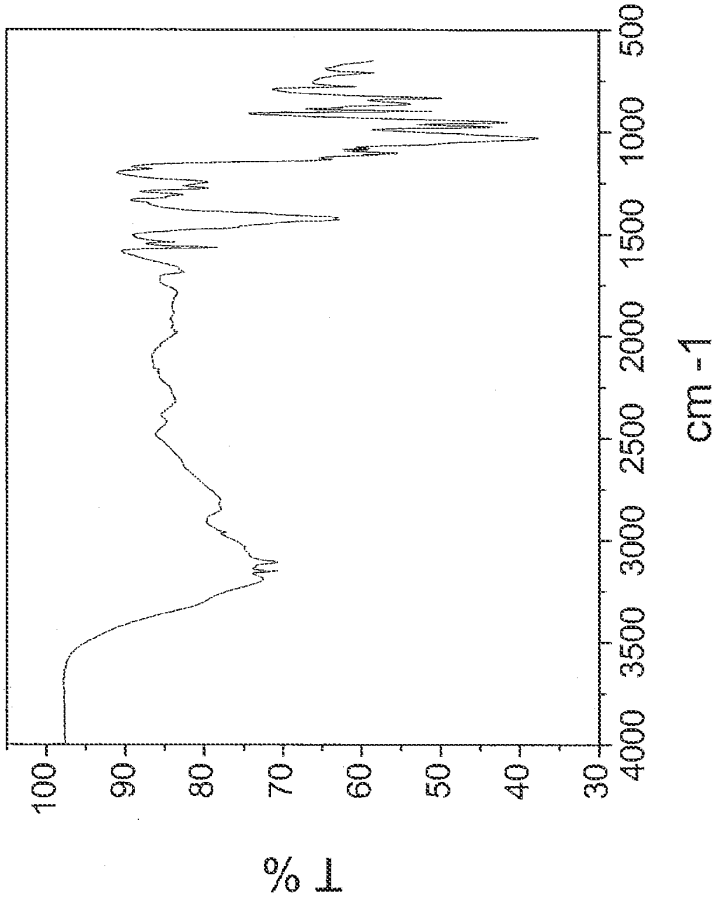

T %
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
500
cm -1

FIG. 18

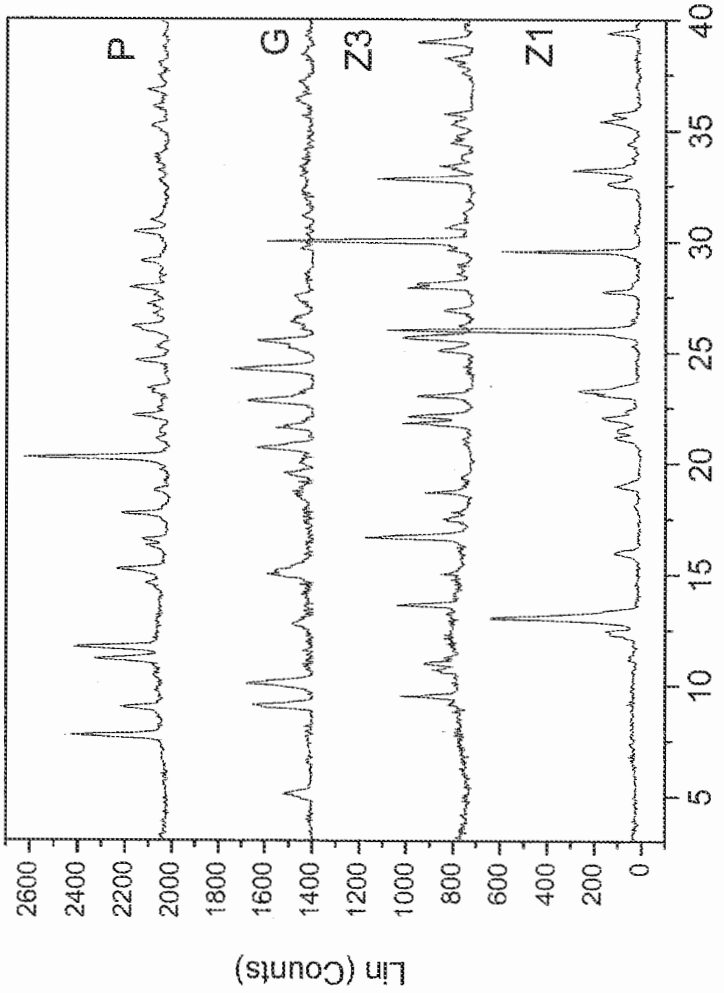

P
G
Z3
Z1
Lin (Counts)
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 19

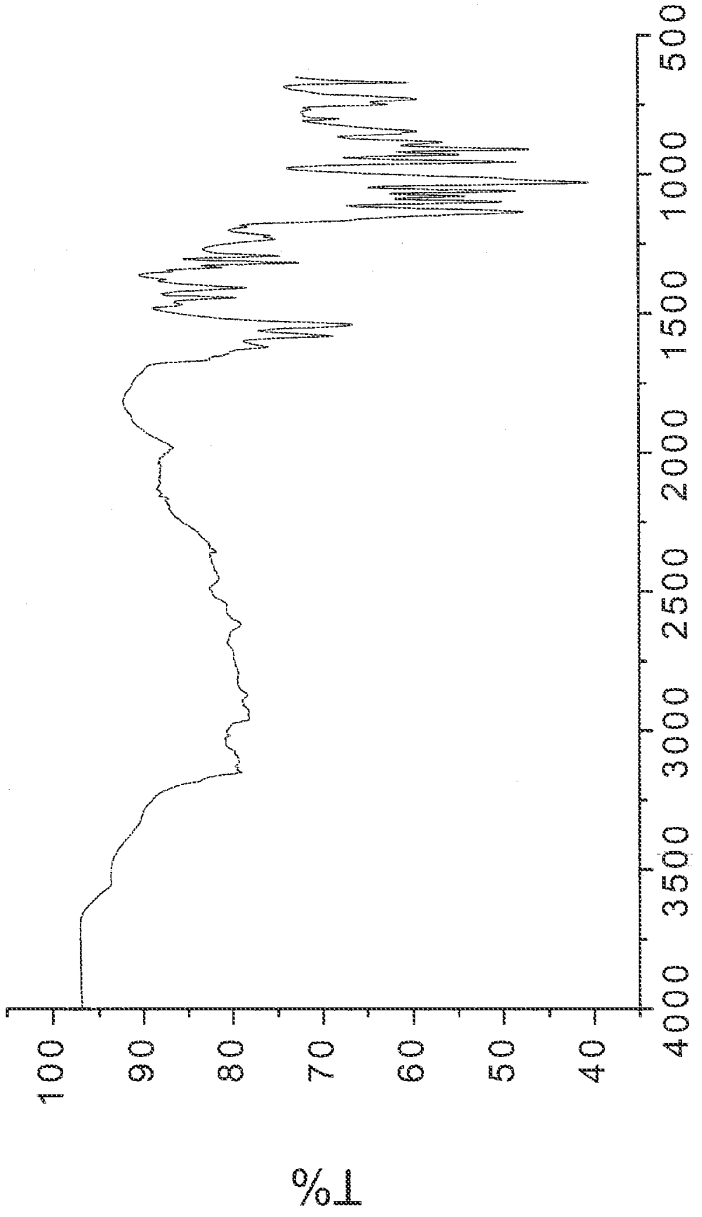

100
90
80
70
60
50
40
T%
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 20

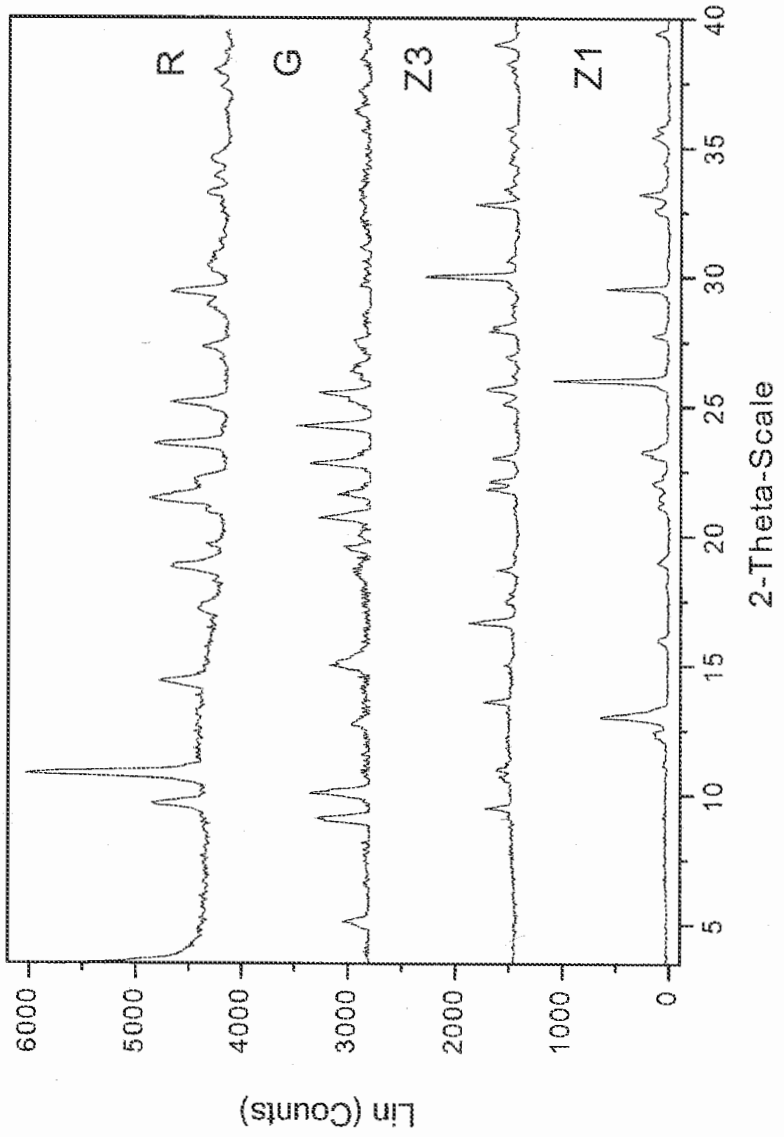

R
G
Z3
Z1
Lin (Counts)
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 21

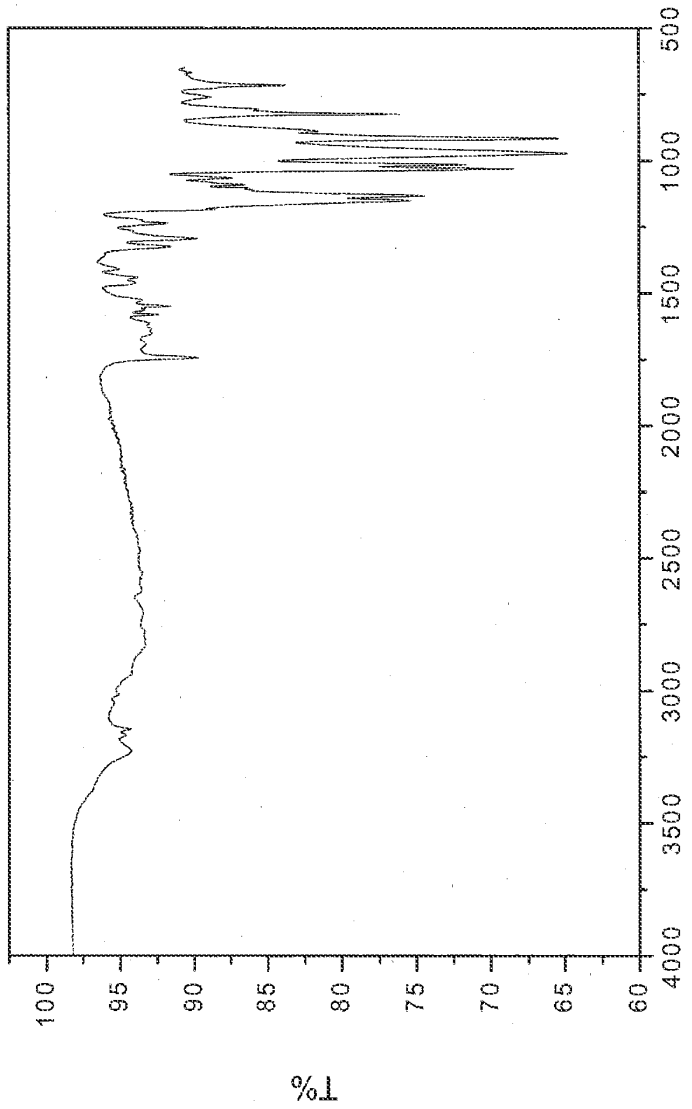

100
95
90
85
80
75
70
65
60
%T
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 22

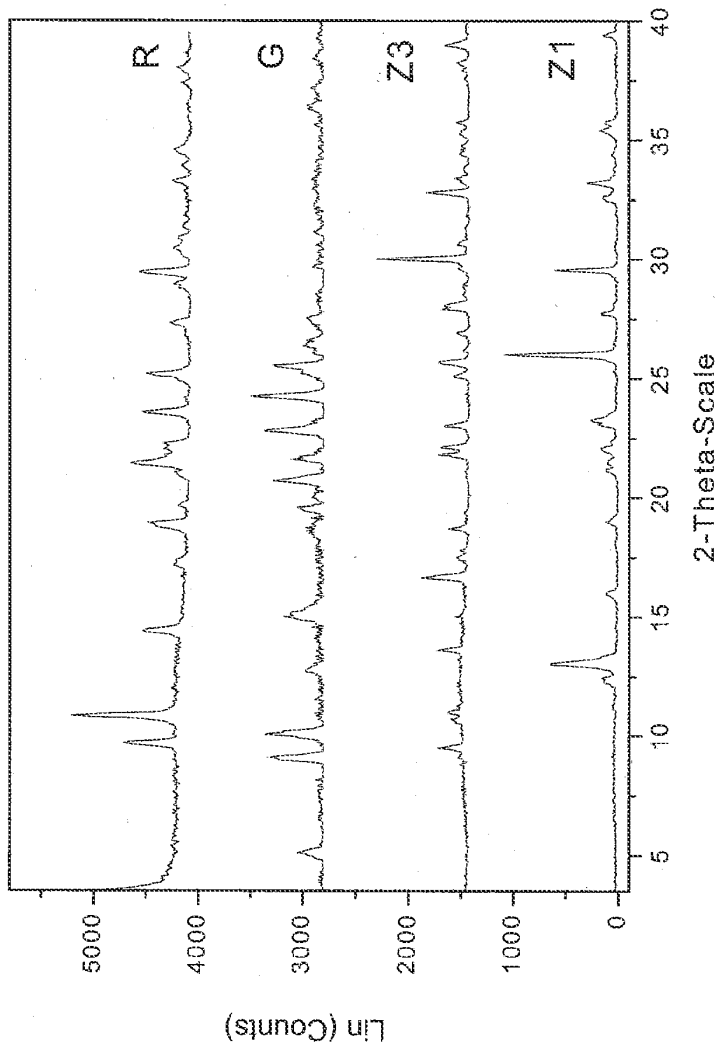

R
G
Z3
Z1
Lin (Counts)
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 23

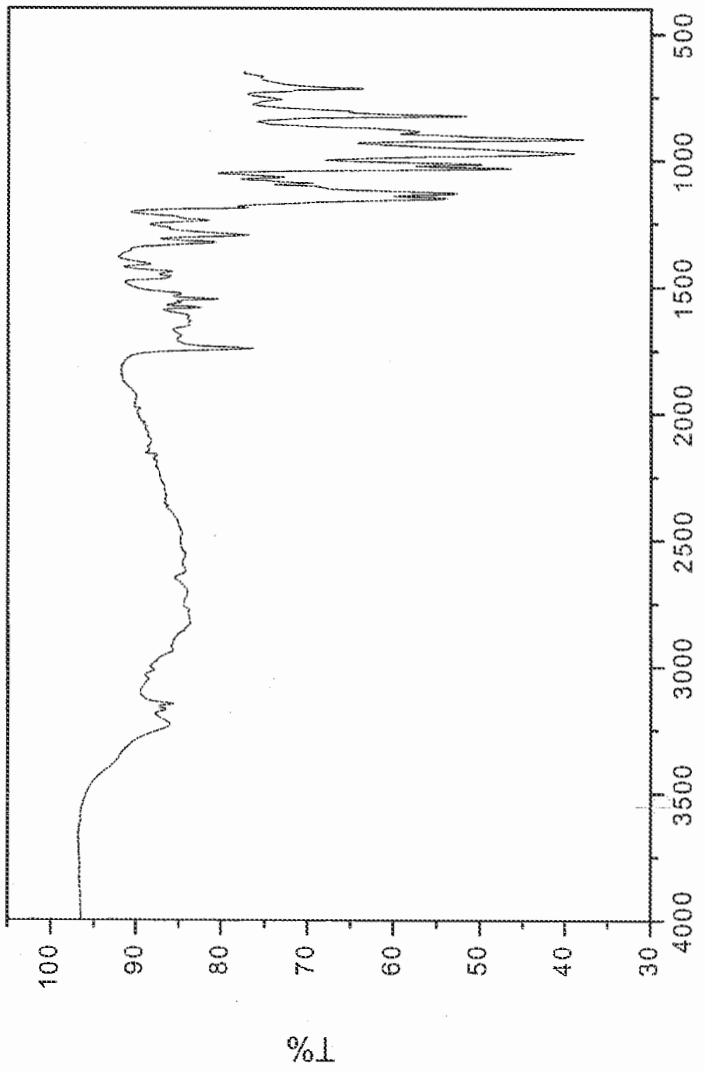

100
90
80
70
60
50
40
30
%T
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 24

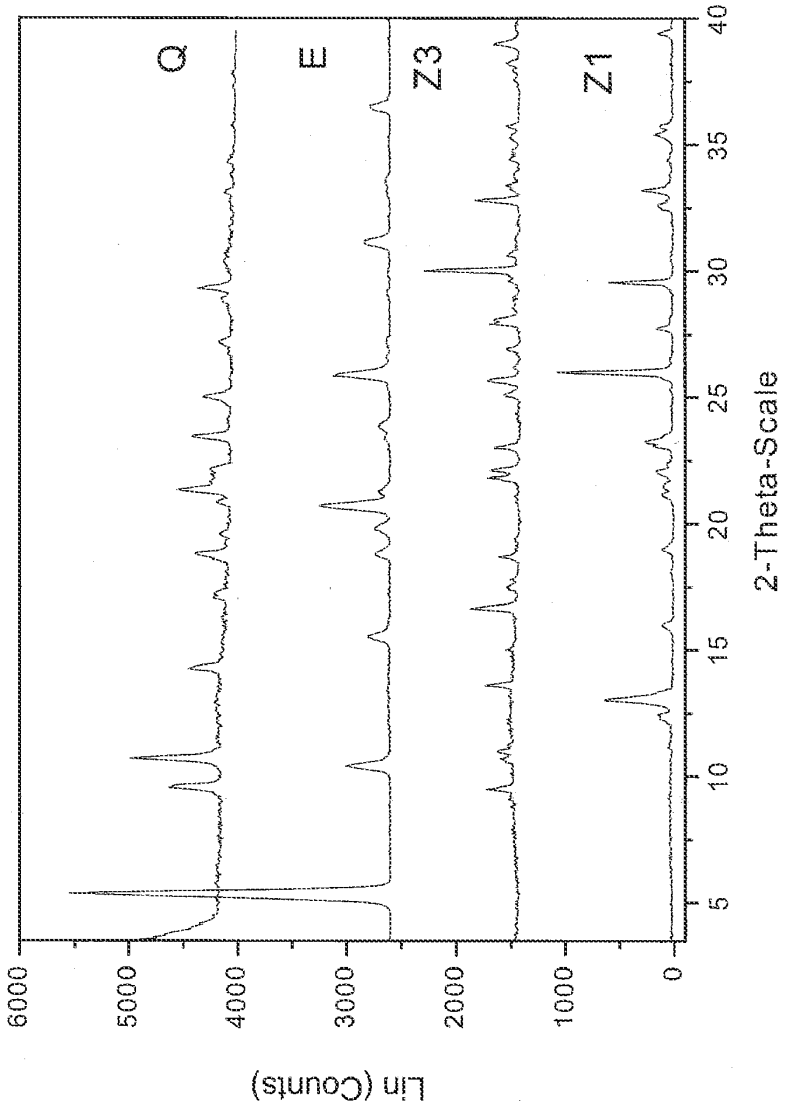

Q
E
Z3
Z1
Lin (Counts)
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
2-Theta-Scale

FIG. 25

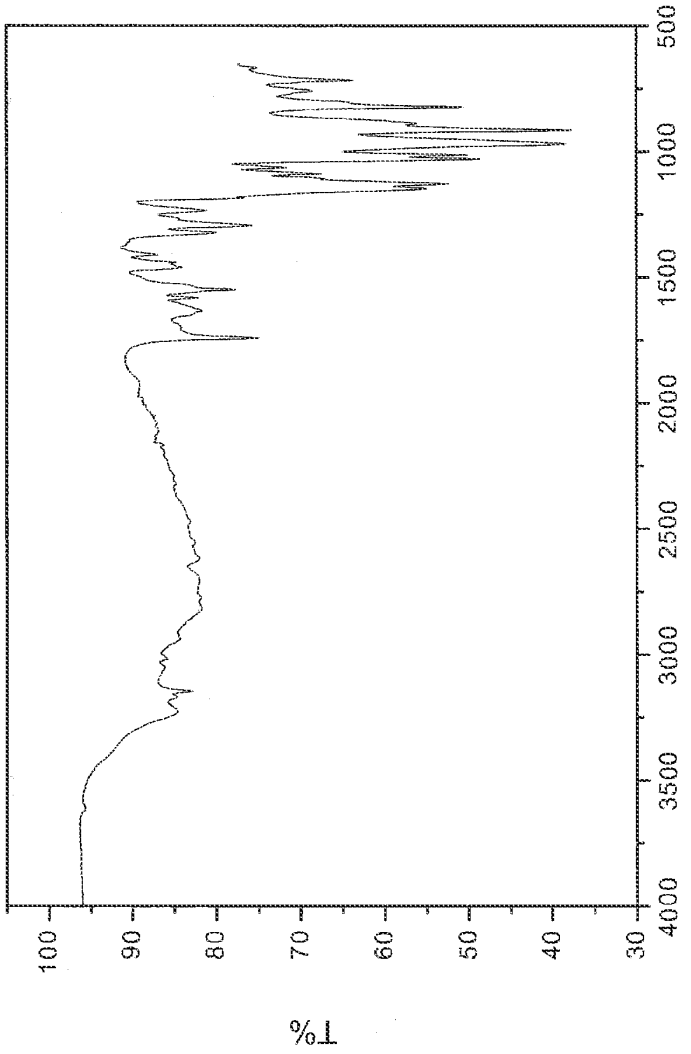

T%
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG. 26

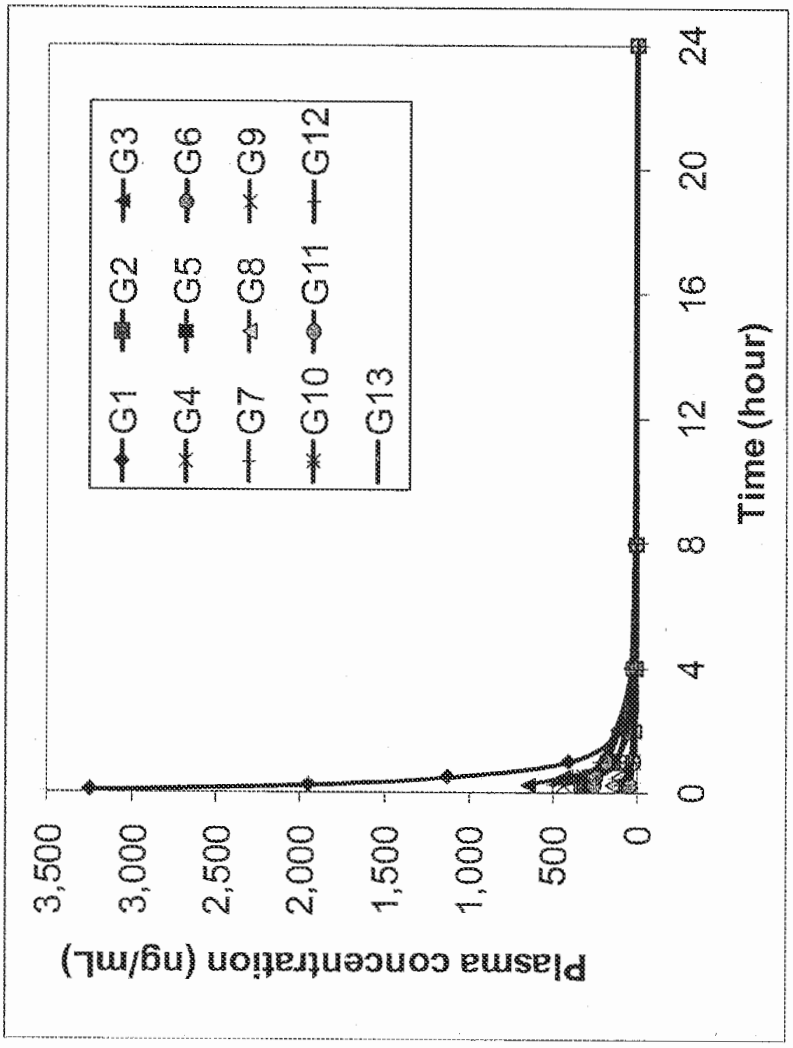

Plasma concentration (ng/mL)
3,500
3,000
2,500
2,000
1,500
1,000
500
0
0
4
8
12
16
20
24
Time (hour)
G1
G2
G3
G4
G5
G6
G7
G8
G9
G10
G11
G12
G13

FIG. 27

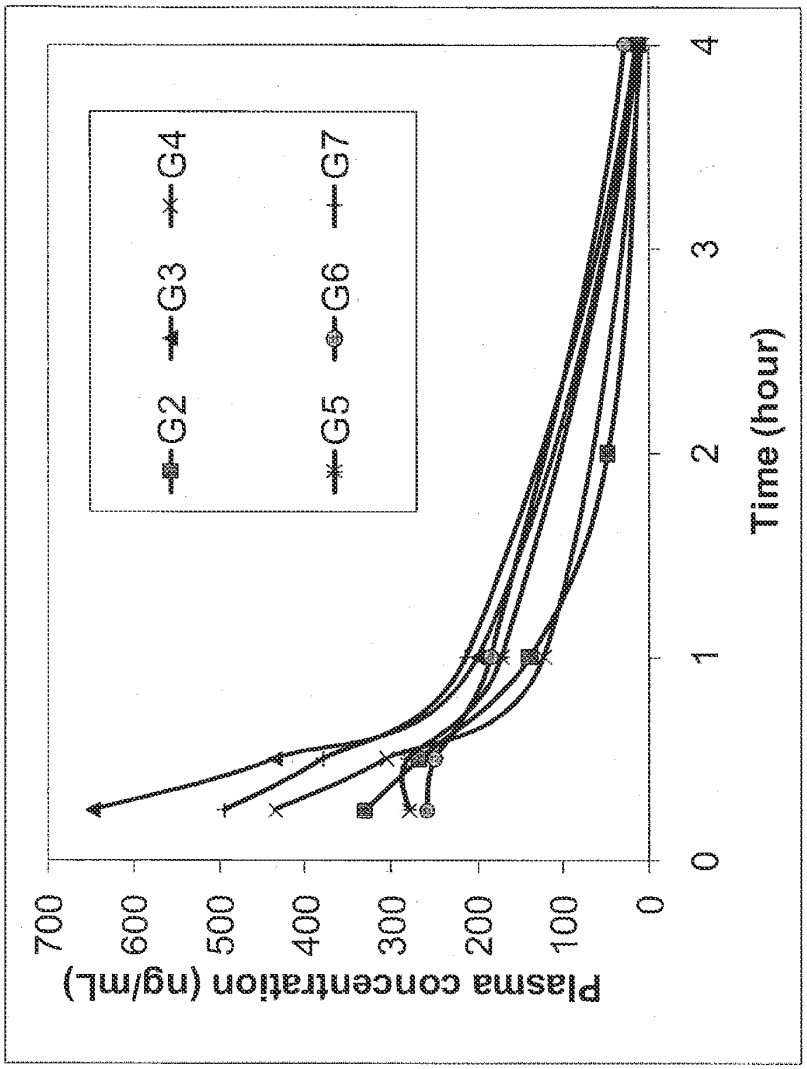

Plasma concentration (ng/mL)
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)
G2
G3
G4
G5
G6
G7

FIG. 28

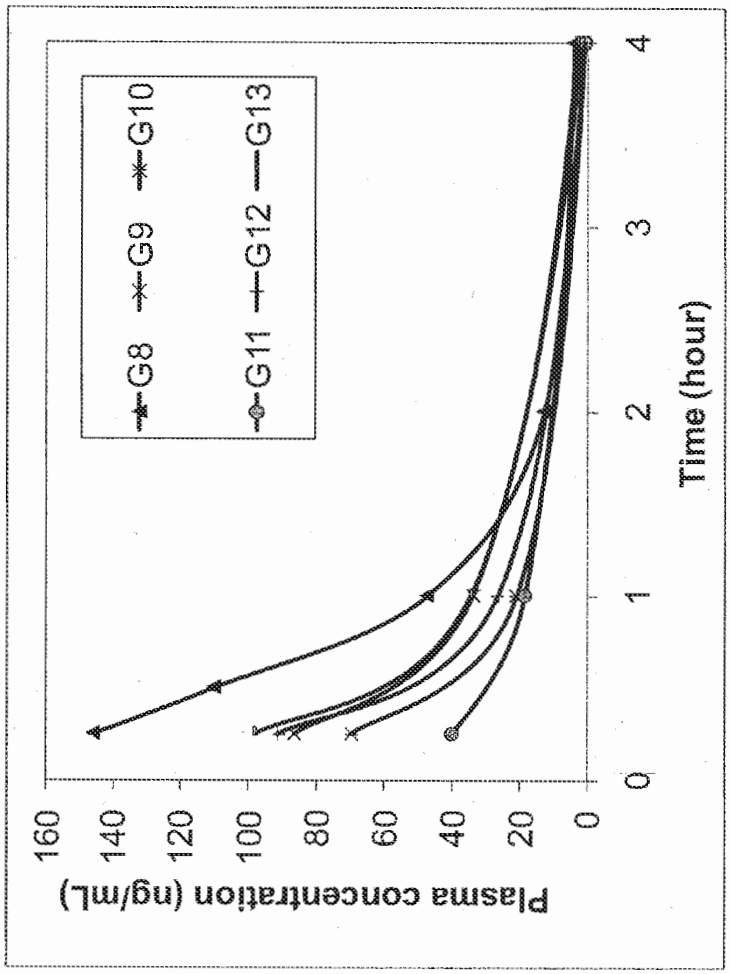

G8
G9
G10
G11
G12
G13
Plasma concentration (ng/mL)
0
20
40
60
80
100
120
140
160
Time (hour)
0
1
2
3
4

FIG. 29

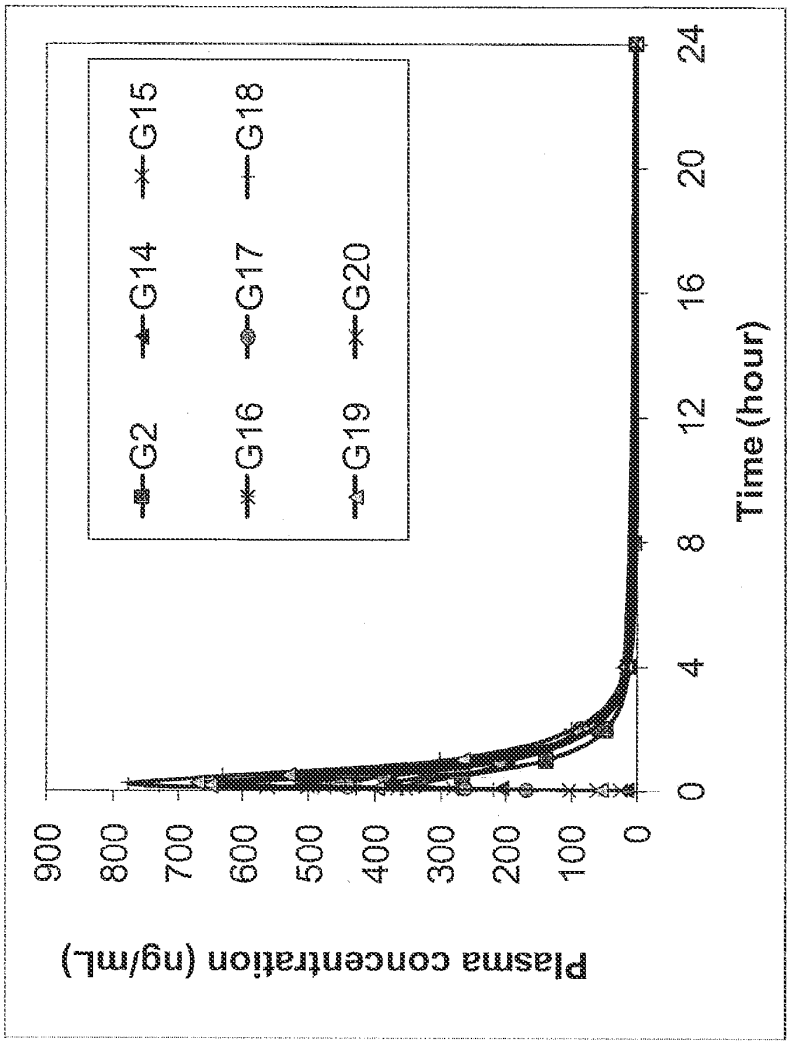

Plasma concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (hour)
G2
G14
G15
G16
G17
G18
G19
G20

FIG. 30

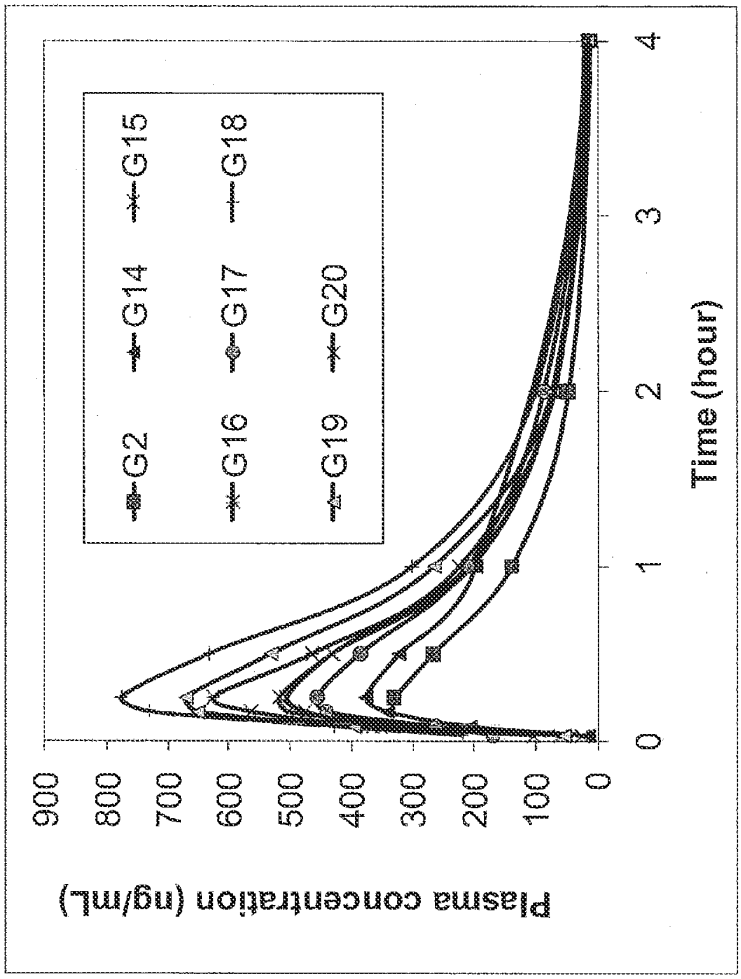

Plasma concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)
G2
G14
G15
G16
G17
G18
G19
G20

FIG. 31

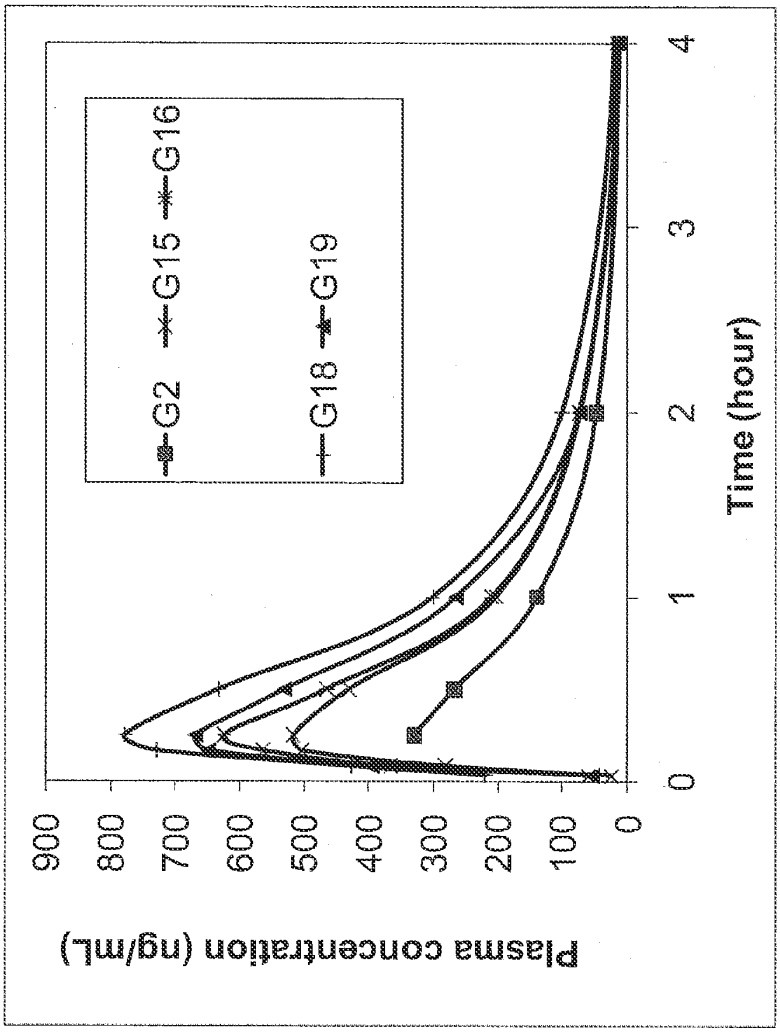

Plasma concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)
G2
G15
G16
G18
G19

FIG. 32

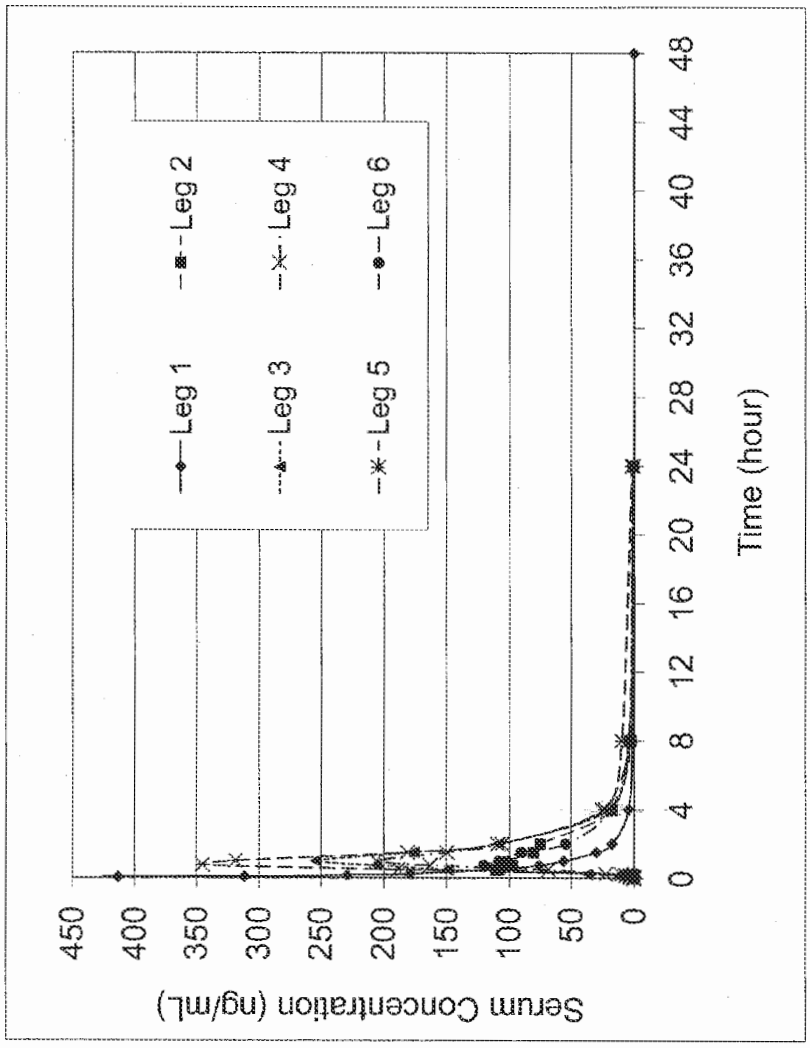

Serum Concentration (ng/mL)
450
400
350
300
250
200
150
100
50
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (hour)
Leg 1
Leg 2
Leg 3
Leg 4
Leg 5
Leg 6

FIG. 33

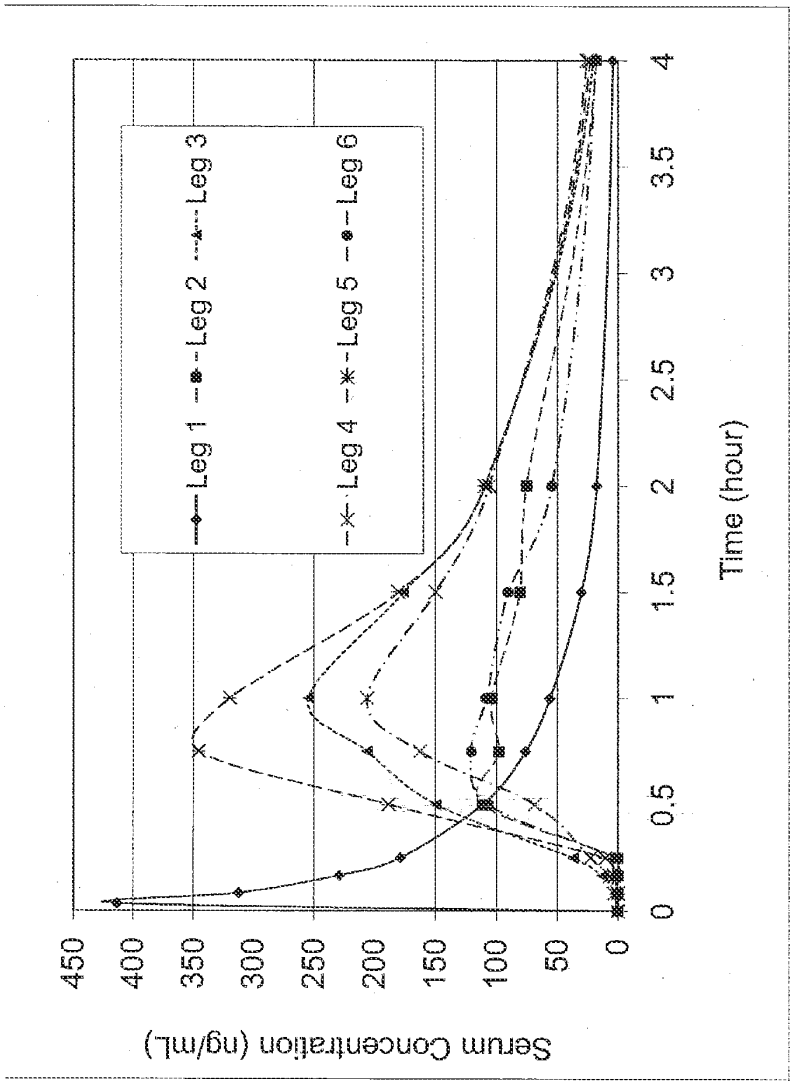

Serum Concentration (ng/mL)
450
400
350
300
250
200
150
100
50
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hour)
Leg 1
Leg 2
Leg 3
Leg 4
Leg 5
Leg 6

FIG. 34

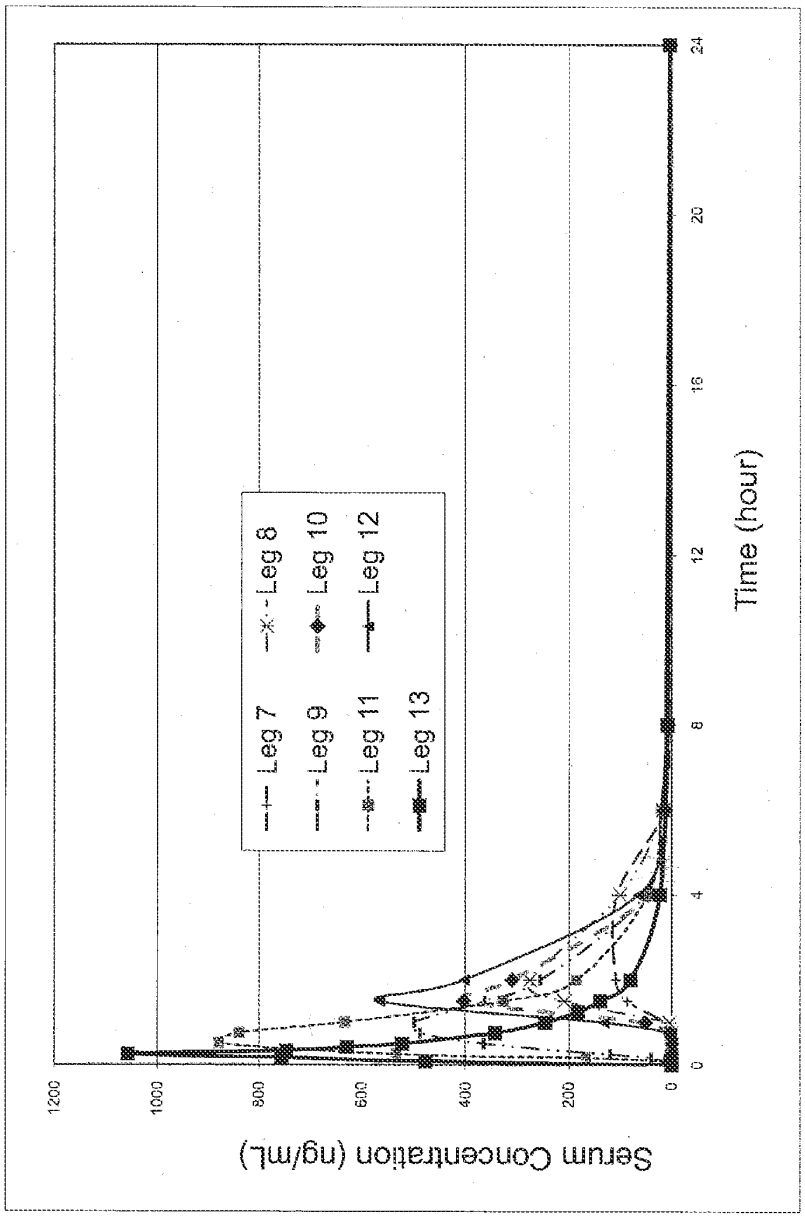

Serum Concentration (ng/mL)
1200
1000
800
600
400
200
0
Time (hour)
0
4
8
12
16
20
24
Leg 7
Leg 8
Leg 9
Leg 10
Leg 11
Leg 12
Leg 13

FIG. 35

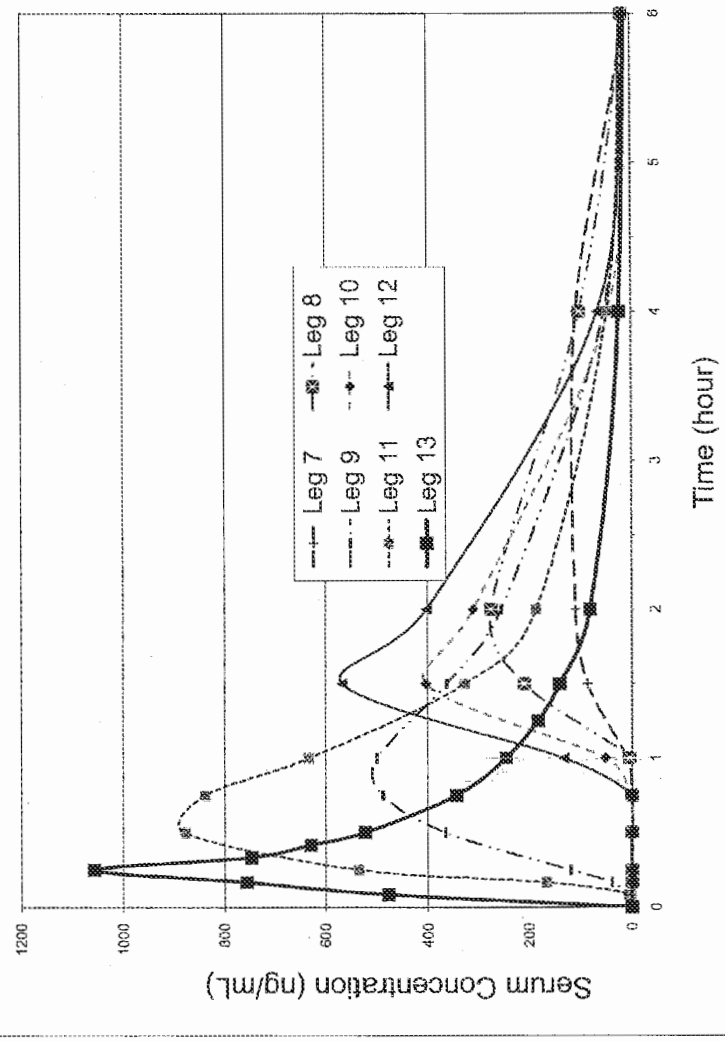

Serum Concentration (ng/mL)
1200
1000
800
600
400
200
0
Time (hour)
0
1
2
3
4
5
6
Leg 7
Leg 8
Leg 9
Leg 10
Leg 11
Leg 12
Leg 13

FIG. 36

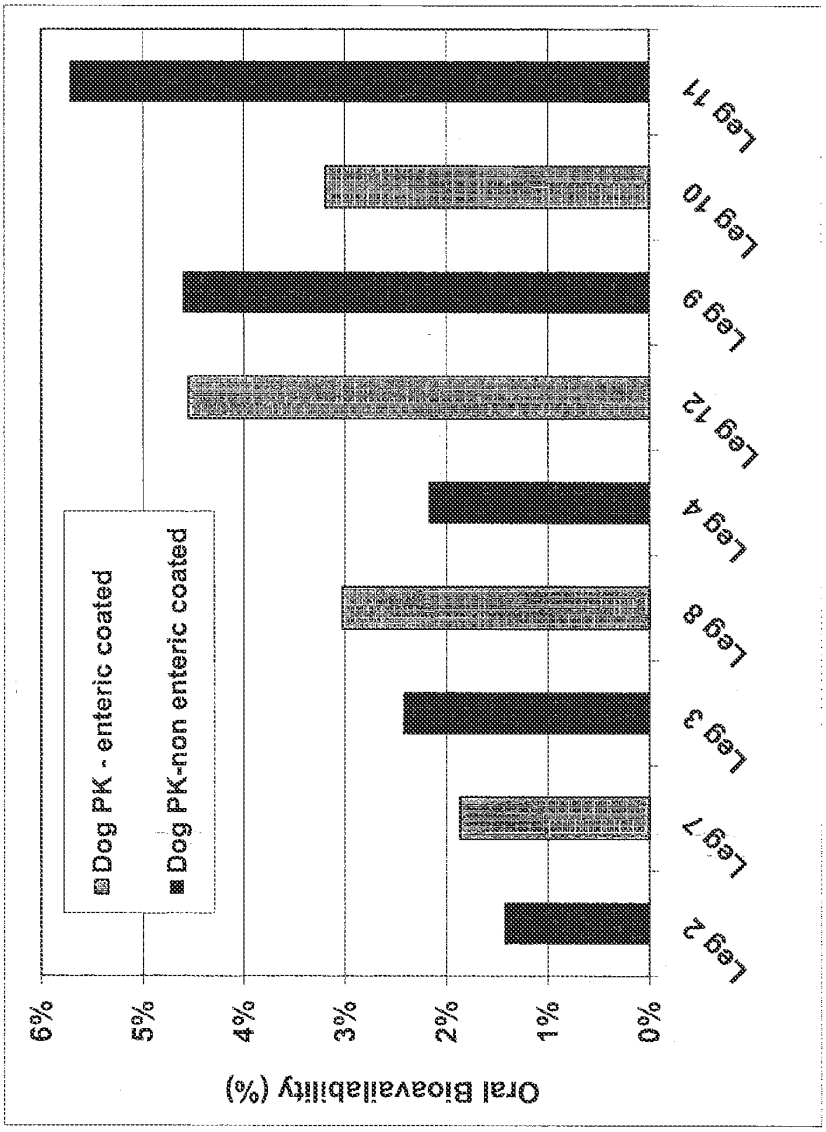

Oral Bioavailability (%)
6%
5%
4%
3%
2%
1%
0%
Dog PK - enteric coated
Dog PK-non enteric coated
Leg 11
Leg 10
Leg 9
Leg 12
Leg 4
Leg 8
Leg 3
Leg 7
Leg 2

FIG. 37

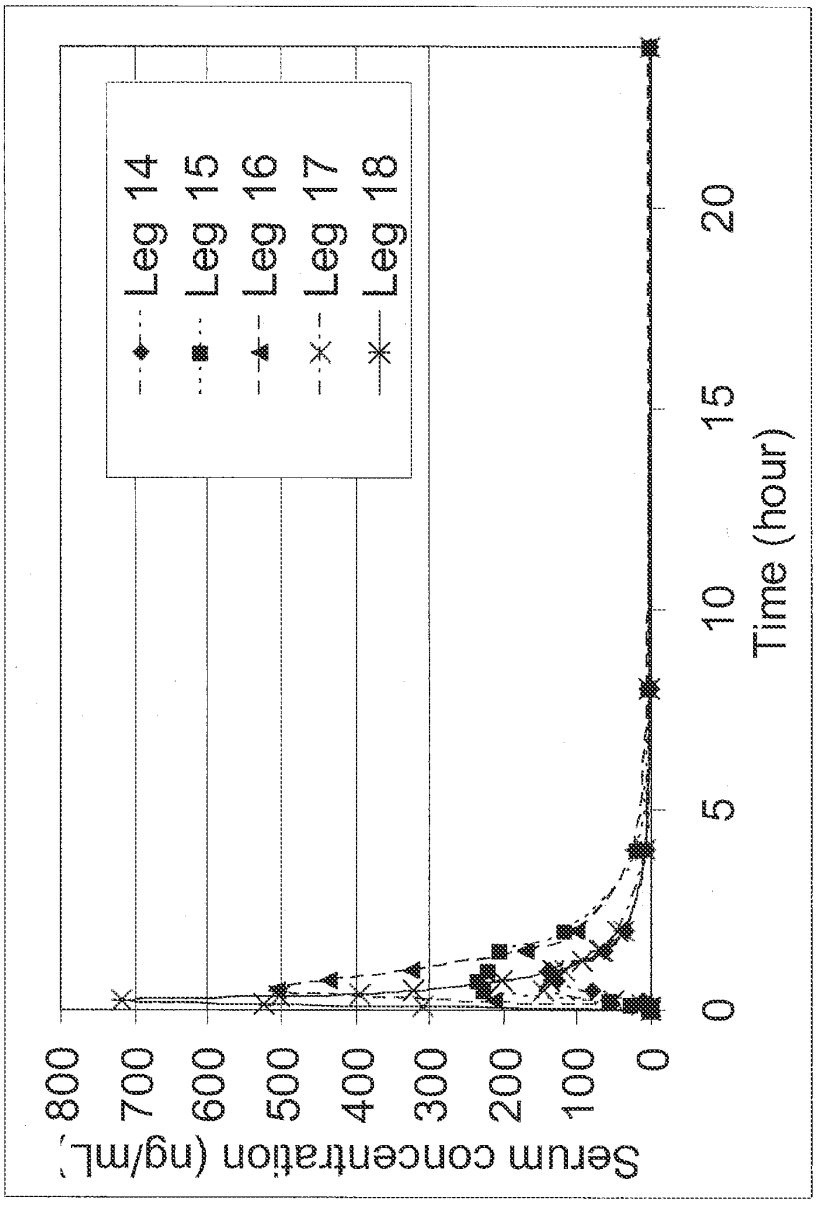

Leg 14
Leg 15
Leg 16
Leg 17
Leg 18
Serum concentration (ng/mL)
800
700
600
500
400
300
200
100
0
0
5
10
15
20
Time (hour)

FIG. 38

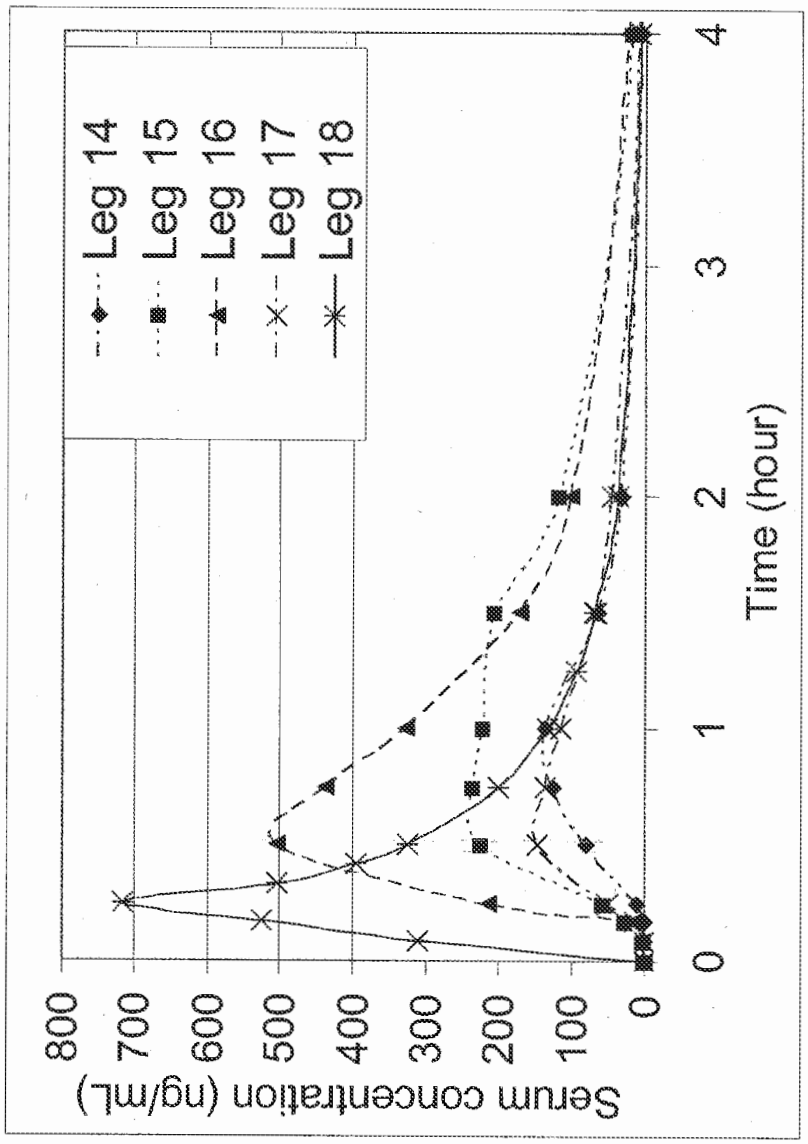

Leg 14
Leg 15
Leg 16
Leg 17
Leg 18
Serum concentration (ng/mL)
800
700
600
500
400
300
200
100
0
0
1
2
3
4
Time (hour)

FIG. 39

CRYSTALLIZATION METHOD AND BIOAVAILABILITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. application 61/230,222, filed Jul. 31, 2009; to U.S. application 61/288,036, filed Dec. 18, 2009; to U.S. application 61/302,110, filed Feb. 6, 2010; to U.S. application 61/312,879, filed Mar. 11, 2010; to U.S. application 61/318,503, filed Mar. 29, 2010; and to U.S. application 61/359,544, filed Jun. 29, 2010; each of which is incorporated herein by reference.

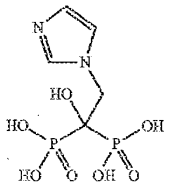
FIELD OF THE INVENTION

[0002] This disclosure pertains to improvement of the aqueous solubility and permeability of poorly permeable and sparingly water soluble drug compounds through generating novel crystalline forms of such drugs. The novel forms include but are not limited to cocrystals, salts, hydrates, solvates, solvates of salts, and mixtures thereof. Methods for the preparation and pharmaceutical compositions suitable for drug delivery systems that include one or more of these new forms are disclosed.

BACKGROUND OF THE INVENTION

[0003] Many Biopharmaceutic Classification System (BCS) class III or IV drugs suffer from the lack of gastrointestinal (GI) tract membrane permeability leading to poor oral bioavailability. Different strategies have been implemented to improve the permeability and subsequently the oral bioavailability of such drugs. For example, the U.S. patent application 20060068010 describes a formulation method for improving the permeability of drugs and subsequently increasing their bioavailability by granulation of the physical solid mixture of the drug with one or more amino acids, at least one intergranular hydrophilic polymer, and an additional immediate release excipient. Another application WO 200602009 A1 disclosed the increase of the oral bioavailability for poorly permeable drugs such as bisphosphonates; risedronate as one of those drugs was mixed with a chelating agent such as ethylenediaminetetraacetate (EDTA) and other excipients to make an oral dosage form. Yet another application, WO 2007093226 A1, describes a method for improving the bioavailability of ibandronate by generating a physical mixture of the drug together with a modified amino acid (acylation or sulphonation of the amino group with phenyl or cyclohexyl) and other excipients. Another application WO 2003007916 A1 reports a gastric retention system to improve the bioavailability of a poorly permeable drug, alendronate, which was orally formulated with vitamin D and released an hour after the immediate release of vitamin D. WO 2006080780 discloses yet another method to improve the permeability and bioavailability of alendronate, a poorly permeable bisphosphonate, by mixing it with a biocompatible cationic polymer (i.e. water soluble chitosan) with up to a 10:1 weight ratio of the chitosan to the drug, while the resulting mixture can be formulated into a solid or liquid oral dosage form. A further method of improving permeability of drug materials was discussed in the U.S. patent application 2007/014319 A1, where an oral dosage form was formulated by a powder mixture of a bisphosphonic acid (e.g. zoledronic acid) together with an inactive ingredient (either an ester of a medium chain fatty acid or a lipophilic polyethylene glycol ester). A similar approach was disclosed in the US application 2007/0238707 A 1 where a medium length fatty acid or its derivative (6-20 carbon atom fatty acid chain) was physically mixed with a poorly permeable drug (e.g. zoledronic acid) in a capsule that was enterically coated.

[0004] Zoledronic acid, known as (1-hydroxy-2-imidazol-1-yl-1-phosphono-ethyl)phosphonic acid, is depicted by the following chemical structure:



Zoledronic acid is a third generation bisphosphonate which far exceeds the previous generations in terms of efficacy and is used predominately for indications of osteoporosis, Paget's disease, hypercalcemia, and inhibition of bone metastasis. It was originally developed by Novartis and marketed as the monohydrate under the brand names Zometa® and Reclast®. Zoledronic acid was first approved in 2000 for the treatment of hypercalcemia in Canada. It was later approved for use in the US for hypercalcemia in 2001, for multiple myeloma and bone metastases from solid tumors in 2002, and for osteoporosis and Paget's disease in 2007. Clinical trials have also been conducted or are on-going exploring the use of zoledronic acid in neoadjuvant or adjuvant cancer therapy, Coleman, et al., British J Cancer 2010; 102(7):1099-1105, Gnant, et al., New England J. Medicine. 2009, 360 (17):679-691 and Davies, et al. J Clinical Oncology, 2010, 28(7s): Abstract 8021. Zoledronic acid is administered as an intravenous (IV) dose of 4 mg over 15 minutes for hypercalcemia of malignancy, multiple myeloma, and bone metastases from solid tumors, while an IV dose of 5 mg over 15 minutes is used for osteoporosis and Paget's disease.

[0005] Zoledronic acid is sparingly soluble in water and 0.1 N HCl solution but is freely soluble in 0.1 N NaOH. Zoledronic acid is practically insoluble in various organic solvents.

[0006] Much effort has been taken to generate novel oral formulations of zoledronic acid through crystallization and metal salt formation to improve its aqueous solubility, permeability, and subsequent oral bioavailability. A crystalline trihydrate was disclosed in the U.S. Patent application 2006/0178439 A1 and world patent application WO2007/032808. Seven hydrated forms, an amorphous form, three monosodium salts, and eleven disodium salts with varying degrees of hydration of zoledronic acid were also disclosed in the patent application WO2005/005447 A2. Zoledronate metal salts including Na^+, Mg^{2+}, Zn^{2+} were reported in the journal of Drugs of the Future (Sorbera et al, 25(3), *Drugs of the Future*, (2000)). Zoledronate, zoledronic, or zoledronic salt represents the ionic form of zoledronic acid. Patent application WO2008/064849 A1 from Novartis disclosed additional metal salts including two Ca^{2+} salts, two Zn^{2+} salts, one Mg^{2+} salt, as well as a monohydrate, a trihydrate, an amorphous form, and an anhydrous form.

[0007] According to the US Food and Drug Administration (FDA) Summary Basis of Approval (SBA) for zoledronic

acid, the poor oral bioavailability (approximately 1%), is partially due to its poor permeability in the GI tract. It was also noted that insoluble metal complexes were formed in the upper intestines, most commonly with calcium. Zoledronic acid has also been shown to cause severe gastric and intestinal irritations.

[0008] All of the above attempts to improve the oral bioavailability of zoledronic acid were either focused on improving the aqueous solubility by generating novel solid forms, or by mixing the drug with an inactive ingredient that has enhanced GI tract permeability. The improvement of aqueous solubility failed to improve the bioavailability of zoledronic acid, since the formation of insoluble zoledronate calcium complexes is unlikely to be prevented. On the other hand, powder mixtures of the poorly permeable drug with inactive permeability enhancers improved the bioavailability of the drug. This approach of mixing different materials with different particle sizes and size distributions could result in a poor blend/physical mixture uniformity. Constituents of the mixture could also segregate during transportation or with shaking and vibration. Additionally, the powder blends require rigorous batch-to-batch consistency to ensure the uniformity of the blend batches.

[0009] To the best of the inventors' knowledge, no attempt has been made prior to this invention towards a deliberate molecular design to create a molecular complex of the drug and additional component(s) (coformer(s)) in a single crystalline structure. The benefit of such design can lead to the elimination of all the batch to batch blend uniformity and particle segregation problems that powder blends often suffer from. In addition, this invention simplifies the manufacturing of the solid dosage form (comprised of drug and excipient) such that the final solid dosage form is, in one embodiment, a powder of the molecular complex.

[0010] Additionally, the resulting molecular complexes possess very different physicochemical properties compared to the parent drug, coformer or their physical mixture. These properties include but are not limited to melting point, thermal and electrical conductivity, aqueous solubility, rate of dissolution and permeability across the GI tract membrane. The permeability improvement could result in the enhancement of the oral bioavailability of the BCS class III and IV drugs. This is the first time that the concept of a molecular complex by design was employed to improve the permeability and subsequent bioavailability of a poorly permeable drug such as zoledronic acid. The mechanisms behind the permeability enhancement, however, are not fully understood.

[0011] The upward trend in the use of oral drugs continues especially in light of the goal to decrease the overall cost of healthcare. Orally administered drugs are becoming more preferred in various therapeutic areas including cancers. Clearly, there is an opportunity to create oral dosage forms of IV drugs where oral dosage forms do not yet exist due to their poor aqueous solubility and/or poor permeability providing a clear clinical benefit for patients. Given the fact that zoledronic acid is only approved for IV administration, there is a need to develop an oral dosage form of zoledronic acid. By using pharmaceutically acceptable and/or approved coformers to hydrogen bond with zoledronic acid, novel molecular complexes (e.g. cocrystals, salts, solvates, and mixtures thereof) with improve solubility and/or permeability can be created. These novel molecular complexes could be used in the development of an oral dosage form for zoledronic acid.

SUMMARY OF THE INVENTION

[0012] The present disclosure is directed towards generating new forms of zoledronic acid, which have the therapeutic efficacy of zoledronic acid discussed above, with improved aqueous solubility, rate of dissolution, and/or improved permeability and thus enhanced bioavailability. One aspect of the present disclosure includes novel molecular complexes of zoledronic acid that includes cocrystals, salts, and solvates (e.g. hydrates and mixed solvates as well as solvates of salts), and mixtures containing such materials. In addition, the disclosure further includes methods for the preparation of such complexes.

[0013] The disclosure further includes compositions of molecular complexes of zoledronic acid suitable for incorporation in a pharmaceutical dosage form. Specific molecular complexes pertaining to the disclosure include, but are not limited to, complexes of zoledronic acid with sodium, ammonium, ammonia, L-lysine, DL-lysine, nicotinamide, adenine, and glycine. Obvious variants of the disclosed zoledronic acid forms in the disclosure, including those described by the drawings and examples, will be readily apparent to the person of ordinary skill in the art having the present disclosure and such variants are considered to be a part of the current invention.

[0014] The disclosure also includes results of an in vivo study of parent (pure) zoledronic acid and selected zoledronic acid complexes prepared by the methods of the invention in rat and dog models. The drug concentrations in the rat plasma and dog serum samples along with the pharmacokinetic (PK) profiles are also included.

[0015] The foregoing and other features and advantages of the disclosed technology will become more apparent from the following detailed description, which proceeds with reference to the accompanying drawings. Such description is meant to be illustrative, but not limiting, of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 shows PXRD diffractograms of: (A=zoledronic acid, sodium zoledronic salt and water complex), (B=NaCl), (Z1=Zoledronic acid monohydrate), (Z3=Zoledronic acid trihydrate).

[0017] FIG. 2 is an FTIR spectrum of a complex comprising zoledronic acid, sodium zoledronic salt, and water.

[0018] FIG. 3 shows PXRD diffractograms of: (C=ammonium zoledronic salt and water complex), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0019] FIG. 4 is an FTIR spectrum of ammonium zoledronic salt and water complex.

[0020] FIG. 5 shows PXRD diffractograms of: (D=zoledronic, L-lysine, and water complex), (E=L-lysine), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0021] FIG. 6 is an FTIR spectrum of zoledronic, L-lysine, and water complex.

[0022] FIG. 7 shows PXRD diffractograms of: (F=zoledronic, DL-lysine, and water complex), (G=DL-lysine), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0023] FIG. 8 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.

[0024] FIG. 9 shows PXRD diffractograms of: (H=zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex), (G=DL-lysine), (Z1=Zoledronic acid monohydrate), (Z3=Zoledronic acid trihydrate).

[0025] FIG. 10 is an FTIR spectrum of zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex.

[0026] FIG. 11 shows PXRD diffractograms of: (I=zoledronic, nicotinamide, and water complex), (J=nicotinamide), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0027] FIG. 12 is an FTIR spectrum of zoledronic, nicotinamide, and water complex.

[0028] FIG. 13 shows PXRD diffractograms of: (K=zoledronic, adenine, and water complex), (L=adenine), (Z1=Zoledronic acid monohydrate), (Z3=Zoledronic acid trihydrate).

[0029] FIG. 14 is an FTIR spectrum of zoledronic, adenine, and water complex.

[0030] FIG. 15 shows PXRD diffractograms of: (M=zoledronic and glycine complex), (N=glycine), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0031] FIG. 16 is an FTIR spectrum of zoledronic and glycine complex.

[0032] FIG. 17 shows PXRD diffractograms of: (O=zoledronic diammonia water complex), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0033] FIG. 18 is an FTIR spectrum of zoledronic diammonia water complex.

[0034] FIG. 19 shows PXRD diffractograms of: (P=zoledronic, DL-lysine, and water complex), (G=DL-lysine), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0035] FIG. 20 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.

[0036] FIG. 21 shows PXRD diffractograms of: (R=zoledronic, DL-lysine, and water complex), (G=DL-lysine), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0037] FIG. 22 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.

[0038] FIG. 23 shows PXRD diffractograms of: (R=zoledronic, DL-lysine, and water complex), (G=DL-lysine), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0039] FIG. 24 is an FTIR spectrum of zoledronic, DL-lysine, and water complex.

[0040] FIG. 25 shows PXRD diffractograms of: (Q=zoledronic, L-lysine, and water complex), (E=L-lysine), (Z1=Zoledronic acid monohydrate), and (Z3=Zoledronic acid trihydrate).

[0041] FIG. 26 is an FTIR spectrum of zoledronic, L-lysine, and water complex.

[0042] FIG. 27 shows the 24 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered via IV, oral, and intraduodenal (ID) routes.

[0043] FIG. 28 shows the 4 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered orally.

[0044] FIG. 29 shows the 4 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered ID.

[0045] FIG. 30 shows the 24 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered by oral gavage.

[0046] FIG. 31 shows the 4 hr rat plasma PK profile of parent zoledronic acid and zoledronic acid complexes delivered orally.

[0047] FIG. 32 shows the 4 hr rat plasma PK profile of parent zoledronic acid and selected zoledronic acid complexes delivered orally.

[0048] FIG. 33 shows the dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally.

[0049] FIG. 34 shows the 4 hr dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally.

[0050] FIG. 35 shows the dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally; enteric and non-enteric coated capsules.

[0051] FIG. 36 shows the 6 hr dog serum PK profile of parent zoledronic acid and zoledronic acid complexes delivered IV and orally; enteric and non-enteric coated capsules.

[0052] FIG. 37 shows the dog PK data for the enteric and non-enteric coated hard gelatin capsules.

[0053] FIG. 38 shows the 24 hr dog serum PK profile of zoledronic acid complexes delivered IV and orally.

[0054] FIG. 39 shows the 4 hr dog serum PK profile of zoledronic acid complexes delivered IV and orally.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0055] In general, active pharmaceutical ingredients (APIs) in the pharmaceutical compositions can be prepared in a variety of different forms including prodrugs, amorphous forms, solvates, hydrates, cocrystals, salts and polymorphs. The discovery of novel API forms may provide an opportunity to improve the performance characteristics of a pharmaceutical product. Additionally, discovery of drug forms expands the array of resources available for designing pharmaceutical dosage forms with targeted release profiles or other desired characteristics.

[0056] A specific characteristic that can be targeted includes the crystal form of an API. The alteration of the crystal form of a given API would result in the modification of the physical properties of the target molecule. For example, various polymorphs of a given API exhibit different aqueous solubility, while the thermodynamically stable polymorph would exhibit a lower solubility than the meta-stable polymorph. In addition, pharmaceutical polymorphs can also differ in properties such as rate of dissolution, shelf life, bioavailability, morphology, vapor pressure, density, color, and compressibility. Accordingly, it is desirable to enhance the properties of an API by forming molecular complexes such as a cocrystal, a salt, a solvate or hydrate with respect to aqueous solubility, rate of dissolution, bioavailability, Cmax, Tmax, physicochemical stability, down-stream processibility (e.g. flowability compressibility, degree of brittleness, particle size manipulation), decrease in polymorphic form diversity, toxicity, taste, production costs, and manufacturing methods.

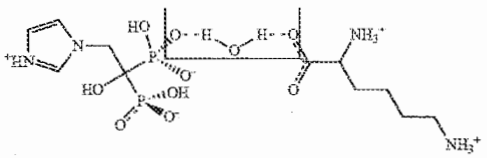
[0057] In the development of orally delivered drugs, it is often advantageous to have novel crystal forms of such drugs that possess improved properties, including increased aqueous solubility and stability. In many cases, the dissolution rate increase of drugs is desired as it would potentially increase their bioavailability. This also applies to the development of

novel forms of zoledronic acid which, when administered orally to a subject could achieve a greater or similar bioavailability and PK profile when compared to an IV or other formulations on a dose-for-dose basis.

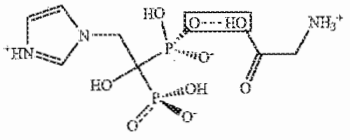
[0058] Cocrystals, salts, solvates and hydrates of zoledronic acid of the present invention could give rise to improved properties of zoledronic acid. For example, a new form of zoledronic acid is particularly advantageous if it can improve the bioavailability of orally delivered zoledronic acid. A number of novel zoledronic acid forms have been synthesized, characterized, and disclosed herein. Of particular interest are the zoledronic acid and the standard amino acids since they have indicated enhanced permeability compared with other molecular complexes of zoledronic acid. The mechanism of enhanced permeability of these complexes is not yet understood and, while not to be bound by this explanation, it is possible that they moderate the formation of the insoluble Ca^{2+} zoledronate salt resulting in more zoledronic acid to be absorbed paracellularly through the tight junctions. It must be stressed that this is a possible mechanism of enhanced permeability.

[0059] Schematic diagrams for zoledronic acid:amino acid complexes (a zoledronic acid:lysine complex and a zoledronic acid:glycine complex, two embodiments of the invention) are shown below. The diagrams show a molecular structure of the complex and possible interactions between the constituents of the complex which is different from the physical mix of the constituents.

[0060] 1. Zoledronic acid: lysine complex



[0061] 2. Zoledronic acid: glycine complex



These represent one of the arrangements that molecules of the drug and the standard amino acids coformers could interact to form a stable complex that even when stressed thermally at elevated relative humidity (RH) environment have not displayed any signs of deterioration or disintegration to its original constituents. Such stability can be attributed to the hydrogen bonding (dashed line in the box) in these molecular complexes. When packing in a crystal structure these complexes have very different morphologies to that of its constituents or their physical mix as indicated by their powder X-ray diffraction (PXRD) patterns and therefore would possess different, unpredictable physicochemical properties.

[0062] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic acid, sodium zoledronate and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 8.1, 13.3, 21.5, 24.6, and 25.6±0.2 degrees two-theta.

[0063] The present invention provides a new crystal form of zoledronic acid in the form of ammonium zoledronic salt and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 11.0, 14.6, 15.4, 19.9, and 29.4±0.2 degrees two-theta.

[0064] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, L-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.0, 14.4, 18.1, 26.0, and 29.6±0.2 degrees two-theta.

[0065] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, DL-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.1, 14.7, 18.0, 21.2, and 26.0±0.2 degrees two-theta.

[0066] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 8.8, 9.7, 17.6, 23.1, and 26.5±0.2 degrees two-theta.

[0067] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic acid, nicotinamide, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 13.1, 15.2, 21.0, 23.9, and 26.5±0.2 degrees two-theta.

[0068] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, adenine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 13.6, 15.9, 19.7, 27.9, and 29.5±0.2 degrees two-theta.

[0069] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic and glycine complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 10.2, 17.8, 19.9, 22.9, and 28.1±0.2 degrees two-theta.

[0070] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic diammonia water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 12.2, 13.0, 14.1, 17.1, and 19.3±0.2 degrees two-theta.

[0071] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, DL-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 8.3, 11.8, 12.3, 15.8, and 20.8±0.2 degrees two-theta.

[0072] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic acid, L-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.6, 10.7, 14.3, 21.4, 23.5±0.2 degrees two-theta.

[0073] The present invention provides a new crystal form of zoledronic acid in the form of zoledronic, DL-lysine, and water complex, characterized by an X-ray powder diffraction pattern having strong peaks at about 9.7, 10.8, 14.4, 18.9, 21.4±0.2 degrees two-theta.

[0074] The present invention provides rat plasma or dog serum concentration levels and PK profiles of IV, orally and ID delivered zoledronic acid parent compound versus complexes of zoledronic acid created using the method of this invention.

[0075] Accordingly, in a first aspect, the present invention includes complexes of zoledronic acid with sodium, ammo-

nium, ammonia, L-lysine, DL-lysine, nicotinamide, adenine and glycine which are capable of complexing in the solid-state, for example, through dry or solvent-drop grinding (liquid assisted grinding), heating or solvent evaporation of their solution in single or mixed solvent systems, slurry suspension, supercritical fluids or other techniques known to a person skilled in the art.

[0076] Another aspect of the invention provides zoledronic and nicotinamide complex by dissolving both compounds in water:ethylacetate (1:1 v/v) and allowing the solvent mixtures to evaporate to form crystalline material.

[0077] Another aspect of the invention provides zoledronic and glycine solid complex from dissolving both compounds in water, and allowing the solvent to evaporate to form crystalline material.

[0078] Another aspect of the invention provides complexes of zoledronic acid and sodium, ammonium, ammonia, L-lysine, DL-lysine, nicotinamide, adenine and glycine suitable for a pharmaceutical formulation than can be delivered orally to the human body. The pharmaceutical formulation contains a therapeutically effective amount of at least one of the novel molecular complexes of zoledronic acid according to the invention and at least one pharmaceutically acceptable carrier, (also known in the art as a pharmaceutically acceptable excipient). The novel molecular complexes of zoledronic acid are therapeutically useful for the treatment and/or prevention of disease states associated with osteoporosis, hypercalcemia (TIH), cancer induced bone metastasis, Paget's disease or adjuvant or neoadjuvant therapies, discussed above.

[0079] The invention also relates to methods of treatment using novel molecular complexes of zoledronic acid of the invention or a pharmaceutical formulation containing them. A pharmaceutical formulation of the invention may be in any pharmaceutical form which contains a novel molecular complex of zoledronic acid according to the invention. The pharmaceutical formulation may be, for example, a tablet, capsule, liquid suspension, injectable, suppository, topical, or transdermal. The pharmaceutical formulations generally contain about 1% to about 99% by weight of at least one novel molecular complex of zoledronic acid of the invention and 99% to 1% by weight of a suitable pharmaceutical excipient.

[0080] Complexes of zoledronic acid and sodium, ammonium, ammonia, L-lysine, DL-lysine, nicotinamide, adenine, and glycine have been observed by their PXRD patterns and FTIR spectra.

[0081] Another aspect of the invention provides in-vivo data in rats concerning the oral bioavailability of zoledronic acid delivered orally and intraduodenally.

[0082] Another aspect of the invention provides PK profiles of the parent compound delivered by different routes; IV, oral and ID.

[0083] Another aspect of the invention provides modified oral bioavailability values of novel zoledronic acid complexes prepared by the method of invention, compared with the orally delivered parent compound.

[0084] Another aspect of the invention provides the addition of excess at least one coformer to the zoledronic acid complexes, which may be the same as the coformer in the complex, a different coformer, or a mixture thereof.

[0085] Another aspect of the invention provides a method where the excess cocrystal formers consist of standard amino acids.

[0086] Another aspect of the invention provides modified PK profiles of zoledronic acid complexes with excess cocrystal formers, compared with that of the orally delivered parent compound.

[0087] Another aspect of the invention provides improved aqueous solubility of novel zoledronic acid complexes compared with the parent compound.

[0088] Another aspect of the invention provides modified oral bioavailability values of novel zoledronic acid complexes with excess cocrystal formers, compared with the orally delivered parent compound.

[0089] Another aspect of the invention provides in vivo data in dogs concerning the oral bioavailability of zoledronic acid delivered IV or orally.

[0090] Another aspect of the invention provides modified oral bioavailability values in dogs of novel zoledronic acid complexes prepared by the method of invention delivered in gelatin capsules compared with the orally delivered parent compound.

[0091] Another aspect of the invention provides modified oral bioavailability values in dogs of novel zoledronic acid complexes prepared by the method of invention delivered in enteric coated gel capsules compared with that of the parent compound.

[0092] Another aspect of the invention provides substantial improvement in oral bioavailability values in dogs of novel zoledronic acid complexes with excess cocrystal formers prepared by the method of invention delivered in hard gelatin capsules.

[0093] Another aspect of the invention provides slight improvement in oral bioavailability values for zoledronic acid in dogs via zoledronic acid and novel zoledronic acid complexes orally delivered through enteric coated capsules.

[0094] Another aspect of the invention provides a reduced oral bioavailability values for zoledronic acid in dogs via novel zoledronic acid complexes with excess physical mix of coformer.

[0095] Another aspect of the invention provides a molecular complex comprising a bisphosphonic acid or salt thereof and at least one coformer, wherein the bioavailability of the bisphosphonic acid or salt thereof from the molecular complex is greater than the bioavailability of the bisphosphonic acid or salt thereof without the coformer. The bisphosphonic acid may be, for example, zoledronic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, residronic acid ibandronic acid or other bisphosphonic acids known in the art.

[0096] Another aspect of the invention provides a method for enhancing the bioavailability or permeability of a bisphosphonic acid comprising the step of administering to a patient in need thereof a therapeutically effective of a bisphosphonic acid in the form of a molecular complex.

[0097] The techniques and approaches set forth in the present disclosure can further be used by the person of ordinary skill in the art to prepare variants thereof, said variants are considered to be part of the inventive disclosure.

EXAMPLES

[0098] The following examples illustrate the invention without intending to limit the scope of the invention.

[0099] Zoledronic acid as a starting material used in all experiments in this disclosure was supplied by Farmkemi Limited (Wuhan Pharma Chemical Co.), China with purity of ca. 98% and was purified further via recrystallization from

water. All other pure chemicals (Analytical Grade) were supplied by Sigma-Aldrich and used without further purification.

[0100] Enteric coating of gelatin capsules was contracted out to AzoPharma, Hollywood, Fla., USA. A 10% w/w coating solution of Eudragit L100-55, and triethyl citrate, 9.09 and 0.91 w/w % respectively, in purified water and acetone was used in the Vector LDCS pan coater to achieve a uniform coating layer on the capsules. The coating uniformity and functionality for duodenal delivery was tested by 2 hr dissolution in simulated gastric fluid stirred at 75 rpm and 37° C. All capsules remained closed for the duration of this test.

Solid Phase Characterization

[0101] Analytical techniques used to observe the crystalline forms include powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FTIR). The particular methodology used in such analytical techniques should be viewed as illustrative, and not limiting in the context of data collection. For example, the particular instrumentation used to collect data may vary; routine operator error or calibration standards may vary; sample preparation method may vary (for example, the use of the KBr disk or Nujol mull technique for FTIR analysis).

[0102] Fourier Transform FTIR Spectroscopy (FTIR): FTIR analysis was performed on a Perkin Elmer Spectrum 100 FTIR spectrometer equipped with a solid-state ATR accessory.

[0103] Powder X-Ray Diffraction (PXRD): All zoledronic acid molecular complex products were observed by a D-8 Bruker X-ray Powder Diffractometer using Cu Kα (λ=1.540562 Å), 40 kV, 40 mA. The data were collected over an angular range of 3° to 40° 2θ in continuous scan mode at room temperature using a step size of 0.05° 2θ and a scan speed of 6.17°/min.

Example 1

Preparation of Zoledronic Acid, Sodium Zoledronic Salt, and Water Complex

[0104] 200 mg of zoledronic acid was slurried with 180 mg of sodium chloride in 1 mL of 1:1 ethanol:water overnight. The material was filtered and rinsed. The particulate material was gathered and stored in a screw cap vial for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **1** and FIG. **2**, respectively.

Example 2

Preparation of Ammonium Zoledronic Salt and Water Complex

[0105] 300 mg of zoledronic acid was slurried in 7N ammonia in methanol overnight. The material was filtered and rinsed. The particulate material was dissolved in water and left to evaporate at ambient conditions to obtain colorless plates after 1 week. The material was characterized by PXRD and FTIR corresponding to FIG. **3** and FIG. **4**, respectively.

Example 3

Preparation of Zoledronic, L-Lysine, and Water Complex

[0106] 200 mg of zoledronic acid and 54 mg of L-lysine were slurried in 2 mL of tetrahydrofuran and 200 μl of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **5** and FIG. **6**, respectively.

Example 4

Preparation of Zoledronic, DL-Lysine, and Water Complex

[0107] 204 mg of zoledronic acid and 59 mg of DL-lysine were slurried in 2 mL of tetrahydrofuran and 200 μl of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **7** and FIG. **8** respectively.

Example 5

Preparation of Zoledronic Acid, Zoledronic, DL-Lysine, Ethanol, and Water Complex

[0108] 103 mg of zoledronic acid and 54 mg of DL-lysine were dissolved in 400 μA of water, capped and stirred overnight. The next day 0.25 mL of ethanol was added drop wise. The vial was capped with a screw cap vial and after 1 day crystals appeared and were filtered off. The material was stored for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **9** and FIG. **10** respectively.

Example 6

Preparation of Zoledronic, Nicotinamide, and Water Complex by Solvent-Drop Grinding

[0109] 99 mg of zoledronic acid was ground with 44 mg of nicotinamide and 40 μl of water was added to the solid mixture. The solids gathered after grinding were stored in screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **11** and FIG. **12**, respectively.

Example 7

Preparation of Zoledronic, Nicotinamide, and Water Complex from Solution Crystallization

[0110] 25 mg of zoledronic acid and 138 mg of nicotinamide were dissolved in 2 mL of a water:ethylacetate mix (1:1 v/v). The solution was then allowed to stand for several hours to effect the slow evaporation of solvent. The solids gathered were characterized and produced very similar PXRD and FTIR patterns to that of Example 7 product.

Example 8

Preparation of Zoledronic, Adenine, and Water Complex by Solvent-Drop Grinding

[0111] 96 mg of zoledronic acid was ground with 65 mg of adenine and 60 μL of water was added to the solid mixture. The solids gathered after grinding were stored in screw cap

vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **13** and FIG. **14**, respectively.

Example 9

Preparation of Zoledronic, Adenine, and Water Complex from Solution Slurry

[0112] 99 mg of zoledronic acid and 54 mg of adenine were slurried in 2 mL of a water:ethanol mix (1:1 v/v) overnight. The solids gathered after filtration were dried, characterized and produced very similar PXRD and FTIR patterns to that of Example 8 product.

Example 10

Preparation of Zoledronic and Glycine Complex

[0113] 178 mg of zoledronic acid and 45 mg of glycine were slurried in 2 mL of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **15** and FIG. **16**, respectively.

Example 11

Preparation of Zoledronic Diammonia Water Complex

[0114] 1.5 g of zoledronic acid was slurried in 7N ammonia in methanol overnight. The material was filtered and rinsed. The particulate material was dissolved in water with medium heat and left to evaporate at ambient conditions to obtain colorless blocks after 1 day. The material was characterized by PXRD and FTIR corresponding to FIG. **17** and FIG. **18**, respectively.

Example 12

Preparation of Zoledronic, DL-Lysine, and Water Complex

[0115] 200 mg of zoledronic acid and 102 mg of DL-lysine were slurried in 2 mL of tetrahydrofuran and 400 μl of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **19** and FIG. **20** respectively.

Example 13

Preparation of Zoledronic, DL-Lysine, and Water Complex

[0116] 1 g of zoledronic acid and 283 mg of DL-lysine were slurried in 80 mL of tetrahydrofuran and 8 mL of water overnight. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **21** and FIG. **22** respectively.

Example 14

Preparation of Zoledronic, DL-Lysine, and Water Complex by Antisolvent Method

[0117] This complex can also be prepared by the antisolvent method by dissolving 1 g of zoledronic acid and 283 mg of DL-lysine in 5 mL of hot water and adding 40 mL of ethanol as an antisolvent stirred overnight. Similar PXRD and FTIR profiles were obtained as shown in FIGS. **23** and **24** respectively.

Example 15

Preparation of Zoledronic, L-Lysine, and Water Complex

[0118] 1 g of zoledronic acid and 255 mg of L-lysine were dissolved in 60 mL of hot water. 100 mL of ethanol was then added as an antisolvent. The solids gathered after filtration were dried and stored in a screw cap vials for subsequent analysis. The material was characterized by PXRD and FTIR corresponding to FIG. **25** and FIG. **26** respectively.

Example 16

The Animal PK Studies

[0119] These studies were conducted on rats and dogs as they are suitable animal models for zoledronic acid. This can be attributed to the fact that both animals have historically been used in the safety evaluation and PK screening studies and are recommended by appropriate regulatory agencies. In addition, rats and dogs have also been established as appropriate species for assessing the absorption of bisphosphonate drugs including zoledronic acid.

[0120] Pure zoledronic acid and zoledronic acid complexes prepared by the methods in this invention were delivered to the rats and dogs through IV or oral routes. Additional tests included ID administration in rats and administration of enteric coated capsules in dogs. All compounds delivered were well tolerated by the animals with no adverse events or physical abnormalities noticed.

[0121] Test Subjects: 8-week male Sprague-Dawley Rats (217-259 grams) were obtained from Hilltop Lab Animals, Scottdale, Pa. USA. Surgical catheters (jugular vein and intraduodenum) were implanted to the animals prior to the study. Beagle dogs from Marshall Farms, N.Y., USA, weighing from (9-12 kg) were used in this study. Surgical catheters (jugular vein) were implanted prior to the study.

[0122] Housing: Rats were individually housed in stainless steel cages to prevent catheter exteriorization. Acclimation (Pre-dose Phase) was for 1 day. Dogs were already in the test facility (Absorption Systems Inc., USA) and did not need acclimation.

[0123] Environment: Environmental controls for the animal room were set to maintain 18 to 26° C., a relative humidity of 30 to 70%, a minimum of 10 air changes/hour, and a 12-hour light/12-hour dark cycle. The light/dark cycle could be interrupted for study-related activities.

[0124] Diet: For rats, water and certified Rodent Diet #8728C (Harlan Teklad) were provided. For dogs, water and the standard dog chow diet were given twice daily (every 12 hours).

[0125] Fasting: All test animals were fasted overnight before IV, oral, or ID administration of zoledronic acid or zoledronic acid complexes.

[0126] Routes of Rat Dosing: Zoledronic acid and its complex formulations were administered through IV, oral and ID. The doses administered to all study rats were measured as zoledronic acid, not as the complex form contained in the suspension:

[0127] i. IV Administration: the dose of zoledronic acid for IV administration was 0.5 mg/kg. The dose of each

rat was calculated on a per rat basis (not on an average weight of all the rats in the lot).

[0128] ii. Oral gavage administration: solid suspensions were administered. The dose of each rat was calculated on a per rat basis (not on an average weight of all the rats in the lot). For solid suspensions, animals were administered 5 mg/kg of zoledronic acid or 5 mg/kg of zoledronic acid in zoledronic acid complexes contained in a suspension of PEG 400.

[0129] iii. Duodenal cannula administration: solid suspensions were administered. The dose of each rat was calculated on a per rat basis (not on an average weight of all the rats in the lot). For solid suspensions, animals were administered 5 mg/kg of zoledronic acid or 5 mg/kg of zoledronic acid in zoledronic acid complexes contained in a suspension of PEG 400.

[0130] Routes of Dog Dosing: Zoledronic acid and its complex formulations were administered IV and orally. The doses administered to all study dogs were measured as zoledronic acid in each complex, not as the complex form contained in the powder in the gelatin capsule or in solution for IV:

[0131] i. IV Administration: The dose volume of each dog was adjusted based upon the average weight of the dog.

[0132] ii. Oral administration: zoledronic acid and its equivalent of zoledronic acid complex formulations were administered through size 0 gelatin capsules based on the average weight of the dogs.

[0133] iii. Oral administration with enteric coated capsules: zoledronic acid and its equivalent of zoledronic acid complex formulations were administered through size 0 enteric coated gelatin capsules based on the average weight of the dogs.

[0134] iv. Oral administration of the molecular complexes with additional coformers: physical mixtures of zoledronic acid complexes with additional coformers were administered through size 0 gelatin capsules based on the average weight of the dogs.

[0135] Groups: Two major groups of animals were selected for the study.

[0136] Group 1, rats that contained four subgroups (I-IV) where the results of each data point on the PK profile graphs was the average drug concentration in the plasma of 3 rats.

[0137] Group 2, dog PK study contained three groups with subgroups (A, B, C, D, E and F) where the results of each data point on the PK profile graphs was the average drug concentration in the serum of 5 dogs.

[0138] Details of Group I Rat Dosing

[0139] Group I (IV administration). Group members, designated IV doses are listed below

Group # I	Designation	# of rats	Dose*	Dose volume
G1	Zoledronic Acid	3	0.5 mg/kg	1 mL

IV comparator group, was conducted to calculate MAT (mean absorption time) and ka (absorption rate constant) for the oral groups.

[0140] Group II (oral gavage): Group designations and oral doses are listed below:

Group # II	Designation	# of Rats	Dose*	Dose volume mL/kg	Compound
G2	Zoledronic Acid in PEG400	3	5 mg/kg	1 mL	Zoledronic acid
G3	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic and glycine complex
G4	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, nicotinamide, and water complex
G5	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic acid, sodium zoledronic salt, and water complex
G6	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, L-lysine, and water complex
G7	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, DL-lysine, and water complex

[0141] Group III (ID administration): Group designating and oral doses are listed below:

Group # III	Designation	# of rats	Dose*	Dose volume mL/kg	Compound
G8	Zoledronic Acid in PEG400	3	5 mg/kg	1 mL	Zoledronic acid
G9	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic and glycine complex

-continued

Group # III	Designation	# of rats	Dose*	Dose volume mL/kg	Compound
G10	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, nicotinamide, and water complex
G11	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic acid, sodium zoledronic salt, and water complex
G12	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, L-lysine, and water complex
G13	Solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Zoledronic, DL-lysine, and water complex

[0142] Group IV (oral gavage): Group designations and oral doses are listed below:

Group # IV	Compound	# of rats	Dose	Dose volume/kg	Excess coformer	Excess coformer amount mg/kg
G14	Zoledronic and glycine complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Glycine	45
G15	Zoledronic and glycine complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Glycine	25
G16	Zoledronic and glycine complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	Glycine	5
G17	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	DL-lysine monohydrate	39.32
G18	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	DL-lysine monohydrate	28.08
G19	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	DL-lysine monohydrate	5.62
G20	Zoledronic, DL-lysine, and water complex, solid suspension in PEG400	3	5 mg/kg equivalent	1 mL	n/a	n/a

[0143] Rat blood sample collection, handling and analysis: Blood (approx. 300 μL per sample) samples were withdrawn from each of 3 animals in Group I (IV administration) at eight (8) time points: 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, and 24 hrs, after initial administration of zoledronic acid or its complexes, into EDTA plasma tubes. Plasma was collected after centrifugation at 13,000 rpm for 5 min at 4° C. and immediately frozen and stored at −60 to −80° C. till analysis.

[0144] Samples were thawed on the day of analysis and the amount of zoledronic acid in the samples was quantified by analyzed by LC/MS/MS method.

[0145] Details of Group 2 dog dosing: Prior to dosing, all dogs received a 20 mL dose of citric acid (24 mg/mL in water) to lower the pH of their stomach. After dosing capsules or IV, all dogs received additional 6.25 mL citric acid solution (24 mg/mL in water) as a rinse.

[0146] Group A, (IV administration). Group members, designated IV doses are listed below:

Group # A	Designation	# of fasted Dogs	Dose*	Dose volume
Leg 1	Zoledronic Acid	5	0.05 mg/kg	1 mL/kg

IV comparator group, was conducted to calculate MAT (mean absorption time) and ka (absorption rate constant) for the oral groups.

[0147] Group B (oral administration): Group designations and oral doses are listed below:

Group # B	Compound	Dosing Route	Dose of compound in the gelatin capsules	# of fasted Dogs (9-12 kg)	Dosing Solution Conc. mg/mL
Leg 2	Zoledronic acid	oral	5 mg/kg equivalent	5	n/a
Leg 3	Zoledronic and glycine complex	oral	5 mg/kg equivalent	5	n/a
Leg 4	Zoledronic, DL-lysine, and water complex	oral	5 mg/kg equivalent	5	n/a
Leg 5	Zoledronic, L-lysine, and water complex	oral	5 mg/kg equivalent	5	n/a
Leg 6	Zoledronic, DL-lysine, and water complex	oral	5 mg/kg equivalent	5	n/a

[0148] Group C (oral administration): Group designations and oral doses are listed below:

Group # C	Compound	# of fasted Dogs (9-12 kg)	Dosing Route	Dose of compound in the gelatin capsules	Excess coformer	Excess coformer amount
Leg 7	Zoledronic acid monohydrate	5	oral	56.0 mg; enteric coated capsules	n/a	n/a
Leg 8	Zoledronic and glycine complex	5	oral	67.0 mg; enteric coated capsules	n/a	n/a
Leg 9	Zoledronic, DL-lysine, and water complex	5	oral	87.7 mg	DL-lysine monohydrate	294.8 mg
Leg 10	Zoledronic, DL-lysine, and water complex	5	oral	87.7 mg; enteric coated capsules	DL-lysine monohydrate	294.8 mg
Leg 11	Zoledronic, DL-lysine, and water complex	5	oral	84.2 mg	DL-lysine monohydrate	294.8 mg
Leg 12	Zoledronic, DL-lysine, and water complex	5	oral	87.7 mg; enteric coated capsules	n/a	n/a

[0149] Group D, (15 min IV infusion): Group members, designated IV doses are listed below:

Group # D	Designation	# of fasted Dogs (9-12 kg)	Dose*	Dosing solution concentration
Leg 13	Zoledronic Acid	5	0.183 mg/kg IV	0.1 mg/mL

[0150] Group E, (oral administration): Group members, designated IV doses are listed below:

Group # E	Compound	# of fasted Dogs (9-12 kg)	Dosing Route	Dose of compound in the gelatin capsules	Excess coformer	Excess coformer amount
Leg 14	Zoledronic, DL-lysine, and water complex	2.1	oral	35.4 mg	DL-lysine monohydrate	123.8 mg
Leg 15	Zoledronic and glycine complex	5	oral	67.0 mg	DL-lysine monohydrate	294.8 mg
Leg 16	Zoledronic, L-lysine, and water complex	5	oral	87.7 mg	DL-lysine monohydrate	294.8 mg
Leg 17	Zoledronic, DL-lysine, and water complex	2.1	oral	35.4 mg	DL-lysine monohydrate	294.8 mg

[0151] Group F, (15 min IV infusion): Group members, designated IV doses are listed below:

Group # F	Designation	# of fasted Dogs (9-12 kg)	Dose*	Dosing solution concentration
Leg 18	Zoledronic Acid	5	0.12 mg/kg IV infusion	0.1 mg/mL

[0152] After initial administration of zoledronic acid or its complexes, blood (approx. 2.5 mL per sample) was withdrawn from each of 5 animals in Group A (IV administration) at 15 time points: Pre-dose (0), 2, 5, 10, 15, 30, 45 min, 1, 1.5, 2, 4, 6, 8, 24 and 48 hrs and at 13 time points for Group B (oral administration): Pre-dose (0), 5, 10, 15, 30, 45 min, 1, 1.5, 2, 4, 6, 8, and 24 hrs. Blood samples were placed without the use of an anticoagulant and allowed to sit at room temperature for approximately 30 minutes. Samples were then centrifuged at a temperature of 4° C., at a speed of 13,000 rpm, for 5 minutes. Serum was collected and split into two aliquots and stored frozen (−80° C.) till analysis. Samples were thawed on the day of analysis and processed using analytical procedures for zoledronic acid containing an LC/MS/MS analysis method.

[0153] Animal PK Studies Results

[0154] Rat study: The results of the first rat study are summarized in Table 1; the concentrations (ng/mL) of zoledronic acid in the plasma samples are the average values of the analytical results of 3 rats. In addition, the PK profiles of the IV, oral and ID groups are shown in FIG. 27. The profiles of oral and ID groups are shown in FIGS. 28 and 29. It suggests that some zoledronic acid complexes have improved oral bioavailability compared with that of the parent zoledronic acid. The complexes with improved bioavailability were further tested in a second rat PK study in which excess coformers were added to the zoledronic acid complexes and then administered to rats by oral gavage. The results of this second study are summarized in Table 2 and their PK profiles are shown in FIGS. 30, 31 and 32. These figures show improved bioavailabilities of several zoledronic acid complexes with excess coformers.

[0155] Dog study: The results of the first dog study are summarized in Table 3. The concentrations (ng/mL) of zoledronic acid are the average values of the analytical results of 5 dogs. The PK profiles of the IV and oral groups are shown in FIGS. 33 and 34 which represent the first four hours of the 48 hr PK profile. These results and FIG. 34 suggest that most if not all zoledronic acid complexes have achieved improved oral bioavailability compared to that of the parent zoledronic acid delivered orally.

[0156] The results of the second dog study are summarized in Table 4; the concentrations (ng/mL) of zoledronic acid shown are the average values of the analytical results of 5 dogs. The PK profiles of the IV and oral groups are shown in FIGS. 35 and 36. FIG. 36 represents the first 6 hours of the 24 hour PK profile. These results and FIG. 35 suggest that most if not all zoledronic acid complexes have achieved improved oral bioavailability compared with that of the parent zoledronic acid delivered orally. Specifically, there was a significant improvement in zoledronic acid bioavailability for the novel zoledronic acid complexes with excess amino acid coformer (Leg 11, FIG. 37) compared to that of the parent drug. The results have also shown that there was improvement in the bioavailability of the enterically coated capsules compared with the non-enterically coated capsules (FIG. 37, Legs 7 and 2, Legs 8 and 3, Legs 12 and 4), but surprisingly the bioavailability was significantly altered when excess amino acid coformer was added to form a physical mixture to the enterically coated capsules (FIG. 37, Legs 9 and 10). The reason behind it is not fully understood.

[0157] The results have shown that there is a slight increase in the oral bioavailability of zoledronic acid from the enteric coated capsules filled with neat (i.e. with no excess coformer) zoledronic acid amino acid complex. Therefore, it is expected that the excess coformer with the novel zoledronic acid complexes would also lead to increased bioavailability when delivered in enterically coated capsules. Surprisingly, when excess coformer was added to the zoledronic acid, the bioavailability of the enterically coated capsules was lower than that of the non-enterically coated capsules. This suggests that a physical powder mixture of the molecular complex and excess coformer might decrease the bioavailability when delivered to the duodenum.

[0158] The analytical results of the third dog study are shown in Table 5, which contains averaged data from five dogs. The PK profiles of the IV and oral groups are shown in FIGS. 38 and 39. FIG. 39 represents the first 4 hours of the 24 hour PK profile.

TABLE 1

Rat plasma concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery.

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G1	Zoledronic acid	IV	Water	0.083333	3254.05
				0.25	1950.62
				0.5	1128.75
				1	404.28
				2	112.68
				4	30.46
				8	10.66
				24	2.98
G2	Zoledronic acid	PO	PEG 400	0.25	330.06
				0.5	267.45
				1	138.91
				2	47.72
				4	11.78
				8	2.00
				24	0.00
G3	Zoledronic and glycine complex	PO	PEG 400	0.25	648.01
				0.5	435.38
				1	200.88
				4	12.78
				8	1.46
				24	0.00
G4	Zoledronic, nicotinamide, and water complex	PO	PEG 400	0.25	434.61
				0.5	304.94
				1	122.35
				4	7.68
				8	1.82
				24	0.00
G5	Zoledronic acid, sodium zoledronic salt, and water complex	PO	PEG 400	0.25	278.47
				0.5	280.20
				1	171.59
				4	13.42
				8	1.78
				24	0.00
G6	Zoledronic, L-lysine, and water complex	PO	PEG 400	0.25	258.43
				0.5	249.82
				1	184.95
				4	28.70
				8	3.27
				24	0.00
G7	Zoledronic, DL-lysine, and water complex	PO	PEG 400	0.25	494.31
				0.5	379.27
				1	213.48
				4	14.57
				8	3.42
				24	0.00
G8	Zoledronic acid	ID	PEG 400	0.25	145.67
				0.5	109.92
				1	47.36
				2	12.94
				4	3.85
				8	0.97
				24	0.00
G9	Zoledronic and glycine complex	ID	PEG 400	0.25	86.51
				1	33.93
				4	1.75
				8	1.55
				24	0.00
G10	Zoledronic, nicotinamide, and water complex	ID	PEG 400	0.25	69.71
				1	21.03
				4	0.86
				8	0.00
				24	0.00
G11	Zoledronic acid, sodium zoledronic salt, and water complex	ID	PEG 400	0.25	39.99
				1	18.50
				4	0.71
				8	0.00
				24	0.00

TABLE 1-continued

Rat plasma concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery.

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G12	Zoledronic, L-lysine, and water complex	ID	PEG 400	0.25	91.21
				1	26.53
				4	0.74
				8	0.00
				24	0.00
G13	Zoledronic, DL-lysine, and water complex	ID	PEG 400	0.25	98.25
				1	34.61
				4	2.65
				8	1.02
				24	0.80

TABLE 2

Rat plasma concentrations for zoledronic acid complexes with excess coformers, delivered by oral gavage

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
G14	Zoledronic and glycine complex and 45 mg/kg glycine	PO	PEG 400	0.0333333	14.61
				0.0833333	206.26
				0.1666667	340.19
				0.25	375.99
				0.5	321.36
				1	197.01
				4	17.35
				24	0.00
G15	Zoledronic and glycine complex and 25 mg/kg glycine	PO	PEG 400	0.0333333	24.48
				0.0833333	281.08
				0.1666667	502.20
				0.25	516.58
				0.5	430.10
				1	203.48
				2	73.27
				4	14.70
				24	0.00
G16	Zoledronic and glycine complex and 5 mg/kg glycine	PO	PEG 400	0.0333333	60.03
				0.0833333	365.23
				0.1666667	563.83
				0.25	625.05
				0.5	464.34
				1	209.65
				2	74.28
				4	12.17
				24	0.00
G17	Zoledronic, DL-lysine, and water complex and 39.32 mg/kg DL-lysine monohydrate	PO	PEG 400	0.0333333	168.19
				0.0833333	263.28
				0.1666667	440.26
				0.25	456.18
				0.5	385.57
				1	209.26
				2	85.65
				4	14.58
				24	0.71
G18	Zoledronic, DL-lysine, and water complex and 28.08 mg/kg DL-lysine monohydrate	PO	PEG 400	0.0333333	219.95
				0.0833333	427.02
				0.1666667	729.65
				0.25	777.54
				0.5	632.07
				1	300.86
				2	100.59

TABLE 2-continued

Rat plasma concentrations for zoledronic acid complexes with excess coformers, delivered by oral gavage

Group #	Complex	Dosing Route	Vehicle	Time (hour)	Average plasma concentration of 3 Rats (ng/mL)
				4	21.14
				24	0.00
G19	Zoledronic, DL-lysine, and water complex and 5.62 mg/kg DL-lysine monohydrate	PO	PEG 400	0.0333333	53.78
				0.0833333	394.73
				0.1666667	649.52
				0.25	669.20
				0.5	530.00
				1	265.20
				2	73.31
				4	15.41
				24	0.00
G20	Zoledronic, DL-lysine, and water complex	PO	PEG 400	0.0333333	103.13
				0.0833333	352.18
				0.1666667	475.33
				0.25	505.48
				0.5	431.41
				1	224.56
				2	69.95
				4	14.96
				24	0.00

TABLE 3

Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery (IV and oral)

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
1	0.05 mg/kg Zoledronic acid	IV	Saline solution	0	0.0
				0.0333	413.44
				0.0833	311.68
				0.1667	228.97
				0.25	178.63
				0.5	111.11
				0.75	75.91
				1	56.07
				1.5	30.35
				2	17.61
				4	4.29
				8	1.13
				24	0.00
				48	0.00
2	56.0 mg Zoledronic acid monohydrate capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	0.00
				0.25	0.31
				0.5	110.73
				0.75	97.98
				1	103.60
				1.5	89.57
				2	75.16
				4	17.86
				8	2.71
				24	0.56
3	67.0 mg Zoledronic and glycine complex capsule	PO	n/a	0	0.00
				0.0833	2.45
				0.1667	12.75
				0.25	37.07
				0.5	149.20
				0.75	206.14

TABLE 3-continued

Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery (IV and oral).

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
				1	254.20
				1.5	176.11
				2	109.25
				4	20.43
				8	3.96
				24	0.97
4	87.7 mg Zoledronic, DL-lysine, and water complex capsule	PO	n/a	0	0.00
				0.0833	3.11
				0.1667	6.49
				0.25	22.55
				0.5	68.28
				0.75	162.72
				1	206.14
				1.5	149.92
				2	105.81
				4	25.51
				8	4.22
				24	0.56
5	87.7 mg Zoledronic, L-lysine, and water complex capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	3.13
				0.25	10.06
				0.5	188.52
				0.75	345.28
				1	318.97
				1.5	180.77
				2	109.23
				4	23.11
				8	9.73
				24	1.93
6	84.2 mg Zoledronic, DL-lysine, and water complex capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	0.20
				0.25	1.92
				0.5	106.47
				0.75	120.13
				1	108.13
				1.5	90.45
				2	54.48
				4	18.14
				8	4.35
				24	1.06

TABLE 4

Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery IV and oral; enteric and non-enteric coated gelatin capsules.

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
7	56.0 mg Zoledronic acid monohydrate enteric coated capsule	PO	n/a	0	0.00
				0.1667	0.00
				0.25	0.00
				0.5	0.00
				0.75	0.00
				1	9.84
				1.5	86.13
				2	109.37
				4	107.64

TABLE 4-continued

Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery (V and oral; enteric and non-enteric coated gelatin capsules.

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
				6	14.15
				8	4.57
				24	0.50
8	67.0 mg Zoledronic and glycine complex enteric coated capsule	PO	n/a	0	0.00
				0.1667	0.00
				0.25	0.00
				0.5	0.00
				0.75	0.00
				1	4.42
				1.5	208.97
				2	274.53
				4	101.20
				6	16.71
				8	7.14
				24	2.17
9	87.7 mg Zoledronic, DL-lysine, and water complex with 294.8 mg DL-lysine monohydrate capsule	PO	n/a	0	0.00
				0.0833	13.31
				0.1667	39.76
				0.25	120.41
				0.5	364.68
				0.75	487.59
				1	499.60
				1.5	362.16
				2	254.72
				4	52.22
				6	16.61
				8	8.93
				24	2.92
10	87.7 mg Zoledronic, DL-lysine, and water complex with 294.8 mg DL-lysine monohydrate enteric coated capsule	PO	n/a	0	0.00
				0.1667	0.00
				0.25	0.00
				0.5	0.00
				0.75	3.71
				1	51.32
				1.5	403.15
				2	309.08
				4	44.83
				6	13.15
				8	7.09
				24	2.66
11	84.2 mg Zoledronic, DL-lysine, and water complex with 294.8 mg DL-lysine monohydrate capsule	PO	n/a	0	0.22
				0.1667	167.03
				0.25	533.96
				0.5	878.63
				0.75	838.82
				1	633.50
				1.5	326.63
				2	185.44
				4	46.86
				6	20.26
				8	11.49
				24	5.95
12	87.7 mg Zoledronic, DL-lysine, and water complex enteric coated capsule	PO	n/a	0	0.57
				0.1667	0.60
				0.25	0.59
				0.5	0.61
				0.75	0.40
				1	132.15
				1.5	566.18
				2	402.12
				4	65.35
				6	21.02
				8	12.18
				24	4.33

TABLE 4-continued

Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery IV and oral; enteric and non-enteric coated gelatin capsules.

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
13	0.183 mg/kg Zoledronic acid	IV	Saline solution	0	0.64
				0.0833	476.79
				0.1667	755.68
				0.25	1057.75
				0.3333	745.67
				0.4167	629.22
				0.5	522.78
				0.75	342.58
				1	245.36
				1.25	182.59
				1.5	139.77
				2	80.87
				4	23.40
				8	8.78
				24	3.84

TABLE 5

Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery (IV and oral).

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
14	35.4 mg Zoledronic, DL-lysine, and water complex, with 123.8 mg DL-lysine monohydrate gelatin capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	0.72
				0.25	11.40
				0.5	78.95
				0.75	126.46
				1	137.38
				1.5	64.73
				2	33.38
				4	6.14
				8	0.89
				24	0.00
15	67.0 mg Zoledronic and glycine complex, with 294.8 mg DL-lysine monohydrate gelatin capsule	PO	n/a	0	0.00
				0.0833	2.58
				0.1667	26.13
				0.25	55.58
				0.5	225.41
				0.75	234.95
				1	221.91
				1.5	204.90
				2	117.22
				4	17.79
				8	3.34
				24	0.77
16	87.7 mg Zoledronic, L-lysine, and water complex, with 294.8 mg DL-lysine monohydrate gelatin capsule	PO	n/a	0	0.00
				0.0833	3.26
				0.1667	17.21
				0.25	213.77
				0.5	504.17
				0.75	436.00
				1	325.21
				1.5	171.42
				2	100.81
				4	23.38
				8	4.65
				24	1.48

TABLE 5-continued

Dog serum concentrations for pure zoledronic acid and zoledronic acid complexes via different routes of delivery (IV and oral).

Leg #	Complex	Dosing Route	Vehicle	Time (hour)	Average serum concentration of 5 dogs (ng/mL)
17	35.4 mg Zoledronic, DL-lysine, and water complex, with 294.8 mg DL-lysine monohydrate gelatin capsule	PO	n/a	0	0.00
				0.0833	0.00
				0.1667	13.47
				0.25	50.04
				0.5	146.68
				0.75	137.24
				1	116.38
				1.5	66.70
				2	44.94
				4	8.87
				8	1.58
				24	0.21
18	0.12 mg/kg Zoledronic acid	IV	Saline solution	0	0.00
				0.0833	309.13
				0.1667	524.58
				0.25	717.15
				0.3333	501.70
				0.4167	392.35
				0.5	322.84
				0.75	201.78
				1	132.86
				1.25	93.22
				1.5	69.06
				2	38.38
				4	9.14
				8	3.24
				24	1.21

TABLE 6

Aqueous solubility of zoledronic acid (ZA) and novel zoledronic acid complexes at room temperature.

Compound	Conc. mg/mL	mMol/L (complex)
ZA monohydrate	1.57	5.41
ZA: Glycine	11.89	34.25
ZA: L-Lysine dihydrate	8.22	18.09
ZA: DL-Lysine dihydrate	6.85	15.08
ZA: DL-Lysine monohydrate	13.9	31.86

1. A molecular complex comprising a bisphosphonic acid or salt thereof and at least one coformer, wherein the bioavailability of the bisphosphonic acid or salt thereof from the molecular complex is greater than the bioavailability of the bisphosphonic acid or salt thereof without the coformer.

2. A molecular complex of claim 1, wherein the bisphosphonic acid is selected from the group consisting of zoledronic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, residronic acid and ibandronic acid.

3. A molecular complex of claim 1, wherein at least one coformer is an amino acid.

4. A molecular complex of claim 1, wherein the bisphosphonic acid is zoledronic acid and at least one coformer is an amino acid.

5. A molecular complex of claim 1, wherein at least one coformer is lysine.

6. A composition comprising a molecular complex of claim 1 and an excess amount of at least one coformer.

7. A composition of claim 6, wherein the excess coformer is present in an amount up 100× the mass of the molecular complex.

8. A pharmaceutical composition comprising a composition of claim 7 and a pharmaceutically acceptable excipient.

9. A pharmaceutical composition comprising a composition of claim 6 and a pharmaceutically acceptable excipient.

10. A pharmaceutical composition of claim 8 wherein the pharmaceutical composition is an oral dosage form.

11. A pharmaceutical composition of claim 9, wherein the pharmaceutical composition is an oral dosage form.

12. A molecular complex of claim 1, wherein the molecular complex is crystalline.

13. A method for enhancing the bioavailabilty or permeability of a bisphosphonic acid or salt thereof comprising the step of administering to a patient in need thereof a therapeutically effective amount of a bisphosphonic acid in the form of a molecular complex according to claim 1.

14. A method for enhancing the bioavailabilty or permeability of a bisphosphonic acid or salt thereof comprising the step of administering to a patient in need thereof a therapeutically effective amount of a bisphosphonic acid in the form of a composition according of claim 5.

15. A method for enhancing the bioavailabilty or permeability of a bisphosphonic acid or salt thereof comprising the step of administering to a patient in need thereof a therapeutically effective amount of a bisphosphonic acid in the form of a composition according of claim 6.

16. A method for the treatment and/or prevention of disease states associated with osteoporosis, hypercalcemia, cancer

induced bone metastasis, Paget's disease or adjuvant or neo-adjuvant cancer therapies comprising the step of administering to a patient in need thereof a therapeutically effective amount of a bisphosphonic acid or salt thereof in the form of a composition according of claim **5**.

17. A method for the treatment and/or prevention of disease states associated with osteoporosis, hypercalcemia, cancer induced bone metastasis, Paget's disease or adjuvant or neo-adjuvant cancer therapies comprising the step of administering to a patient in need thereof a therapeutically effective amount of a bisphosphonic acid or salt thereof in the form of a composition according of claim **6**.

18. A crystalline form of zoledronic acid comprising zoledronic acid, water, and a compound selected from L-lysine; DL-lysine; nicotinamide; adenine; and a zoledronic acid salt.

19. A crystalline form of zoledronic acid according to claim **18**, wherein the crystalline form is

a crystalline zoledronic acid, sodium zoledronate and water complex characterized by an X-ray powder diffraction pattern having peaks at about 8.1, 13.3, 21.5, 24.6, and 25.6±0.2 degrees two-theta;

a crystalline ammonium zoledronic acid salt and water complex characterized by an X-ray powder diffraction pattern having strong peaks at about 11.0, 14.6, 15.4, 19.9, and 29.4±0.2 degrees two-theta;

a zoledronic diammonia water complex characterized by an X-ray powder diffraction pattern having strong peaks at about 12.2, 13.0, 14.1, 17.1, and 19.3±0.2 degrees two-theta;

a crystalline zoledronic acid, L-lysine, and water complex characterized by an X-ray powder diffraction pattern having peaks at about 9.0, 14.4, 18.1, 26.0, and 29.6±0.2 degrees two-theta;

a crystalline zoledronic acid, L-lysine, and water complex characterized by an X-ray powder diffraction pattern having peaks at about 9.6, 10.7, 14.3, 21.4, 23.5±0.2 degrees two-theta;

a crystalline zoledronic acid DL-lysine and water complex characterized by an X-ray powder diffraction pattern having peaks at about 8.3, 11.8, 12.3, 15.8, and 20.8±0.2 degrees two-theta;

a crystalline zoledronic acid, DL-lysine, and water complex characterized by an X-ray powder diffraction pattern having peaks at about 9.1, 14.7, 18.0, 21.2, and 26.0±0.2 degrees two-theta;

a crystalline zoledronic acid, DL-lysine, and water complex characterized by an X-ray powder diffraction pattern having peaks at about 9.7, 10.8, 14.4, 18.9, 21.4±0.2 degrees two-theta;

a crystalline zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex characterized by an X-ray powder diffraction pattern having peaks at about 8.8, 9.7, 17.6, 23.1, and 26.5±0.2 degrees two-theta;

a crystalline zoledronic acid, adenine, and water complex characterized by an X-ray powder diffraction pattern having peaks at about 13.6, 15.9, 19.7, 27.9, and 29.5±0.2 degrees two-theta; or

a crystalline zoledronic acid, nicotinamide, and water complex characterized by an X-ray powder diffraction pattern having strong peaks at about 13.1, 15.2, 21.0, 23.9, and 26.5±0.2 degrees two-theta.

20. A crystalline form of zoledronic acid comprising zoledronic acid and glycine.

21. A molecular complex of zoledronic acid comprising zoledronic acid and glycine.

22. A crystalline form of zoledronic acid according to claim **20**, wherein the crystalline form is a crystalline zoledronic acid and glycine complex characterized by an X-ray powder diffraction pattern having peaks at about 10.2, 17.8, 19.9, 22.9, and 28.1±0.2 degrees two-theta.

23. A molecular complex of zoledronic acid comprising zoledronic acid, water, and a compound selected from L-lysine; D,L-lysine; nicotinamide; adenine; and a zoledronic acid salt or comprising zoledronic acid and glycine.

24. A molecular complex of zoledronic acid according to claim **23** selected from the group consisting of:

a zoledronic acid, sodium zoledronate and water complex,

an ammonium zoledronic acid salt and water complex,

a zoledronic diammonia water complex,

a zoledronic acid, L-lysine, and water complex,

a zoledronic acid DL-lysine and water complex,

a zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex,

a zoledronic acid, adenine, and water complex,

a zoledronic acid, nicotinamide, and water complex, or

a zoledronic acid glycine complex.

25. A molecular complex comprising zoledronic acid and lysine.

26. A crystalline form comprising zoledronic acid and lysine.

27. A pharmaceutical composition comprising a complex of claim **18** and a pharmaceutically acceptable excipient.

28. A pharmaceutical composition according to claim **27**, wherein the composition is a oral solid dosage form.

29. A method for the treatment and/or prevention of disease states associated with osteoporosis, hypercalcemia, cancer induced bone metastasis, Paget's disease or adjuvant or neo-adjuvant cancer therapies comprising the step of administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim **27**.

29. (canceled)

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US 20140051669A1

(19) **United States**

(12) **Patent Application Publication**

Tabuteau

(10) **Pub. No.: US 2014/0051669 A1**

(43) **Pub. Date: Feb. 20, 2014**

(54) **COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE**

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(73) Assignee: **Antecip Bioventures II LLC**, New York, NY (US)

(21) Appl. No.: **14/063,979**

(22) Filed: **Oct. 25, 2013**

Related U.S. Application Data

(63) Continuation-in-part of application No. 13/894,274, filed on May 14, 2013.

(60) Provisional application No. 61/646,538, filed on May 14, 2012, provisional application No. 61/647,478, filed on May 15, 2012, provisional application No. 61/654,292, filed on Jun. 1, 2012, provisional application No. 61/654,383, filed on Jun. 1, 2012, provisional application No. 61/655,527, filed on Jun. 5, 2012, provisional application No. 61/655,541, filed on Jun. 5, 2012, provisional application No. 61/764,563, filed on Feb. 14, 2013, provisional application No. 61/762,225, filed on Feb. 7, 2013, provisional application No. 61/767,647, filed on Feb. 21, 2013, provisional application No. 61/767,676, filed on Feb. 21, 2013, provisional application No. 61/803,721, filed on Mar. 20, 2013.

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(52) **U.S. Cl.**
CPC *A61K 31/675* (2013.01)
USPC **514/94**; 548/112

(57) **ABSTRACT**

Oral dosage forms of bisphosphonate compounds, such as zoledronic acid, can be used to treat or alleviate pain or related conditions. The oral bioavailability of zoledronic acid can be enhanced by administering the zoledronic acid in the disodium salt form

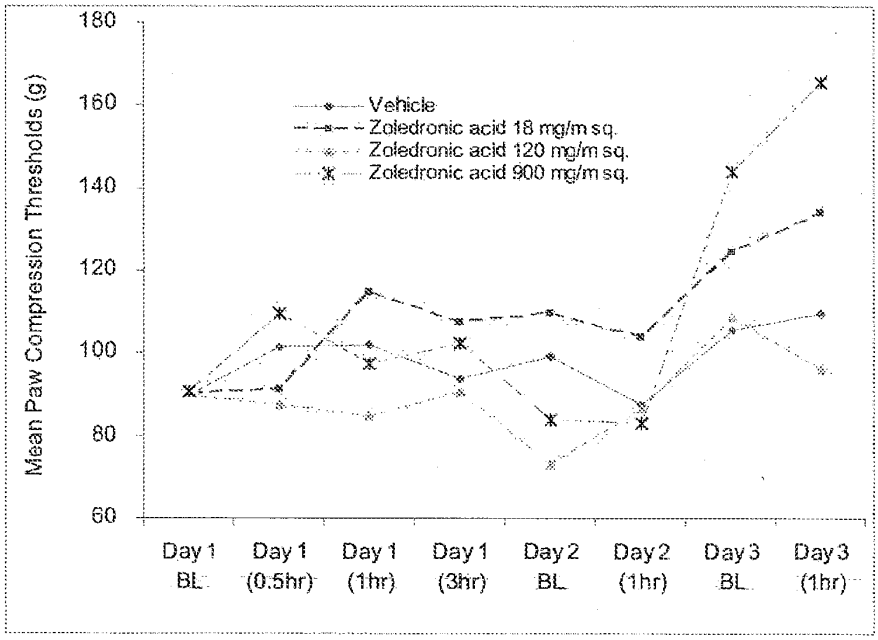

Mean Paw Compression Thresholds (g)
180
160
140
120
100
80
60
Vehicle
Zoledronic acid 18 mg/m sq.
Zoledronic acid 120 mg/m sq.
Zoledronic acid 900 mg/m sq.
Day 1 BL
Day 1 (0.5hr)
Day 1 (1hr)
Day 1 (3hr)
Day 2 BL
Day 2 (1hr)
Day 3 BL
Day 3 (1hr)

FIG. 1

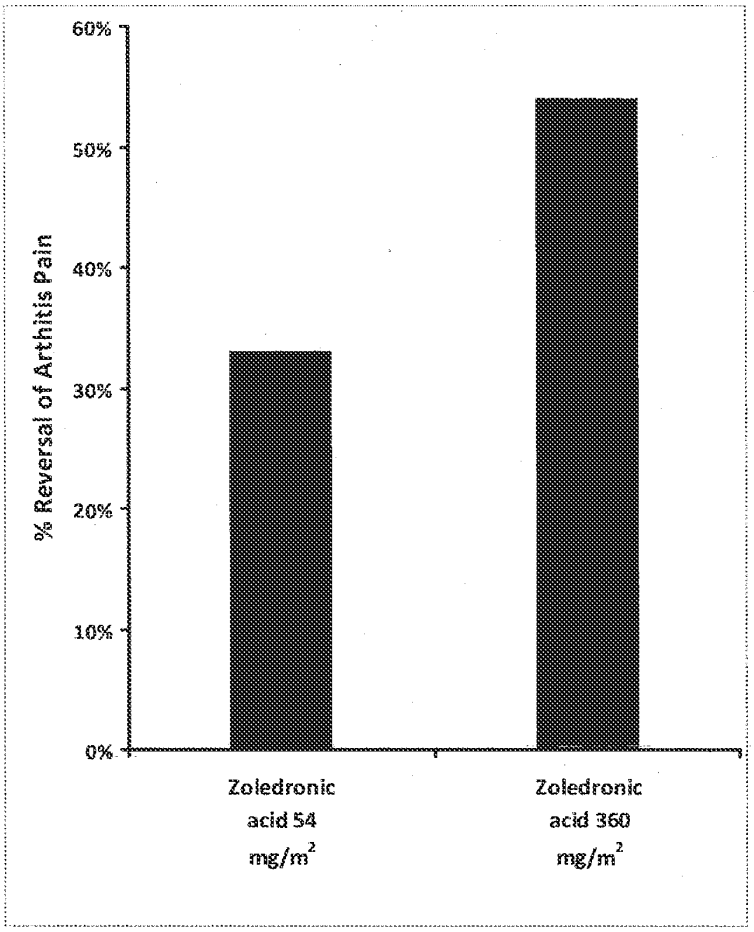

60%
50%
40%
30%
20%
10%
0%
% Reversal of Arthitis Pain
Zoledronic acid 54 mg/m2
Zoledronic acid 360 mg/m2

FIG. 2A

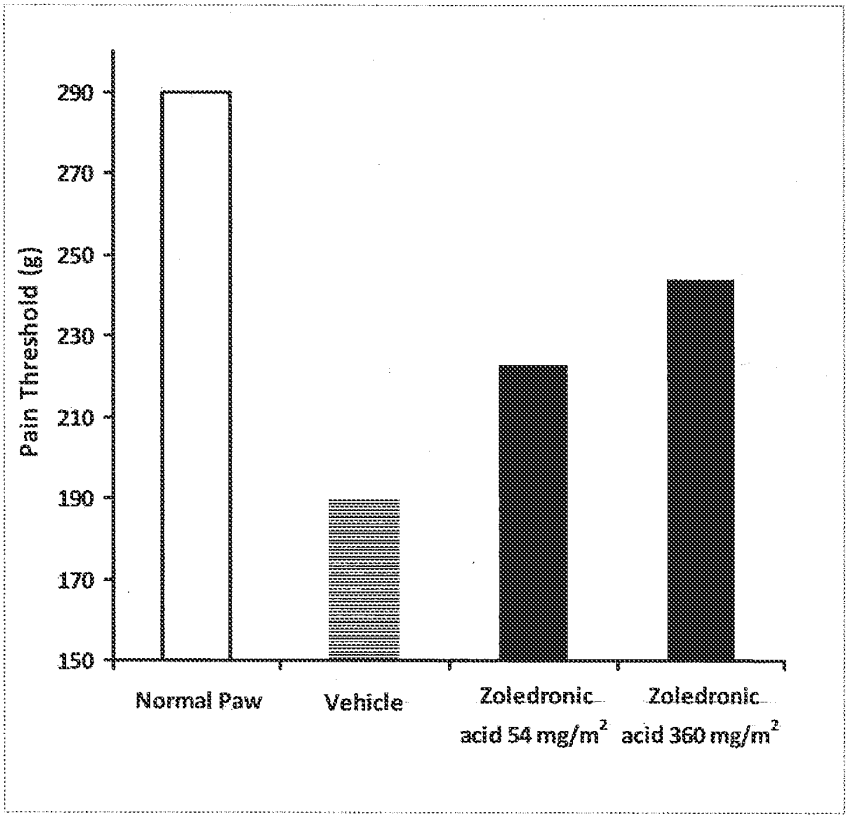

Pain Threshold (g)
290
270
250
230
210
190
170
150
Normal Paw
Vehicle
Zoledronic acid 54 mg/m2
Zoledronic acid 360 mg/m2

FIG. 2B

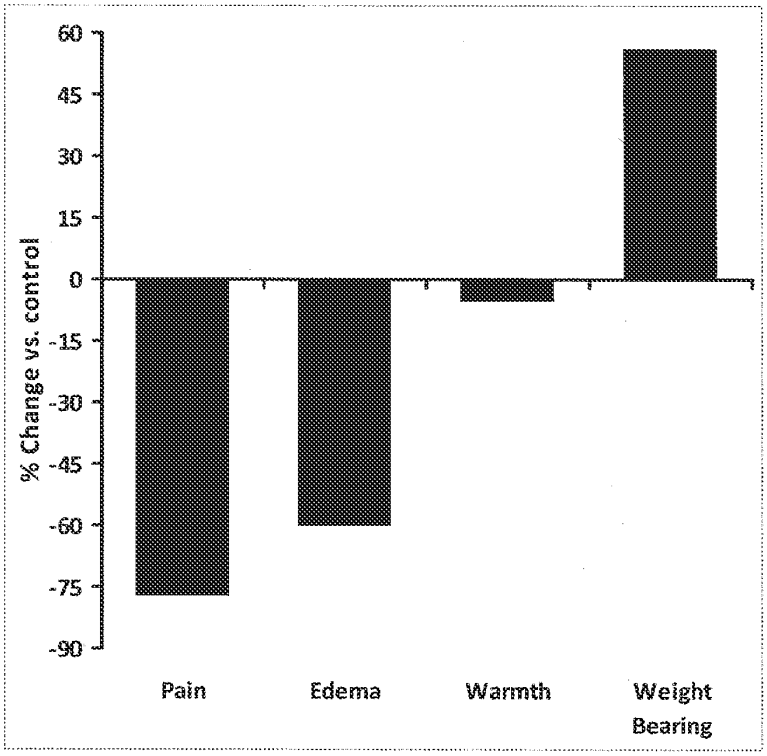

60
45
30
15
0
-15
-30
-45
-60
-75
-90
% Change vs. control
Pain
Edema
Warmth
Weight Bearing

FIG. 3

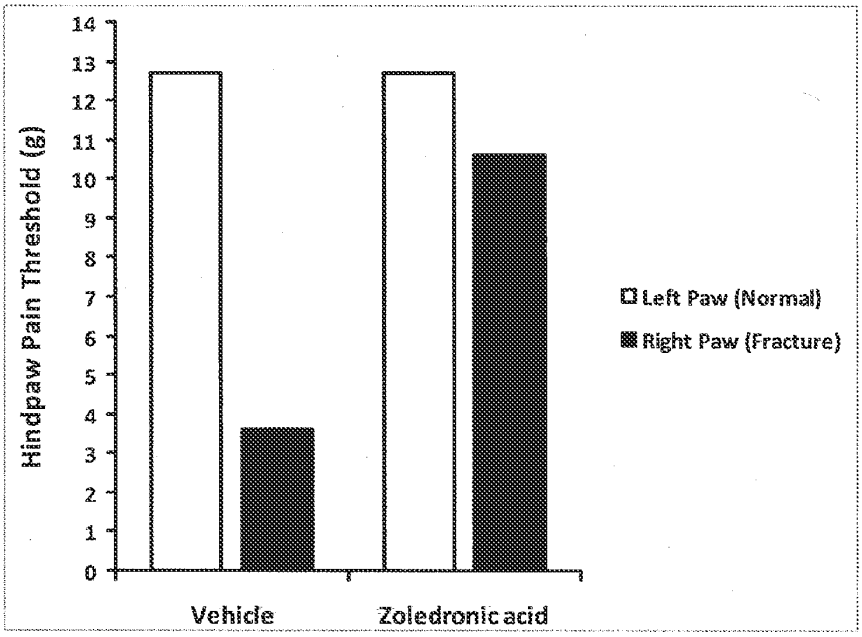

Hindpaw Pain Threshold (g)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Vehicle
Zoledronic acid
Left Paw (Normal)
Right Paw (Fracture)

FIG. 4

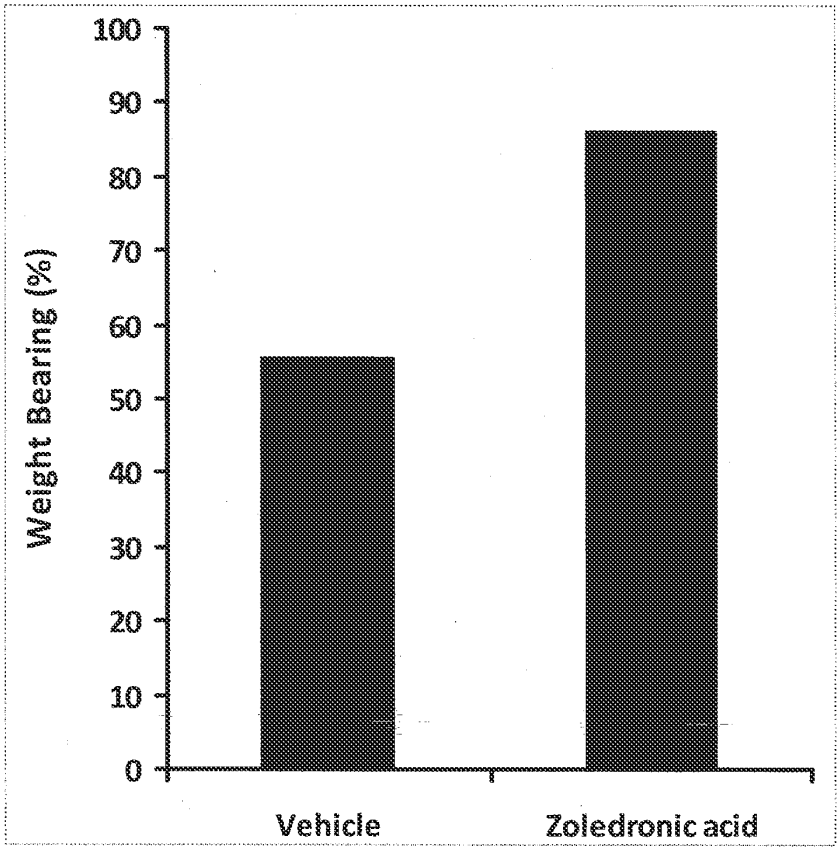

100
90
80
70
60
50
40
30
20
10
0
Weight Bearing (%)
Vehicle
Zoledronic acid

FIG. 5

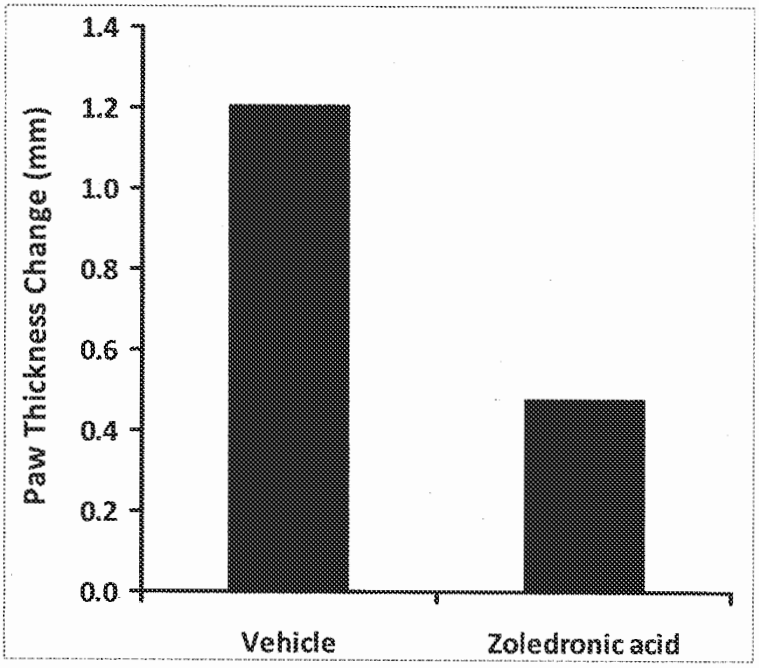

Paw Thickness Change (mm)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Vehicle
Zoledronic acid

FIG. 6

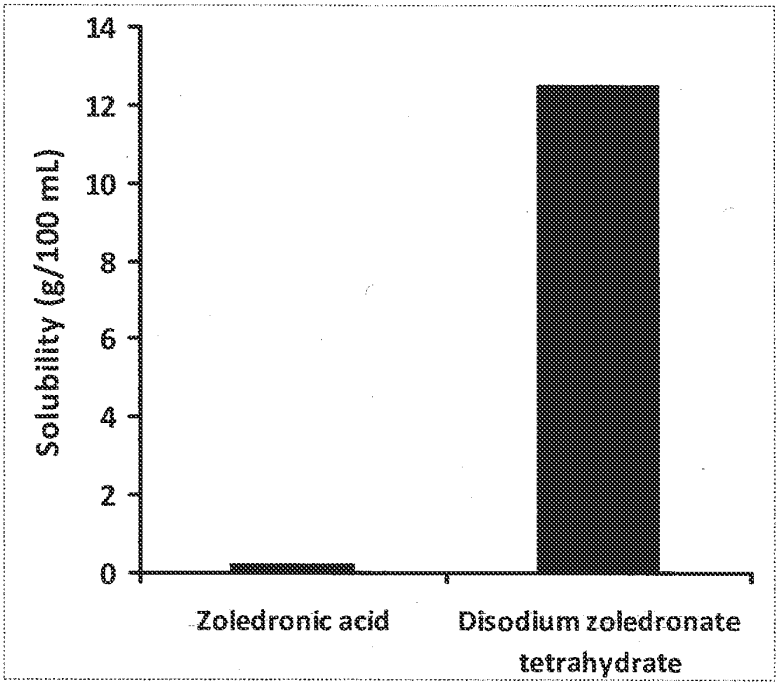

Solubility (g/100 mL)
14
12
10
8
6
4
2
0
Zoledronic acid
Disodium zoledronate tetrahydrate

FIG. 7

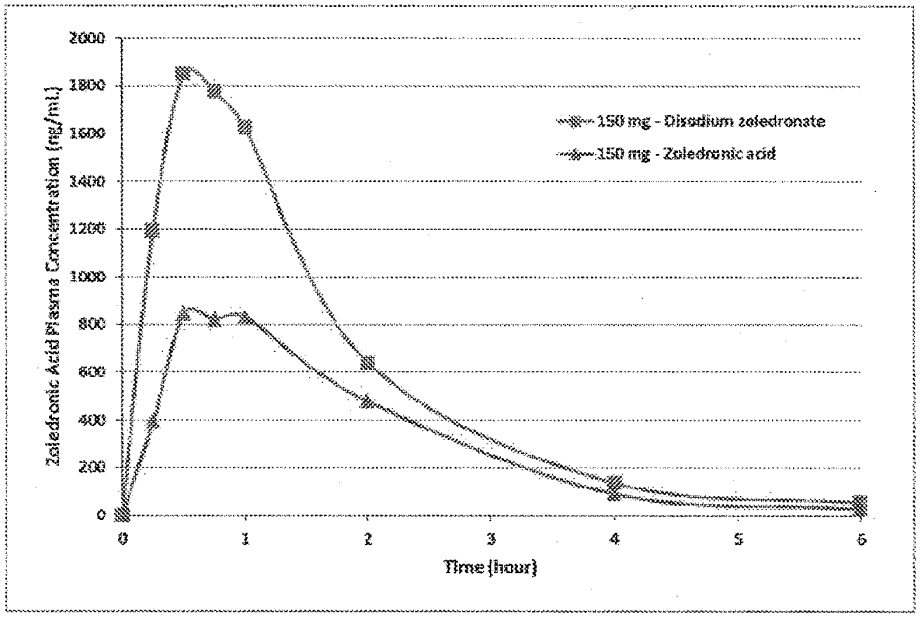

2600
1800
1600
1400
1200
1000
800
600
400
200
0
Zoledronic Acid Plasma Concentration (ng/mL)
0
1
2
3
4
5
6
Time (hour)
150 mg - Disodium zoledronate
150 mg - Zoledronic acid

FIG. 8

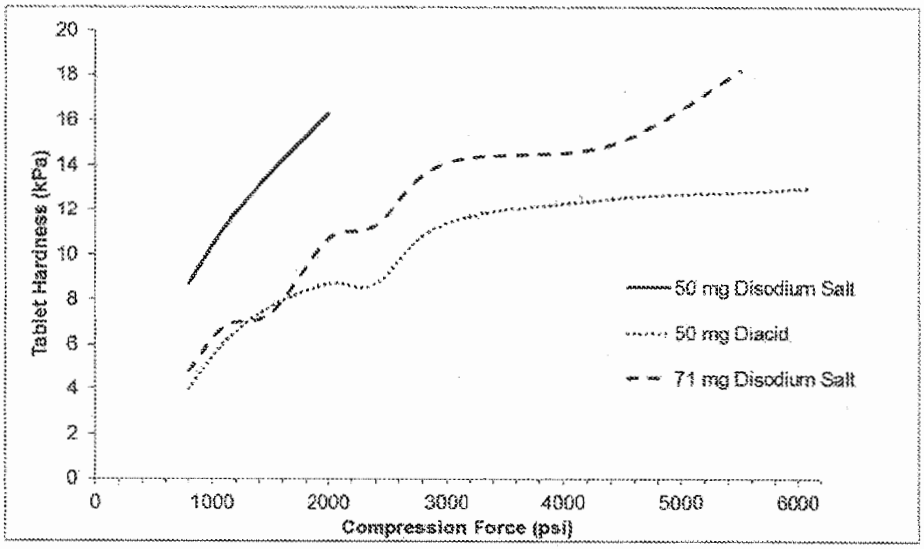

Tablet Hardness (kPa)
20
18
16
14
12
10
8
6
4
2
0
0
1000
2000
3000
4000
5000
6000
Compression Force (psi)
50 mg Disodium Salt
50 mg Diacid
71 mg Disodium Salt

FIG. 9

COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 13/894,274, filed May 14, 2013, which claims the benefit of U.S. Provisional Applications 61/646,538, filed May 14, 2012; 61/647,478, filed May 15, 2012; 61/654,292, filed Jun. 1, 2012; 61/654,383, filed Jun. 1, 2012; 61/655,527, filed Jun. 5, 2012; 61/655,541, filed Jun. 5, 2012; 61/764,563, filed Feb. 14, 2013; 61/762,225, filed Feb. 7, 2013; 61/767,647, filed Feb. 21, 2013; 61/767,676, filed Feb. 21, 2013; and 61/803,721, filed Mar. 20, 2013, all of which are incorporated by reference in their entirety herein.

BACKGROUND

[0002] Bisphosphonate compounds are potent inhibitors of osteoclast activity, and are used clinically to treat bone-related conditions such as osteoporosis and Paget's disease of bone; and cancer-related conditions including multiple myeloma, and bone metastases from solid tumors. They generally have low oral bioavailability.

SUMMARY

[0003] It has been discovered that oral dosage forms of bisphosphonate compounds, such as zoledronic acid, can be used to treat or alleviate pain or related conditions.

[0004] Some embodiments include a method of enhancing the oral bioavailability of zoledronic acid comprising orally administering a dosage form containing zoledronic acid in the disodium salt form.

[0005] Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the bioavailability, in a mammal, of zoledronic acid in the disodium salt form is greater than the bioavailability of zoledronic acid in the diacid form would be in the same dosage form.

[0006] Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng·h/mL to about 2000 ng·h/mL to a human being to which the dosage form is administered.

[0007] Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the disodium salt form is present in a lower molar amount than would be present if the zoledronic acid were in the diacid form; and wherein the zoledronic acid in the disodium salt form has an improved bioavailability as compared to the zoledronic acid in the diacid form to the extent that the lower molar amount of the disodium salt in the dosage form does not reduce the amount of zoledronic acid delivered to the plasma of a mammal.

[0008] Although an oral dosage form with enhanced bioavailability with respect to the bisphosphonate compound can be used, the treatment can also be effective using an oral dosage form that includes a bisphosphonate compound, such as zoledronic acid, wherein the bioavailability of the bisphosphonate is unenhanced, or is substantially unenhanced.

[0009] Some embodiments include a method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof, wherein the mammal experiences significant pain relief more than 3 hours after administration of the dosage form.

[0010] Some embodiments include a method of relieving pain associated with an arthritis comprising administering an oral dosage form containing zoledronic acid to a human being in need thereof.

[0011] Some embodiments include a method of treating complex regional pain syndrome comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

[0012] Some embodiments include an oral dosage form comprising zoledronic acid, wherein the oral bioavailability of zoledronic acid is substantially unenhanced. For example, in some embodiments, the oral bioavailability in the dosage form is about 0.01% to about 4%.

[0013] Some embodiments include a pharmaceutical product comprising more than one unit of an oral dosage form described herein. In some embodiments, each unit of the oral dosage form contains about 1 mg to about 50 mg of zoledronic acid.

[0014] Some embodiments include a method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

[0015] In some embodiments, the mammal receives a total monthly dose of zoledronic acid that is about 800 mg/m^2 or less.

[0016] In some embodiments, the dosage form contains about 10 mg/m^2 to about 20 mg/m^2 based upon the body surface area of the mammal.

[0017] Some embodiments include a method of relieving inflammatory pain comprising orally administering zoledronic acid to a mammal in need thereof.

[0018] In some embodiments, about 300 mg/m^2 to about 600 mg/m^2 of zoledronic acid is administered per month, based upon the body surface area of the mammal.

[0019] In some embodiments, about 50 mg/m^2 to about 600 mg/m^2 of zoledronic acid is administered per month, based upon the body surface area of the mammal.

BRIEF DESCRIPTION OF DRAWINGS

[0020] FIG. 1 is a plot of pain compression thresholds in a rat model of inflammatory pain using three different doses of zoledronic acid. Measurements were taken at baseline (BL) and at various time points after dosing on the days indicated.

[0021] FIG. 2A is a graph depicting reversal of arthritis pain for two different doses of zoledronic acid in a rat model of arthritis pain.

[0022] FIG. 2B is a graph depicting pain thresholds for two different doses of zoledronic acid in a rat model of arthritis pain.

[0023] FIG. 3 is a graph summarizing the results for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0024] FIG. 4 depicts hindpaw pain thresholds for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0025] FIG. 5 depicts weight bearing for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0026] FIG. 6 depicts paw thickness change for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0027] FIG. 7 depicts the aqueous solubility of disodium zoledronate tetrahydrate as compared to the diacid form of zoledronic acid.

[0028] FIG. 8 depicts the plasma concentration of zoledronic acid in dogs over time after administration of 150 mg of the disodium salt form of zoledronic acid and the diacid form of zoledronic acid.

[0029] FIG. 9 depicts the compressibility of dosage forms containing zoledronic acid in the disodium salt form as compared to the diacid form.

DETAILED DESCRIPTION

[0030] Bisphosphonate compounds such as pamidronate or pamidronic acid, neridronate or neridronic acid, olpadronate or olpadronic acid, alendronate or alendronic acid, incadronate or incadronic acid, ibandronate or ibandronic acid, risedronate or risedronic acid, zoledronate or zoledronic acid, etidronate or etidronic acid, clodronate or clodronic acid, tiludronate or tiludronic acid, etc., may be used for a number of medical purposes, such as treatment of undesirable conditions or diseases, including pain relief. This may be accomplished in many instances by administration of oral dosage forms. Generally, an oral dosage form comprising a bisphosphonate such as zoledronic acid is administered orally to a mammal, such as a human being, at least once, to treat a disease or condition, or to relieve pain.

[0031] The term "treating" or "treatment" broadly includes any kind of treatment activity, including the diagnosis, cure, mitigation, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

[0032] An oral dosage form of a bisphosphonate such as zoledronic acid may be used to treat, or provide relief of, any type of pain including, but not limited to, inflammatory pain, arthritis pain, complex regional pain syndrome, lumbosacral pain, musculoskeletal pain, neuropathic pain, chronic pain, cancer-related pain, acute pain, postoperative pain, etc. In some instances, pain relief may be palliative, or pain relief may be provided independent of improvement of the disease or condition or the underlying cause of the disease or condition. For example, although the underlying disease may not improve, or may continue to progress, an individual suffering from the disease may experience pain relief. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0033] In some embodiments, the mammal being treated is not suffering from bone metastasis. In some embodiments, the mammal being treated is not suffering from cancer. In some embodiments, the mammal being treated is not suffering from osteoporosis.

[0034] For example, zoledronic acid or another bisphosphonate may be administered orally to relieve musculoskeletal pain including low back pain, and pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis including ankylosing spondylitis, Paget's disease, fibrous dysplasia, SAPHO syndrome, transient osteoarthritis of the hip, vertebral crush fractures, osteoporosis, etc. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0035] In some embodiments, zoledronic acid or another bisphosphonate may also be administered orally to relieve neuropathic pain, including diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain, and central pain. Other causes of neuropathic pain include cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio-therapy or chemo-therapy associated neuropathy. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0036] In some embodiments, zoledronic acid or another bisphosphonate may be administered orally to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0037] Examples of musculoskeletal pain include low back pain; and pain associated with vertebral crush fractures, fibrous dysplasia, osteogenesis imperfecta, Paget's disease of bone, transient osteoporosis, and transient osteoporosis of the hip.

[0038] Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis pain include pain associated with osteoarthritis, erosive osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, neuropathic arthropaties including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

[0039] In some embodiments, a human being that is treated for arthritis by an oral dosage form of zoledronic acid has an age of about 10 years to about 90 years, about 20 years to about 80 years, about 30 years to about 75 years old, about 40 years to about 70 years, about 1 year to about 16 years, or about 80 years to about 95 years.

[0040] In some embodiments, a human being that is treated for arthritis by an oral dosage form of zoledronic acid has suffered from the arthritis for at least 1 month, at least 2 months, at least 6 months, or at least 1 year.

[0041] In some embodiments, the arthritis affects, a knee, an elbow, a wrist, a shoulder, or a hip.

[0042] In some embodiments, zoledronic acid or another bisphosphonate may be administered orally to relieve complex regional pain syndrome, such as complex regional pain syndrome type I (CRPS-I), complex regional pain syndrome

type II (CRPS-II), CRPS-NOS, or another type of CRPS. CRPS is a type of inflammatory pain. CRPS can also have a neuropathic component.

[0043] Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb accompanied by edema, and autonomic, motor and sensory changes.

[0044] With respect to use of oral zoledronic acid for relieving pain associated with an inflammatory condition, relief of pain can be short-term, e.g. for a period of hours after administration of the dosage form, and/or relief of pain can be long-term, e.g. lasting for days, weeks, or even months after oral administration of zoledronic acid. In some embodiments, a mammal, such as a human being, experiences significant pain relief at least about 3 hours, at least about 6 hours, at least about 12 hours, at least about 24 hours, at least about 48 hours, at least about one week, at least about 2 weeks, or at least about 3 weeks after administration of an oral dosage form comprising zoledronic acid. In some embodiments, a mammal, such as a human being, experiences significant pain relief during at least part of the time from about 3 hours to about 2 weeks, about 3 hours to about 3 weeks, about 3 hours to about 24 hours, about 6 hours to about 2 weeks, or about 6 hours to about 24 hours, about 3 days to about 2 weeks, about 6 days to about 2 weeks, after administration of an oral dosage form comprising zoledronic acid.

[0045] With respect to the treatment of any condition recited herein, in some embodiments a first oral dosage form comprising zoledronic acid is administered and a second oral dosage form comprising oral zoledronic acid is administered. The timing of the administration of the two dosage forms may be such that, with respect to the first oral dosage form, the second oral dosage with respect to the first oral dosage form, the second oral dosage form is administered at $5\times T_{max}$ or greater (e.g., if T_{max} is 1 hour, at 5 hours or later), at least $10\times T_{max}$ or greater, at least about $15\times T_{max}$ or greater, at least about $20\times T_{max}$ or greater, at least about $50\times T_{max}$ or greater, or at least about $200\times T_{max}$ or greater, wherein T_{max} is the time of maximum plasma concentration for the first oral dosage

[0046] Some embodiments include treatment of a condition recited herein, such as inflammatory pain, arthritis, or complex regional pain syndrome, wherein the treatment comprises either: administering only one dosage form to a mammal to treat the condition, or administering a first dosage form to the mammal, followed by administering a second dosage form to the mammal. If two or more dosage forms are administered, the second oral dosage form is administered before the maximum pain relieving effect of the first oral dosage form is achieved, or before a peak in the pain relieving effect of the first oral dosage form is experienced by a mammal, receiving the dosage form. In some embodiments, the second oral dosage form is administered before an observable pain relieving effect is achieved. In some embodiments, the second dosage form is administered about 12 hours to about 60 days, about 24 hours to about 28 days, about 24 hours to about 7 days, about 24 hours to about 14 days, or about 24 hours to about 21 days, after the first dosage form is administered.

[0047] Some embodiments include treatment of a condition recited herein, such as inflammatory pain, arthritis, or complex regional pain syndrome, wherein the treatment comprises administering a first dosage form to the mammal, followed by administering a second dosage form to the mammal, wherein the second dosage form is administered after the maximum pain relieving effect of the first oral dosage form is achieved, and the second oral dosage form is administered while the mammal is still experiencing pain relief from the first oral dosage form, or while the pain relieving effect from the first oral dosage form is observable. In some embodiments, the second dosage form is administered about 12 hours to about 60 days, about 24 hours to about 28 days, about 24 hours to about 7 days, about 24 hours to about 14 days, or about 24 hours to about 21 days, after the first dosage form is administered.

[0048] Zoledronic acid or another bisphosphonate may also be administered orally to relieve cancer-related pain, including pain associated with multiple myeloma and bone metastases from solid tumors. In some embodiments, zoledronic acid is used to treat pain that is not cancer-related pain. For example, zoledronic acid may be used to treat pain that is not associated with multiple myeloma, bone metastasis from solid tumors, hypercalcemia of malignancy, giant cell tumor of bone, blood cancers or leukemias, or solid tumors or cancers. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

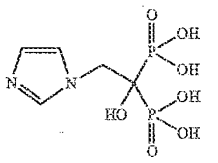
[0049] In addition to relieving pain, oral administration of zoledronic acid or another bisphosphonate may also be useful to treat diseases or conditions that may or may not include a pain component. For example, zoledronic acid or another bisphosphonate may be useful to treat any of the pain conditions or types of conditions listed above, including treatment that does not simply relieve the pain of those conditions, and treatment that is carried out in such a way that the condition is treated without pain relief occurring. In addition to any pain relief zoledronic acid or another bisphosphonate may or may not provide, zoledronic acid or another bisphosphonates may be used to treat a disease or condition such as a metabolic disease or condition; an inflammatory disease or condition, including an inflammatory disease or condition that is not associated with pain; a cancer disease or condition; a neurological disease or condition; etc. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0050] In some embodiments, oral administration of zoledronic acid or another bisphosphonate may also be useful to treat complex regional pain syndrome, rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, axial spondyloarthritis including ankylosing spondylitis, acute vertebral crush fracture, fibrous dysplasia, SAPHO syndrome, osteoporosis, transient osteoporosis, or transient osteoporosis of the hip. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0051] In some embodiments, oral administration of zoledronic acid or another bisphosphonate may also be useful to treat hypercalcemia of malignancy, multiple myeloma, bone metastases from solid tumors, Paget's disease of bone, giant cell tumor of bone, blood cancers or leukemias, or solid

tumors or cancers. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0052] Zoledronic acid has the structure shown below, and is also referred to as zoledronate.



Zoledronic acid

[0053] Unless otherwise indicated, any reference to a compound herein, such as zoledronic acid, by structure, name, or any other means, includes pharmaceutically acceptable salts, such as the disodium salt; alternate solid forms, such as polymorphs, solvates, hydrates, etc.; tautomers; or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.

[0054] In some embodiments, zoledronic acid is administered in a dosage form comprising a salt form, such as a salt of a dianion of zoledronic acid. In some embodiments, zoledronic acid is administered in a dosage form comprising a disodium salt form of zoledronic acid. In some embodiments, zoledronic acid is administered in a sodium salt form, such as a monosodium salt, a disodium salt, a trisodium salt, etc. In some circumstances, use of the disodium salt may be desirable. For example, the disodium salt is much more soluble in water than the diacid form. As a result, in some processes, the disodium salt can be easier to work with than the diacid form. Additionally, the sodium salt may be more bioavailable and/or more rapidly absorbed when taken orally as compared to the diacid form.

[0055] The oral bioavailability of zoledronic acid may be enhanced by orally administering the zoledronic acid in the disodium salt form. For example, the bioavailability of zoledronic acid may be improved by at least about 10%, at least about 20%, at least about 30%, at least about 50%, and/or up to about 100%, or up to about 200%, as compared to administration of zoledronic acid in the diacid form.

[0056] Because of the improved bioavailability of the disodium salt a dosage form may contain, or a mammal, such as a human being, may receive, on a molar basis, less of the disodium salt form of zoledronic acid than would otherwise be administered of the diacid form of zoledronic acid. For example, a dosage form may contain, or a mammal may receive, at least about 10 mole % less, at least about 20 mole % less, at least about 40 mole % less, at least about 50 mole % less, and/or up to about 90 mole % less or 95 mole % less, of the disodium salt form as compared the amount of the diacid form of zoledronic acid that would otherwise be administered, such as a molar amount that would be administered of zoledronic acid in the diacid form in order to achieve the same plasma levels of zoledronic acid.

[0057] In some embodiments, a dosage form contains, or a mammal (such as a human being) is administered, an amount of the disodium salt form, on a molar basis, that has a value of about $0.8n_d$ to about $1.2n_d$ or about $0.9n_d$ to about $1.1n_d$, wherein:

$$n_d=(b_a/b_d)(n_a)$$

wherein b_a is the bioavailability of the diacid form, b_d is the bioavailability of the disodium salt form, and n_a is the number of moles of the diacid that would be administered in a dosage form containing the diacid form of zoledronic acid. For example, if the diacid form has a bioavailability (b_a) of 0.01 and the disodium salt form has a bioavailabity (b_d) of 0.015, and a dosage form would normally contain 0.001 moles of the diacid, n_d would be (0.01/0.015)(0.001 moles), or about 0.00067 moles. In some embodiments, the disodium salt is administered in an amount that has a value of about n_d.

[0058] With respect to oral dosage forms comprising a reduced molar amount of the disodium salt of zoledronic acid as compared to the diacid form of zoledronic acid, in some embodiments, the bioavailability of the zoledronic acid in the disodium salt form is sufficiently high that, if the drug is administered to a mammal, at least as much zoledronic acid is present in the blood of the mammal as would be present if zoledronic acid were administered in the diacid form.

[0059] With respect to oral dosage forms comprising the disodium salt form of zoledronic acid, in some embodiments, the disodium salt form is present in a lower molar amount than would be present if the zoledronic acid were in the diacid form; and the zoledronic acid in the disodium salt form has an improved bioavailability as compared to the zoledronic acid in the diacid form to the extent that the lower molar amount of the disodium salt in the dosage form does not reduce the amount of zoledronic acid delivered to the plasma of a mammal.

[0060] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 4 ng·h/mL to about 2000 ng·h/mL to the mammal each time the zoledronic acid in the disodium salt is administered.

[0061] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 100 ng·h/mL to about 2000 ng·h/mL, about 100 ng·h/mL to about 1000 ng·h/mL, about 500 ng·h/mL to about 1000 ng·h/mL, or about 500 ng·h/mL to about 700 ng·h/mL in the mammal to which the dosage form is administered. This amount may be suitable for administration of the oral dosage form about every 3 to 4 weeks.

[0062] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 20 ng·h/mL to about 700 ng·h/mL, about 50 ng·h/mL to about 500 ng·h/mL, or about 100 ng·h/mL to about 200 ng·h/mL, in the mammal to which the dosage form is administered. This amount may be suitable for weekly administration of the oral dosage, or for administration of 3 to 5 individual dosages during a month. The individual dosages could be given at regular intervals, given during the first week, or at any other schedule that provides 3 to 5 dosages during the month. Weekly

[0063] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 4 ng·h/mL to about 100

ng·h/mL, about 10 ng·h/mL to about 50 ng·h/mL, or about 10 ng·h/mL to about 30 ng·h/mL, in the mammal to which the dosage form is administered. This amount may be suitable for daily administration of the oral dosage form.

[0064] Oral administration of zoledronic acid, particularly oral administration of the disodium salt form of zoledronic acid, can result in more sustained plasma levels of the drug as compared to parenteral modes of administration, such intravenous or subcutaneous. For example, the amount of zoledronic acid in the plasma can be significantly higher for oral administration of the disodium salt about 24 hours or 48 hours, or longer, after administration. In some embodiments, oral zoledronic acid has a 24 hour sustained plasma level factor of about 1 or higher, such as about 1 to about 10, about 1 to about 5, about 3 to about 5, or about 3 to about 4. In some embodiments, an orally administered dosage form of zoledronic acid has a 24 hour sustained plasma level factor or a 48 hour sustained plasma level factor that is higher, such as at least 1.2 times, at least about 2 times, at least about 5 times, about 1.2 times to about 20 times, about 2 times to about 15 times, about 5 times to about 10 times, or about 8 to about 15 times that of intravenously administered zoledronic acid. A "sustained plasma level factor," p_f, is determined by the equation:

$$p_f=1000(C_t/C_{max})$$

wherein C_{max} is the maximum plasma concentration of zoledronic acid after it is administered and C_t is the plasma concentration of zoledronic acid at the time of interest, such as 24 hours. For parenteral administration, the C_{max} can be about the C_0, or the concentration right after injection of the entire amount of the drug into the body. Sustained plasma level factors can also be obtained for other times, such as 48 hours, by using the plasma concentration of zoledronic acid for C_t in the equation above. For example, if the maximum plasma level of zoledronic acid after administration is 1000 ng/mL and the plasma level of zoledronic acid at 24 hours is 1 ng/mL, the 24 hour sustained plasma level factor is 1.

[0065] In some embodiments, the disodium salt form of zoledronic acid provides an enhancement to bioavailability, as compared to the diacid form of zoledronic acid, which adds to any enhancement to bioavailability provided by any bioavailability-enhancing agents in the dosage form. In some embodiments, the disodium salt form of zoledronic acid provides an enhancement to bioavailability, as compared to the diacid form of zoledronic acid, which is greater than any enhancement to bioavailability provided by any bioavailability-enhancing agents in the dosage form. In some embodiments, the disodium salt form of zoledronic acid may be administered in a dosage form that is substantially free of bioavailability-enhancing agents.

[0066] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is a solid.

[0067] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is used to treat an inflammatory condition.

[0068] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is used to treat arthritis.

[0069] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is used to treat complex regional pain syndrome.

[0070] In some embodiments, zoledronic acid is in a form that has an aqueous solubility, meaning the solubility in water, greater than 1% (w/v), about 5% (w/v) to about 50% (w/v), about 5% (w/v) to about 20% (w/v), about 10% (w/v) to about 15% (w/v), or about 12% (w/v) to about 13% (w/v).

[0071] The disodium salt form of zoledronic acid can be more compressible than the diacid form of zoledronic acid. This can make it easier for a dosage form to have a desired hardness. It can also make it easier to increase the drug load, so that a smaller tablet can be given for a given dosage strength. In some embodiments, a solid dosage form of zoledronic acid, such as the diacid form of zoledronic acid or the disodium salt form of zoledronic acid, can have a hardness of about 5 kPa to about 20 kPa or about 5 kPa to about 14 kPa.

[0072] Zoledronic acid or another bisphosphonate may be combined with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice as described, for example, in Remington's Pharmaceutical Sciences, 2005, the disclosure of which is hereby incorporated herein by reference, in its entirety. The relative proportions of active ingredient and carrier may be determined, for example, by the solubility and chemical nature of the compounds, chosen route of administration and standard pharmaceutical practice.

[0073] Zoledronic acid or another bisphosphonate may be administered by any means that may result in the contact of the active agent(s) with the desired site or site(s) of action in the body of a patient. The compounds may be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. For example, they may be administered as the sole active agents in a pharmaceutical composition, or they can be used in combination with other therapeutically active ingredients.

[0074] Zoledronic acid or another bisphosphonate may be administered to a human patient in a variety of forms adapted to the chosen route of administration, e.g., orally, rectally, or parenterally. Parenteral administration in this respect includes, but is not limited to, administration by the following routes: pulmonary, intrathecal, intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepithelial including transdermal, sublingual and buccal; topically; nasal inhalation via insufflation; and rectal systemic.

[0075] The effective amount of zoledronic acid or another bisphosphonate will vary depending on various factors known to the treating physicians, such as the severity of the condition to be treated, route of administration, formulation and dosage forms, physical characteristics of the bisphosphonate compound used, and age, weight and response of the individual patients.

[0076] The amount of zoledronic acid or another bisphosphonate in a therapeutic composition may vary. For example, some liquid compositions may comprise about 0.0001% (w/v) to about 50% (w/v), about 0.01% (w/v) to about 20% (w/v), about 0.01% to about 10% (w/v), about 0.001% (w/v) to about 1% (w/v), about 0.1% (w/v) to about 0.5% (w/v), about 1% (w/v) to about 3% (w/v), about 3% (w/v) to about 5% (w/v), about 5% (w/v) to about 7% (w/v), about 7% (w/v) to about 10% (w/v), about 10% (w/v) to about 15% (w/v), about 15% (w/v) to about 20% (w/v), about 20% (w/v) to about 30% (w/v), about 30% (w/v) to about 40% (w/v), or about 40% (w/v) to about 50% (w/v) of zoledronic acid.

[0077] Some solid compositions may comprise at least about 5% (w/w), at least about 10% (w/w), at least about 20% (w/w), at least about 50% (w/w), at least about 70% (w/w), at least about 80%, about 10% (w/w) to about 30% (w/w), about 10% (w/w) to about 20% (w/w), about 20% (w/w) to about

30% (w/w), about 30% (w/w) to about 50% (w/w), about 30% (w/w) to about 40% (w/w), about 40% (w/w) to about 50% (w/w), about 50% (w/w) to about 80% (w/w), about 50% (w/w) to about 60% (w/w), about 70% (w/w) to about 75% (w/w), about 70% (w/w) to about 80% (w/w), or about 80% (w/w) to about 90% (w/w) of zoledronic acid.

[0078] Any suitable amount of zoledronic acid may be used. Some solid or liquid oral dosage forms, or units of oral dosage forms (referred to collectively herein as "oral dosage form(s)") may contain about 0.005 mg to about 20 mg, about 0.1 mg to about 10 mg, about 0.5 mg to about 10 mg, about 0.2 mg to about 5 mg, about 1 mg to about 500 mg, about 1 mg to about 50 mg, about 10 mg to about 250 mg, about 100 mg to about 300 mg, about 20 mg to about 200 mg, about 20 mg to about 150 mg, about 30 mg to about 100 mg, about 1 mg to about 1,000 mg, about 10 mg to about 50 mg, about 10 mg to about 300 mg, about 10 mg to about 150 mg, about 10 mg to about 100 mg, about 40 mg to about 150 mg, about 10 mg to about 600 mg, about 40 mg to about 600 mg, about 40 mg to about 2000 mg, about 40 mg to about 800 mg, about 25 mg to about 800 mg, about 30 mg to about 800 mg, about 10 mg to about 500 mg, about 50 mg to about 150 mg, about 50 mg, about 100 mg, about 50 mg to about 500 mg, about 100 mg to about 2000 mg, about 300 mg to about 1500 mg, about 200 mg to about 1000 mg, about 100 mg to about 500 mg, or about 150 mg of zoledronic acid, or any amount of zoledronic in a range bounded by, or between, any of these values. In some embodiments, the oral zoledronic acid is administered daily, weekly, monthly, every two or three months, once a year, or twice a year.

[0079] In some embodiments, an oral dosage form may contain about 10 mg/m^2 to about 20 mg/m^2, about 15 mg/m^2 to about 20 mg/m^2, about 18 mg/m^2, about 80 mg/m^2 to about 150 mg/m^2, about 90 mg/m^2 to about 150 mg/m^2, about 100 mg/m^2 to about 150 mg/m^2 of zoledronic acid, or any amount of zoledronic in a range bounded by, or between, any of these values. All dosage ranges or amounts expressed in mg/m^2 are based upon the body surface area of the mammal.

[0080] In some embodiments the daily oral dose of zoledronic acid is about 0.005 mg to about 20 mg, about 0.1 mg to about 10 mg, about 0.5 mg to about 10 mg, about 0.2 mg to about 5 mg, or any amount of zoledronic acid in a range bounded by, or between, any of these values. In some embodiments, the daily oral dose of zoledronic acid is less than about 35 mg/m^2, less than about 30 mg/m^2, less than about 25 mg/m^2, about 1 mg/m^2 to about 35 mg/m^2, about 1 mg/m^2 to about 30 mg/m^2, about 1.5 mg/m^2 to about 25 mg/m^2, about 1.8 mg/m^2 to about 20 mg/m^2, about 10 mg/m^2 to about 20 mg/m^2, about 10 mg/m^2 to about 30 mg/m^2, about 15 mg/m^2 to about 20 mg/m^2, about 18 mg/m^2, or any amount of zoledronic acid in a range bounded by, or between, any of these values.

[0081] In some embodiments the weekly or dose of zoledronic add is about 1 mg to about 1000 mg, about 1 mg to about 500 mg, about 10 mg to about 250 mg, about 100 mg to about 300 mg, about 10 mg to about 100 mg, about 10 mg to about 150 mg, about 10 mg to about 100 mg, about 10 mg to about 300 mg, about 20 mg to about 150 mg, or about 30 mg to about 100 mg. In some embodiments, the weekly oral dose of zoledronic acid is less than about 250 mg/m^2, less than about 200 mg/m^2, less than about 175 mg/m^2, about 6 mg/m^2 to about 250 mg/m^2, about 10 mg/m^2 to about 210 mg/m^2, about 10 mg/m^2 to about 170 mg/m^2, about 4 mg/m^2 to about 140 mg/m^2, about 100 mg/m^2 to about 140 mg/m^2, about 126 mg/m^2, or any amount of zoledronic acid in a range bounded by, or between, any of these values. The weekly oral dose may be given as a single dose, given once during the week, or may be given in 2, 3, 4, 5, 6, or 7 individual doses during the week.

[0082] In some embodiments, the monthly dose of zoledronic acid, or the amount of zoledronic acid that is administered over a period of a month, is about 5000 mg or less, about 4000 mg or less, about 3000 mg or less, about 2000 mg or less, about 1000 mg or less, about 700 mg or less, about 600 mg or less, about 1 mg to about 4,000 mg, about 1 mg to about 1,000 mg, about 10 mg to about 1000 mg, about 50 mg to about 1000 mg, about 10 mg to about 600 mg, about 40 mg to about 600 mg, about 50 mg to about 600 mg, or about 100 mg to about 600 mg, about 40 mg to about 2000 mg, about 40 mg to about 800 mg, about 50 mg to about 800 mg, or about 100 mg to about 800 mg, about 40 mg to about 1000 mg, about 50 mg to about 1000 mg, or about 100 mg to about 1000 mg, or any monthly dose in a range bounded by, or between, any of these values. In some embodiments, the monthly oral dose of zoledronic acid is less than about 1000 mg/m^2, less than about 800 mg/m^2, less than about 600 mg/m^2, about 10 mg/m^2 to about 1000 mg/m^2, about 50 mg/m^2 to about 800 mg/m^2, about 70 mg/m^2 to about 700 mg/m^2, about 100 mg/m^2 to about 700 mg/m^2, about 100 mg/m^2 to about 600 mg/m^2, about 50 mg/m^2 to about 200 mg/m^2, about 300 mg/m^2 to about 600 mg/m^2, about 450 mg/m^2 to about 600 mg/m^2, about 300 mg/m^2 to about 1000 mg/m^2, about 400 mg/m^2 to about 1000 mg/m^2, about 500 mg/m^2 to about 1000 mg/m^2, about 400 mg/m^2 to about 700 mg/m^2, about 500 mg/m^2 to about 600 mg/m^2, about 540 mg/m^2, or any amount of zoledronic acid in a range bounded by, or between, any of these values. A monthly dose may be given as a single dose, or as two or more individual doses administered during the month. In some embodiments, the monthly dose is administered in 2 or 3 weekly doses. In some embodiments, the monthly dose is administered in 4 or 5 weekly doses. In some embodiments, the monthly dose is administered in 28 to 31 daily doses. In some embodiments, the monthly dose is administered in 5 to 10 individual doses during the month. The monthly dose may be administered for only 1 month, or may be repeatedly administered for 2 or more months.

[0083] The oral zoledronic acid, or disodium salt thereof, may be administered in combination with about 0.1 mg to about 10 mg of zoledronic acid, or a salt thereof, administered parenterally, such as intravenously. In some embodiments, about 50 mg, about 100 mg, or about 150 mg of the disodium salt of zoledronic acid is administered orally in combination with 1 mg parenteral, such as intravenous, zoledronic acid. In some embodiments the parenteral dose of zoledronic acid is about 0.25 mg to about 25 mg, about 0.25 mg to about 10 mg, or about 0.5 mg to about 7.5 mg.

[0084] With respect to oral administration of zoledronic acid, or another bisphosphonate, for the treatment of pain associated with inflammation, arthritis, CRPS, or any other condition recited herein, it may helpful if the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage, (other than any water required to swallow the oral dosage form) for at least about 1 hour, at least about 2 hours, at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 10 hours, or at least about 12 hours before the zoledronic acid is administered. It may also be helpful if the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least about 30 minutes, at least about

1 hour, at least about 2 hours, at least about 3 hours, or at least about 4 hours after the zoledronic acid is administered. In some embodiments, a human being to which the zoledronic acid is administered avoids lying down, or remains upright or sits upright, for at least about 30 minutes or about 1 hour after receiving a dosage form containing zoledronic acid. Avoiding food or beverage before or after oral administration of zoledronic acid can improve the bioavailability of the zoledronic acid.

[0085] The oral bioavailability of zoledronic acid in a dosage form can vary. Some dosage forms may have ingredients added to enhance the bioavailability. However, bioavailability enhancement is not necessary for an oral dosage form to be effective. In some embodiments, the dosage form is substantially free of bioavailability-enhancing agents. In some embodiments, an oral dosage form may have an oral bioavailability of zoledronic acid of about 0.01% to about 10%, about 0.1% to about 7%, about 0.1% to about 5%, etc. Without ingredients or other methods to enhance bioavailability, zoledronic acid typically has a low bioavailability in an oral dosage form. In some embodiments, the oral bioavailability of zoledronic acid is unenhanced or substantially unenhanced. For example, the oral bioavailability of zoledronic acid can be about 0.01% to about 5%, about 0.01% to about 4%, about 0.1% to about 3%, about 0.1% to about 2%, about 0.2% to about 2%, about 0.2% to about 1.5%, about 0.3% to about 1.5%, about 0.3% to about 1%, about 0.1% to about 0.5%, about 0.3% to about 0.5%, about 0.5% to about 1%, about 0.6% to about 0.7%, about 0.7% to about 0.8%, about 0.8% to about 0.9%, about 0.9%, about 1% to about 1.1%, about 1.1% to about 1.2%, about 1.2% to about 1.3%, about 1.3% to about 1.4%, about 1.4% to about 1.5%, about 1.5% to about 1.6%, about 1.6% to about 1.8%, or about 1.8% to about 2%.

[0086] One embodiment is a pharmaceutical composition comprising zoledronic acid wherein the oral bioavailability of zoledronic acid in the dosage form is from about 0.01% to about 10%.

[0087] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.01% to about 5%.

[0088] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 7%.

[0089] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 5%.

[0090] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 3%.

[0091] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%.

[0092] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.2% to about 2%.

[0093] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.2% to about 1.5%.

[0094] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.3% to about 1.5%.

[0095] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.3% to about 1.0%.

[0096] In some embodiments, an oral dosage form comprises about 10 mg to about 300 mg of zoledronic acid, and is administered daily for about 2 to about 15 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[0097] In some embodiments, an oral dosage form comprises about 10 mg to about 150 mg or about 10 mg to about 100 mg of zoledronic acid, and is administered daily for about 2 to about 15 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[0098] In some embodiments, an oral dosage form comprises about 10 mg to about 150 mg or about 10 mg to about 100 mg of zoledronic acid, and is administered daily for about 5 to about 10 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[0099] In some embodiments, an oral dosage form comprises about 40 mg to about 150 mg of zoledronic acid, and is administered daily for about 5 to about 10 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[0100] In some embodiments, the oral zoledronic acid may be administered as one dose of about 100 mg to about 2000 mg. In some embodiments, the oral zoledronic acid may be administered as one dose of about 300 mg to about 1500 mg. In some embodiments, the oral zoledronic acid may be administered as one dose of about 200 mg to about 1000 mg. The dose of zoledronic acid may be administered in a single or divided dose.

[0101] Zoledronic acid may be formulated for oral administration, for example, with an inert diluent or with an edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, compressed into tablets, or incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, coated tablets, troches, capsules, elixirs, dispersions, suspensions, solutions, syrups, wafers, patches, and the like.

[0102] Tablets, troches, pills, capsules and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient, such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coating, for instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. It may be desirable for material in a dosage form or pharmaceutical composition to be pharmaceutically pure and substantially non toxic in the amounts employed.

[0103] Some compositions or dosage forms may be a liquid, or may comprise a solid phase dispersed in a liquid.

[0104] Zoledronic acid may be formulated for parental or intraperitoneal administration. Solutions of the active compounds as free acids or pharmacologically acceptable salts

can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also have an oil dispersed within, or dispersed in, glycerol, liquid polyethylene glycols, and mixtures thereof. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

[0105] In some embodiments, an oral dosage form may comprise a silicified microcrystalline cellulose such as Prosolv. For example, about 20% (wt/wt) to about 70% (wt/wt), about 10% (wt/wt) to about 20% (wt/wt), about 20% (wt/wt) to about 40% (wt/wt), about 25% (wt/wt) to about 30% (wt/wt), about 40% (wt/wt) to about 50% (wt/wt), or about 45% (wt/wt) to about 50% (wt/wt) silicified microcrystalline cellulose may be present in an oral dosage form or a unit of an oral dosage form.

[0106] In some embodiments, an oral dosage form may comprise a crosslinked polyvinylpyrrolidone such as crospovidone. For example, about 1% (wt/wt) to about 10% (wt/wt), about 1% (wt/wt) to about 5% (wt/wt), or about 1% (wt/wt) to about 3% (wt/wt) crosslinked polyvinylpyrrolidone may be present in an oral dosage form or a unit of an oral dosage form.

[0107] In some embodiments, an oral dosage form may comprise a fumed silica such as Aerosil. For example, about 0.1% (wt/wt) to about 10% (wt/wt), about 0.1% (wt/wt) to about 1% (wt/wt), or about 0.4% (wt/wt) to about 0.6% (wt/wt) fumed silica may be present in an oral dosage form or a unit of an oral dosage form.

[0108] In some embodiments, an oral dosage form may comprise magnesium stearate. For example, about 0.1% (wt/wt) to about 10% (wt/wt), about 0.1% (wt/wt) to about 1% (wt/wt), or about 0.4% (wt/wt) to about 0.6% (wt/wt) magnesium stearate may be present in an oral dosage form or a unit of an oral dosage form.

[0109] An or dosage form comprising zoledronic acid or another bisphosphonate may be included in a pharmaceutical product comprising more than one unit of the or dosage form.

[0110] A pharmaceutical product containing oral dosage forms for daily use can contain 28, 29, 30, or 31 units of the oral dosage form for a monthly supply. An approximately 6 week daily supply can contain 40 to 45 units of the oral dosage form. An approximately 3 month daily supply can contain 85 to 95 units of the oral dosage form. An approximately six-month daily supply can contain 170 to 200 units of the oral dosage form. An approximately one year daily supply can contain 350 to 380 units of the oral dosage form.

[0111] A pharmaceutical product containing oral dosage forms for weekly use can contain 4 or 5 units of the oral dosage form for a monthly supply. An approximately 2 month weekly supply can contain 8 or 9 units of the oral dosage form. An approximately 6 week weekly supply can contain about 6 units of the oral dosage form. An approximately 3 month weekly supply can contain 12, 13 or 14 units of the oral dosage form. An approximately six-month weekly supply can contain 22 to 30 units of the oral dosage form. An approximately one year weekly supply can contain 45 to 60 units of the oral dosage form.

[0112] A pharmaceutical product may accommodate other dosing regimes. For example, a pharmaceutical product may comprise 5 to 10 units of the oral dosage form, wherein each unit of the oral dosage form contains about 40 mg to about 150 mg of zoledronic acid. Some pharmaceutical products may comprise 1 to 10 units of the oral dosage form, wherein the product contains about 200 mg to about 2000 mg of zoledronic acid. For such a product, each unit of the oral dosage form may be taken daily for 1 to 10 days or 5 to 10 days during a month, such as at the beginning of a month.

[0113] Some oral dosage forms comprising zoledronic acid or a salt thereof may have enteric coatings or film coatings.

[0114] In the examples below, zoledronic acid was administered in the disodium salt form as disodium zoledronate tetrahydrate. No bioavailability enhancing agents were used in the test compositions.

Example 1

Effect of Orally Administered Zoledronic Acid in Rat Model of Inflammatory Pain

Method:

[0115] The effect of orally administered zoledronic acid on inflammatory pain was examined using the rat complete Freund's adjuvant (CFA) model. Inflammatory pain was induced by injection of 100% CFA in a 75 μL volume into the left hind paws of Sprague-Dawley rats on day 0, followed by assessments on days 1-3. Animals were orally administered vehicle (control), zoledronic acid 18 mg/m^2 (or 3 mg/kg), zoledronic acid 120 mg/m^2 (or 20 mg/kg), or zoledronic acid 900 mg/m^2 (or 150 mg/kg) daily on days 1-3. Drug was dissolved in distilled water and prepared fresh daily. Animals were fasted prior to dosing. Under current FDA guidelines for extrapolating starting dosages from animals to humans, dosages expressed in mg/m^2 are considered equivalent between mammalian species. Thus, for example, 18 mg/m^2 in a rat is considered equivalent to 18 mg/m^2 in a human being, while 3 mg/kg in a rat may not be equivalent to 3 mg/kg in a human being.

[0116] Values for inflammatory pain (mechanical hyperalgesia) in the vehicle and drug-treated animals were obtained on day 0 prior to CFA injection, and at baseline and post-treatment on days 1-3. Pain was assessed using a digital Randall-Selitto device (dRS; IITC Life Sciences, Woodland Hills, Calif.). Animals were placed in a restraint sling that suspended the animal, leaving the hind limbs available for testing. Paw compression threshold was measured by applying increasing pressure to the plantar surface of the hind paw with a dome-shaped tip placed between the 3rd and 4th metatarsus. Pressure was applied gradually over approximately 10 seconds. Measurements were taken from the first observed nocifensive behavior of vocalization, struggle or withdrawal. A cut-off value of 300 g was used to prevent injury to the animal.

[0117] Reversal of inflammatory pain was calculated according to the formula:

$$\%\ \text{reversal}=(\text{Post-treatment}-\text{Post-CFA baseline})/(\text{Pre-CFA baseline}-\text{Post-CFA baseline})\times 100.$$

[0118] The experiment was carried out using 9-10 animals per group.

Results:

[0119] Oral administration of zoledronic acid significantly improved inflammatory pain thresholds compared to vehicle. Pain threshold measurements taken at various times are shown in FIG. 1. Paw compression thresholds in the 18 mg/m^2 group were higher than for vehicle during the entire measurement period after 30 minutes from the start of treatment. On day three, paw compression thresholds for both the

18 mg/m^2 and 900 mg/m^2 groups were greater than for vehicle. An improvement in pain threshold of 49% and 83% from baseline was observed for the 18 mg/m^2 and the 900 mg/m^2 groups respectively.

[0120] Orally administered zoledronic acid produced a 29% reversal of inflammatory pain at the 18 mg/m^2, and a 48% reversal at the 900 mg/m^2 dose. This magnitude of effect is comparable to that obtained with clinical doses of commercially available NSAIDs when tested in a similar model of inflammatory pain. Under current FDA guidelines, the reference body surface area of a human adult is 1.62 m^2. Thus, a daily dose of 18 mg/m^2 corresponds to a monthly dose of about 500-560 mg/m^2 or a human dose of about 800-900 mg.

[0121] Surprisingly, the two higher doses resulted in thresholds that were lower than vehicle on the first two days of dosing. The 120 mg/m^2 group was approximately equal or inferior to vehicle at all time points during the assessment period. While the 900 mg/m^2 group showed effectiveness on day 3, this result was accompanied by significant toxicity necessitating euthanization of all the animals in this group two days after cessation of dosing.

Example 2

Effect of Orally Administered Zoledronic Acid in Rat Model of Arthritis Pain

Method:

[0122] The effect of orally administered zoledronic acid on arthritis pain was examined in the rat complete Freund's adjuvant (CFA) model of arthritis pain. In this model, injection of 100% complete Freund's adjuvant (CFA) in a 75 μL volume into the left hind paws is followed by a 10-14 day period to allow for the development of arthritis pain. Animals were orally administered vehicle (control), zoledronic acid 54 mg/m^2 (or 9 mg/kg), or zoledronic acid 360 mg/m^2 (or 60 mg/kg), divided in three equal daily doses on the first three days post CFA injection. Drug was dissolved in distilled water and prepared fresh daily. Animals were fasted prior to dosing.

[0123] Arthritis pain (mechanical hyperalgesia) in the vehicle and drug-treated animals was evaluated on day 14 post CFA injection using a digital Randall-Selitto device (dRS; IITC Life Sciences, Woodland Hills, Calif.). Animals were placed in a restraint sling that suspended the animal, leaving the hind limbs available for testing. Paw compression threshold was measured by applying increasing pressure to the plantar surface of the hind paw with a dome-shaped tip placed between the 3rd and 4th metatarsus. Pressure was applied gradually over approximately 10 seconds. Measurements were taken from the first observed nocifensive behavior of vocalization, struggle or withdrawal. A cut-off value of 300 g was used to prevent injury to the animal.

[0124] Reversal of arthritis pain in the ipsilateral (CFA-injected) paw was calculated according to the formula:

> % reversal=(ipsilateral drug threshold−ipsilateral vehicle threshold)/(contralateral vehicle threshold−ipsilateral vehicle threshold)×100.

[0125] The experiment was carried out using 7-10 animals per group.

Results:

[0126] Oral administration of zoledronic acid significantly improved arthritis pain thresholds compared to vehicle. As shown in FIGS. 2A and 2B, orally administered zoledronic acid produced a dose-dependent reversal of arthritis pain. A reversal of 33% was observed in the 54 mg/m^2 group, and reversal of 54% was observed in the 360 mg/m^2 group. Under current FDA guidelines, the reference body surface area of a human adult is 1.62 m^2. Thus, 54 mg/m^2 in a rat is equivalent to an implied human dose of about 87 mg, and 360 mg/m^2 in a rat is equivalent to an implied human dose of about 583 mg.

Example 3

Treatment of Complex Regional Pain Syndrome with Orally Administered Zoledronic Acid

[0127] The effect of orally administered zoledronic acid was examined in the rat tibia fracture model of complex regional pain syndrome (CRPS). CRPS was induced in the rats by fracturing the right distal tibias of the animals and casting the fractured hindpaws for 4 weeks, as described in Guo T Z et al. (*Pain.* 2004; 108:95-107). This animal model has been shown to replicate the inciting trauma, natural history, signs, symptoms, and pathologic changes observed in human CRPS patients (Kingery W S et al., *Pain.* 2003; 104: 75-84).

[0128] Animals were orally administered either vehicle (control) or zoledronic acid, in a dosage of 18 mg/m^2/day (3 mg/kg/day) for 28 days, starting on the day of fracture and casting. Drug was dissolved in distilled water and administered by gavage. Animals were fasted for 4 hours before and 2 hours after dosing. At the end of the 28-day period, casts were removed, and on the following day, the rats were tested for hindpaw pain, edema, and warmth.

Pain Assessments

[0129] Pain was assessed by measuring hyperalgesia, and weight bearing.

[0130] To measure hyperalgesia, an up-down von Frey testing paradigm was used. Rats were placed in a clear plastic cylinder (20 cm in diameter) with a wire mesh bottom and allowed to acclimate for 15 minutes. The paw was tested with one of a series of eight von Frey hairs ranging in stiffness from 0.41 g to 15.14 g. The von Frey hair was applied against the hindpaw plantar skin at approximately midsole, taking care to avoid the tori pads. The fiber was pushed until it slightly bowed and then it was jiggled in that position for 6 seconds. Stimuli were presented at an interval of several seconds. Hindpaw withdrawal from the fiber was considered a positive response. The initial fiber presentation was 2.1 g and the fibers were presented according to the up-down method of Dixon to generate six responses in the immediate vicinity of the 50% threshold. Stimuli were presented at an interval of several seconds.

[0131] An incapacitance device (IITC Inc. Life Science, Woodland, Calif., USA) was used to measure hindpaw weight bearing, a postural effect of pain. The rats were manually held in a vertical position over the apparatus with the hindpaws resting on separate metal scale plates and the entire weight of the rat was supported on the hindpaws. The duration of each measurement was 6 seconds and 10 consecutive measurements were taken at 60-second intervals. Eight readings (excluding the highest and lowest ones) were averaged to

calculate the bilateral hindpaw weight-bearing values. Weight bearing data were analyzed as the ratio between right (fracture) and left hindpaw weight bearing values ((2R/(R+L))×100%).

Edema Assessment

[0132] A laser sensor technique was used to determine the dorsal-ventral thickness of the hindpaw. Before baseline testing the bilateral hindpaws were tattooed with a 2 to 3 mm spot on the dorsal skin over the midpoint of the third metatarsal. For laser measurements each rat was briefly anesthetized with isoflurane and then held vertically so the hindpaw rested on a table top below the laser. The paw was gently held flat on the table with a small metal rod applied to the top of the ankle joint. Using optical triangulation, a laser with a distance measuring sensor was used to determine the distance to the table top and to the top of the hindpaw at the tattoo site and the difference was used to calculate the dorsal-ventral paw thickness. The measurement sensor device used in these experiments (4381 Precicura, Limab, Goteborg, Sweden) has a measurement range of 200 mm with a 0.01 mm resolution.

Hindpaw Temperature Measurement

[0133] The temperature of the hindpaw was measured using a fine wire thermocouple (Omega, Stanford, Conn., USA) applied to the paw skin. Six sites were tested per hindpaw. The six measurements for each hindpaw were averaged for the mean temperature.

Results

[0134] As illustrated in FIG. **3**, treatment with orally administered zoledronic acid reversed pain, restored weight bearing, and prevented edema as compared to vehicle treated animals.

[0135] As illustrated in FIG. **4**, von Frey pain thresholds for the right (fracture) hindpaw were reduced by 72% versus the contralateral (normal) hindpaw in vehicle treated animals. Zoledronate treatment reversed fracture induced pain by 77% as compared to vehicle treatment.

[0136] As illustrated in FIG. **5**, reduction in weight bearing, a postural effect of pain, was significantly higher in the vehicle treated group as compared to the zoledronic acid treated group. Weight bearing on the fracture hindlimb was reduced to 55% of normal in the vehicle treated group. Zoledronate treatment significantly restored hindlimb weight bearing as compared to vehicle treatment (86% of normal).

[0137] As illustrated in FIG. **6**, the expected increase in hindpaw thickness was greater in the vehicle treated group as compared to the zoledronic acid treated group, reflecting the development of edema. Zoledronate treatment reduced hindpaw edema by 60% versus vehicle treatment.

[0138] Zoledronic acid reduced hindpaw warmth by 5% versus vehicle treatment.

[0139] The daily dose in the above experiment was 18 mg/m^2/day. Under current FDA guidelines, the reference body surface area of a human adult is 1.62 m^2. Thus, a daily dose of 18 mg/m^2 corresponds to a monthly dose of about 500-560 mg/m^2 or a human dose of about 800-900 mg.

Example 6

Solubility of Disodium Salt of Zoledronic Acid

[0140] The aqueous solubility of zoledronic acid and disodium zoledronate tetrahydrate was determined. One gram of the test compound was measured in to a beaker. Demineralized water (pH 5.5) was then added in small increments to the test compound, and sonification was applied to the mixture. The procedure was continued until complete dissolution was achieved. Full dissolution was determined to have been reached when a clear solution was present with no visible material. The volume of water required to reach full dissolution was used to calculate a solubility value expressed in grams per 100 mL. The procedure was performed for each compound.

Results

[0141] As shown in FIG. **7**, the aqueous solubility of disodium zoledronate tetrahydrate is approximately 50 times that of zoledronic acid. Disodium zoledronate tetrahydrate has a solubility of 12.5 g/100 mL compared to only 0.25 g/100 mL for zoledronic acid.

Example 7

Bioavailability of Orally Administered Zoledronic Acid and Disodium Zoledronate

[0142] Tablets were manufactured containing either pure zoledronic acid or the disodium salt of zoledronic acid (disodium zoledronate tetrahydrate). Both types of tablets contained 50 mg of zoledronic acid equivalent per tablet. Identical excipients were used in both types of tablets, with amounts adjusted to account for the difference in molecular weights between the acid and the disodium salt.

[0143] Beagle dogs were orally administered tablets containing 150 mg zoledronic acid equivalent either in the form of disodium zoledronate (Group 1) or pure zoledronic acid (Group 2). Each animal was given three 50 mg equivalent tablets (150 mg total), which were administered together. The animal's oral cavity was wetted with water before placing the tablets on the back of the animal's tongue. Animals were fasted before and after dosing. Animals were 6 to 9 months of age and weighed 6 to 10 kg on the day of dosing. There were three dogs per group.

[0144] Serial blood samples were collected from each animal by venipuncture of the jugular vein at various points after dosing for measurement of plasma concentrations of zoledronic acid. Blood samples were collected into chilled tubes containing K_2EDTA as the anticoagulant. Samples were then centrifuged at approximately 3000 rpm at +4° C. for 10 minutes for plasma derivation. Plasma concentrations of zoledronic acid were measured using an LC/MS/MS method.

Results

[0145] The average plasma concentrations of zoledronic acid for each group of dogs is summarized in Table 1 and illustrated in FIG. **8**. Detectable plasma levels of zoledronic acid were observed for the entire 48 hours that they were measured.

TABLE 1

Zoledronic Acid plasma concentrations in beagle dogs

		Time (hour)	Plasma concentration (ng/mL)
Group 1 (N = 3)	Disodium Zoledronate Tablets (150 mg acid equivalent)	0	0.00
		0.25	1193.97
		0.5	1852.12
		0.75	1776.51
		1	1626.56
		2	640.57
		4	136.93
		6	53.11
		8	26.97
		12	13.74
		24	6.78
		48	5.39
Group 2 (N = 3)	Zoledronic Acid Tablets (150 mg acid equivalent)	0	0.00
		0.25	390.92
		0.5	846.19
		0.75	819.15
		1	831.77
		2	477.76
		4	90.11
		6	28.22
		8	15.10
		12	6.13
		24	3.18
		48	1.84

[0146] Disodium zoledronate produced significantly higher plasma levels zoledronic acid than pure zoledronic acid, indicating improved oral absorption with the salt form. Measured using peak plasma concentrations (C_{max}), the disodium salt resulted in a 119% actual and 74% weight-adjusted increase in bioavailability as compared to pure zoledronic acid. Measured using area under the plasma concentration curve ($AUC_{0-\infty}$), bioavailability was 84% and 46% greater with the disodium salt than with pure zoledronic acid, on an actual and weight-adjusted basis respectively. The average $AUC_{0-\infty}$ for the disodium salt was 4073 ng·hr/mL and the average $AUC_{0-\infty}$ for the diacid was 2217 ng·hr/mL. The $AUC_{0-\infty}$ was found to be dose proportional. Thus, for beagle dogs similar to those tested, about 3 mg to about 4 mg of the disodium salt would be expected to result in an $AUC_{0-\infty}$ of about 100 ng·hr/mL, and about 7 mg to about 8 mg of the disodium salt would be expected to result in an $AUC_{0-\infty}$ of about 200 ng·hr/mL.

Example 8

[0147] Tablets were prepared by blending zoledronic acid, either in the form of the free acid or the disodium salt, with identical excipients. For dosage forms with a greater amount of active, the amount of the excipients was reduced proportionally to keep the weight of the tablet at about 100 mg. After blending, the ingredients were compressed at varying pressures, followed by a film coating. The resulting tablets were then tested for hardness using a Dr. Schleuniger Pharmatron 8M Tablet Hardness Tester. The results are shown in Table 2 and FIG. 9.

TABLE 2

	Hardness (kPa)		
Compression Force (psi)	Diacid 50 mg	Disodium Salt 50 mg	Disodium Salt 71 mg
800	4.0	8.7	4.8
1100	6.1	11.2	6.8
1500	7.7	13.7	7.4
2000	8.7	16.3	10.7
2400	8.7		11.3
3000	11.4		14.1
4400	12.5		14.9
5500	12.8		18.2
6100	13.0		

[0148] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood in all instances as indicating both the exact values as shown and as being modified by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0149] The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0150] Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0151] Certain embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described

elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

[0152] In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

1-166. (canceled)

167. A method of enhancing the oral bioavailability of zoledronic acid comprising orally administering a dosage form containing zoledronic acid in the disodium salt form.

168. The method of claim 167, wherein the zoledronic acid in the disodium salt form provides an enhancement to bioavailability, as compared to zoledronic acid in the diacid form, which adds to any enhancement to bioavailability provided by any bioavailability-enhancing agents in the dosage form.

169. The method of claim 167, wherein the zoledronic acid in the disodium salt form is administered to a mammal in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng·h/mL to about 2000 ng·h/mL to the mammal each time the zoledronic acid in the disodium salt form is administered.

170. The method of claim 169, wherein the zoledronic acid in the disodium salt form is administered at an interval of about 3 to about 4 weeks in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 100 ng·h/mL to about 2000 ng·h/mL to the mammal each time the zoledronic acid in the disodium salt form is administered.

171. The method of claim 169, wherein the zoledronic acid in the disodium salt form is administered weekly, or 3 to 5 times in a month, in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 20 ng·h/mL to about 700 ng·h/mL to the mammal each time the zoledronic acid in the disodium salt form is administered.

172. The method of claim 169, wherein the zoledronic acid in the disodium salt form is administered daily in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng·h/mL to about 100 ng·h/mL to the mammal each time the zoledronic acid in the disodium salt form is administered.

173. The method of claim 167, wherein the dosage form is a solid.

174. The method of claim 167, wherein the bioavailability of zoledronic acid is improved by at least about 20% as compared to administration of zoledronic acid in the diacid form.

175. The method of claim 167, further comprising administering, on a molar basis, less of the zoledronic acid in the disodium salt form than would be administered of zoledronic acid in the diacid form in order to achieve the same plasma levels of zoledronic acid.

176. The method of claim 175, wherein at least about 10 mole % less of the disodium salt form is administered as compared to the amount of zoledronic acid in the diacid form that would be administered in order to achieve the same plasma levels of zoledronic acid.

177. The method of claim 175, wherein the disodium salt form is administered in an amount, on a molar basis, that has a value of about $0.8n_d$ to about $1.2n_d$, wherein:

$$n_d=(b_a/b_d)(n_a)$$

wherein b_a is the bioavailability of the diacid form, b_d is the bioavailability of the disodium salt form, and n_a is the number of moles of zoledronic acid in the diacid form that would be administered in order to achieve the same plasma levels of zoledronic acid.

178. The method of claim 167, wherein the zoledronic acid is used to treat an inflammatory condition.

179. The method of claim 167, wherein the zoledronic acid is used to treat arthritis or complex regional pain syndrome.

180. The method of claim 167, wherein the zoledronic acid is for the treatment of an inflammatory condition, arthritis, or complex regional pain syndrome, and wherein:

a first oral dosage form is administered; and

a second oral dosage form is administered;

wherein, with respect to the first oral dosage form, the second oral dosage form is administered at $10\times T_{max}$ or greater, wherein T_{max} is the time of maximum plasma concentration for the first oral dosage form.

181. An oral dosage form comprising zoledronic acid in the disodium salt form, wherein the bioavailability, in a mammal, of zoledronic acid in the disodium salt form is greater than the bioavailability of zoledronic acid in the diacid form would be in the same dosage form.

182. The oral dosage form of claim 181, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 100 ng·h/mL to about 2000 ng·h/mL to a human being to which the dosage form is administered.

183. The oral dosage form of claim 181, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 20 ng·h/mL to about 700 ng·h/mL to a human being to which the dosage form is administered.

184. The oral dosage form of claim 181, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng·h/mL to about 100 ng·h/mL to a human being to which the dosage form is administered.

185. The oral dosage form of claim 181, wherein the disodium salt form is present in a lower molar amount than would be present if the zoledronic acid were in the diacid form; and wherein the zoledronic acid in the disodium salt form has an improved bioavailability as compared to the zoledronic acid in the diacid form to the extent that the lower molar amount of the disodium salt in the dosage form does not reduce the amount of zoledronic acid delivered to the plasma of a mammal.

186. The oral dosage form of claim 185, containing at least about 20 mole % less of the disodium salt form as compared to the amount of the zoledronic acid in the diacid form that would be present if the zoledronic acid were in the diacid form.

187. The oral dosage form of claim 185, wherein the disodium salt form is present in an amount, on a molar basis, that has a value of about $0.9n_d$ to about $1.1n_d$, wherein:

$$n_d=(b_a/b_d)(n_a)$$

wherein b_a is the bioavailability of the diacid form, b_d is the bioavailability of the disodium salt form, and n_a is the number of moles of the diacid form that would be present if the zoledronic acid were in the diacid form.

188. The oral dosage form of claim **187**, wherein the disodium salt is administered in an amount that has a value of about n_d.

189. The oral dosage form of claim **181**, wherein the dosage form is a solid.

190. The oral dosage form of claim **181**, wherein the bioavailability of zoledronic acid in the disodium salt form is improved by at least about 10% as compared to an otherwise identical dosage form containing zoledronic acid in the diacid form.

191. The method of claim **167**, wherein the zoledronic acid is for the treatment of an inflammatory condition, arthritis, or complex regional pain syndrome, and wherein:

only a single oral dosage form is administered; or

a first oral dosage form is administered, and a second oral dosage form is administered after the first oral dosage form;

wherein the second oral dosage form is administered before the maximum pain relieving effect of the first oral dosage form is achieved, or the second oral dosage form is administered before an observable pain relieving effect is achieved.

192. The method of claim **191** wherein the second oral dosage form is administered before an observable pain relieving effect is achieved.

193. The method of claim **167**, wherein the zoledronic acid is for the treatment of an inflammatory condition, arthritis, or complex regional pain syndrome, and

wherein a first oral dosage form is administered, followed by administration of a second oral dosage form;

wherein the second oral dosage form is administered after the maximum pain relieving effect of the first oral dosage form is achieved; and

the second oral dosage form is administered while a pain relieving effect from the first oral dosage form is observable.

194. The method of claim **193**, wherein the second oral dosage form is administered about 24 hours to about 28 days after the first oral dosage form is administered.

195. The oral dosage form of claim **181**, wherein the zoledronic acid in the oral dosage form has a 24 hour sustained plasma level factor of about 1 or higher.

196. The oral dosage form of claim **181**, wherein the zoledronic acid in the oral dosage form has a 24 hour sustained plasma level factor that is higher than that of intravenously administered zoledronic acid.

* * * * *

23. Zometa product label (2012).

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zometa safely and effectively. See full prescribing information for Zometa.

Zometa® (zoledronic acid) Injection
Ready-to-Use Solution for Intravenous Infusion (For Single Use)
Concentrate for Intravenous Infusion
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

Dosage and administration, preparation of solution, 4 mg/100 mL Ready-to-Use Bottle (2.3) 06/2011
Warnings and Precautions, addition of atypical subtrochanteric and diaphyseal femoral fractures (5.6) 03/2012

----------INDICATIONS AND USAGE----------

Zometa is a bisphosphonate indicated for the treatment of:

- Hypercalcemia of malignancy. (1.1)
- Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. (1.2)

Important limitation of use: The safety and efficacy of Zometa has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia. (1.3)

----------DOSAGE AND ADMINISTRATION----------

Hypercalcemia of malignancy (2.1)

- 4 mg as a single-use intravenous infusion over no less than 15 minutes
- 4 mg as retreatment after a minimum of 7 days

Multiple myeloma and bone metastasis from solid tumors (2.2)

- 4 mg as a single-use intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of greater than 60 mL/min
- Reduce the dose for patients with renal impairment.
- Coadminister oral calcium supplements of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Administer through a separate vented infusion line and do not allow to come in contact with any calcium or divalent cation-containing solutions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

4 mg/100 mL single-use ready-to-use bottle (3)
4 mg/5 mL single-use vial of concentrate (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to any component of Zometa (4)

----------WARNINGS AND PRECAUTIONS----------

- Patients being treated with Zometa should not be treated with Reclast®. (5.1)
- Adequately rehydrate patients with hypercalcemia of malignancy prior to administration of Zometa and monitor electrolytes during treatment. (5.2)
- Renal toxicity may be greater in patients with renal impairment. Do not use doses greater than 4 mg. Treatment in patients with severe renal impairment is not recommended. Monitor serum creatinine before each dose. (5.3)
- Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting Zometa. Avoid invasive dental procedures. (5.4)
- Severe incapacitating bone, joint, muscle pain may occur. Discontinue Zometa if severe symptoms occur. (5.5)
- Zometa can cause fetal harm. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.9, 8.1)
- Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy. These fractures may occur after minimal or no trauma. Evaluate patients with thigh or groin pain to rule out a femoral fracture. Consider drug discontinuation in patients suspected to have an atypical femur fracture. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse events (greater than 25%) were nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Aminoglycosides: May have an additive effect to lower serum calcium for prolonged periods. (7.1)
- Loop diuretics: Concomitant use with Zometa may increase risk of hypocalcemia. (7.2)
- Nephrotoxic drugs: Use with caution. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: It is not known whether Zometa is excreted in human milk. (8.3)
- Pediatric Use: Not indicated for use in pediatric patients. (8.4)
- Geriatric Use: Special care to monitor renal function. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypercalcemia of Malignancy

Zometa is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of greater than or equal to 12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL=Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin (g/dL)).

1.2 Multiple Myeloma and Bone Metastases of Solid Tumors

Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

1.3 Important Limitation of Use

The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions has not been established.

2 DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.1 Hypercalcemia of Malignancy

The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium greater than or equal to 12 mg/dL [3.0 mmol/L]) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over **no less than 15 minutes**. Patients who receive Zometa should have serum creatinine assessed prior to each treatment.

Dose adjustments of Zometa are not necessary in treating patients for hypercalcemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine less than 400 µmol/L or less than 4.5 mg/dL).

Patients should be adequately rehydrated prior to administration of Zometa [*see Warnings And Precautions (5.2)*].

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zometa. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia.

Retreatment with Zometa 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zometa and serum creatinine must be assessed prior to retreatment with Zometa [*see Warnings And Precautions (5.2)*].

2.2 Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors

The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance greater than 60 mL/min is 4 mg infused over **no less than 15 minutes** every 3-4 weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are listed in Table 1. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula [*see Warnings And Precautions (5.2)*].

Table 1: Reduced Doses for Patients with Baseline CrCl less than or equal to 60 mL/min

Baseline Creatinine Clearance (mL/min)	Zometa Recommended Dose*
greater than 60	4 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3 mg

*Doses calculated assuming target AUC of 0.66(mg·hr/L) (CrCl = 75 mL/min)

During treatment, serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

For patients with normal baseline creatinine, increase of 0.5 mg/dL
For patients with abnormal baseline creatinine, increase of 1.0 mg/dL

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zometa should be reinitiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

2.3 Preparation of Solution

Zometa must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

4 mg / 100 mL Single-Use Ready-to-Use Bottle

Bottles of Zometa ready-to-use solution for infusion contain overfill allowing for the administration of 100 mL of solution (equivalent to 4 mg zoledronic acid). This solution is ready-to-use and may be administered directly to the patient without further preparation. For single use only

To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of the Zometa solution from the bottle (see Table 2) and replace with an equal volume of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Administer the newly-prepared dose-adjusted solution to the patient by infusion. Follow proper aseptic technique. Properly discard previously withdrawn volume of ready-to-use solution - do not store or reuse.

Table 2: Preparation of Reduced Doses – Zometa ready-to-use bottle

Remove and discard the following Zometa ready-to-use solution (mL)	Replace with the following volume of sterile 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP (mL)	Dose (mg)
12.0	12.0	3.5
18.0	18.0	3.3
25.0	25.0	3.0

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C - 8°C (36°F 46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

4 mg / 5 mL Single-Use Vial

Vials of Zometa concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, following proper aseptic technique, and administered to the patient by infusion. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection.

To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of the Zometa concentrate from the vial for the dose required (see Table 3).

Table 3: Preparation of Reduced Doses – Zometa concentrate

Remove and Use Zometa Volume (mL)	Dose (mg)
4.4	3.5
4.1	3.3
3.8	3.0

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP.

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C-8°C (36°F-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

2.4 Method of Administration

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zometa should not exceed 4 mg and the duration of infusion should be no less than 15 minutes [*see Warnings And Precautions (5.2)*]. In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.

3 DOSAGE FORMS AND STRENGTHS

4 mg/100 mL single-use ready-to-use bottle

4 mg/5 mL single-use vial of concentrate

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Zoledronic Acid or Any Components of Zometa

Hypersensitivity reactions including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Drugs with Same Active Ingredient or in the Same Drug Class

Zometa contains the same active ingredient as found in Reclast® (zoledronic acid). Patients being treated with Zometa should not be treated with Reclast or other bisphosphonates.

5.2 Hydration and Electrolyte Monitoring

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zometa. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zometa in order to avoid hypocalcemia. Zometa should be used with caution with other nephrotoxic drugs.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zometa. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

5.3 Renal Impairment

Zometa is excreted intact primarily via the kidney, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Safety and pharmacokinetic data are limited in patients with severe renal impairment and the risk of renal deterioration is increased [*see Adverse Reactions (6.1)*]. Preexisting renal insufficiency and multiple cycles of Zometa and other bisphosphonates are risk factors for subsequent renal deterioration with Zometa. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Zometa treatment in patients with hypercalcemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine greater than 400 µmol/L or greater than 4.5 mg/dL were excluded.

Zometa treatment is not recommended in patients with bone metastases with severe renal impairment. In the clinical studies, patients with serum creatinine greater than 265 µmol/L or greater than 3.0 mg/dL were excluded and there were only 8 of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline creatinine greater than 2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance less than 30 mL/min [*see Clinical Pharmacology (12.3)*].

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection including osteomyelitis.

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment [*see Adverse Reactions (6.2)*].

5.5 Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes Zometa. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate [*see Adverse Reactions (6.2)*].

5.6 Atypical subtrochanteric and diaphyseal femoral fractures

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, including Zometa. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to just above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. These fractures occur after minimal or no trauma. Patients may experience thigh or groin pain weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. A number of case reports noted that patients were also receiving treatment with glucocorticoids (such as prednisone or dexamethasone) at the time of fracture. Causality with bisphosphonate therapy has not been established.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain in the absence of trauma should be suspected of having an atypical fracture and should be evaluated. Discontinuation of Zometa therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.

5.7 Patients with Asthma

While not observed in clinical trials with Zometa, there have been reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates.

5.8 Hepatic Impairment

Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zometa in these patients.

5.9 Use in Pregnancy

Bisphosphonates, such as Zometa, are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy.

Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in pregnant rats, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral, and external malformations. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypercalcemia of Malignancy

The safety of Zometa was studied in 185 patients with hypercalcemia of malignancy (HCM) who received either Zometa 4 mg given as a 5-minute intravenous infusion (n=86) or pamidronate 90 mg given as a 2-hour intravenous infusion (n=103). The population was aged 33-84 years, 60% male and 81% Caucasian, with breast, lung, head and neck, and renal cancer as the most common forms of malignancy. NOTE: pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

Renal Toxicity

Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes [*see Warnings And Precautions (5) and Dosage And Administration (2)*].

The most frequently observed adverse events were fever, nausea, constipation, anemia, and dyspnea (see Table 4).

Table 4 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or Pamidronate 90 mg from the two HCM trials. Adverse events are listed regardless of presumed causality to study drug.

Table 4: Percentage of Patients with Adverse Events ≥10% Reported in Hypercalcemia of Malignancy Clinical Trials by Body System

	Zometa 4 mg n (%)		Pamidronate 90 mg n (%)	
Patients Studied				
Total No. of Patients Studied	86	(100)	103	(100)
Total No. of Patients with any AE	81	(94)	95	(92)
Body as a Whole				
Fever	38	(44)	34	(33)
Progression of Cancer	14	(16)	21	(20)
Cardiovascular				
Hypotension	9	(11)	2	(2)
Digestive				
Nausea	25	(29)	28	(27)
Constipation	23	(27)	13	(13)
Diarrhea	15	(17)	17	(17)
Abdominal Pain	14	(16)	13	(13)
Vomiting	12	(14)	17	(17)
Anorexia	8	(9)	14	(14)
Hemic and Lymphatic System				
Anemia	19	(22)	18	(18)
Infections				
Moniliasis	10	(12)	4	(4)
Laboratory Abnormalities				
Hypophosphatemia	11	(13)	2	(2)
Hypokalemia	10	(12)	16	(16)

Hypomagnesemia	9	(11)	5	(5)
Musculoskeletal				
Skeletal Pain	10	(12)	10	(10)
Nervous				
Insomnia	13	(15)	10	(10)
Anxiety	12	(14)	8	(8)
Confusion	11	(13)	13	(13)
Agitation	11	(13)	8	(8)
Respiratory				
Dyspnea	19	(22)	20	(19)
Coughing	10	(12)	12	(12)
Urogenital				
Urinary Tract Infection	12	(14)	15	(15)

The following adverse events from the two controlled multicenter HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug: Asthenia, chest pain, leg edema, mucositis, dysphagia, granulocytopenia, thrombocytopenia, pancytopenia, nonspecific infection, hypocalcemia, dehydration, arthralgias, headache and somnolence.

Rare cases of rash, pruritus, and chest pain have been reported following treatment with Zometa.

Acute Phase Reaction-like Events

Symptoms consistent with acute phase reaction (APR) can occur with intravenous bisphosphonate use. Fever has been the most commonly associated symptom, occurring in 44% of patients treated with Zometa 4 mg and 33% of patients treated with Pamidronate 90 mg. Occasionally, patients experience a flu-like syndrome consisting of fever, chills, flushing, bone pain and/or arthralgias, and myalgias.

Mineral and Electrolyte Abnormalities

Electrolyte abnormalities, most commonly hypocalcemia, hypophosphatemia and hypomagnesemia, can occur with bisphosphonate use.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 5 and 6.

Table 5: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

	Grade 3			
Laboratory Parameter	**Zometa 4 mg**		**Pamidronate 90 mg**	
	n/N	**(%)**	**n/N**	**(%)**
Serum Creatinine[1]	2/86	(2%)	3/100	(3%)
Hypocalcemia[2]	1/86	(1%)	2/100	(2%)
Hypophosphatemia[3]	36/70	(51%)	27/81	(33%)
Hypomagnesemia[4]	0/71	—	0/84	—

Table 6: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

	Grade 4	
Laboratory Parameter	**Zometa**	**Pamidronate**

	4 mg		90 mg	
	n/N	(%)	n/N	(%)
Serum Creatinine[1]	0/86	----	1/100	(1%)
Hypocalcemia[2]	0/86	----	0/100	----
Hypophosphatemia[3]	1/70	(1%)	4/81	(5%)
Hypomagnesemia[4]	0/71	----	1/84	(1%)

1 Grade 3 (greater than 3x Upper Limit of Normal), Grade 4 (greater than 6x Upper Limit of Normal)

2 Grade 3 (less than 7 mg/dL); Grade 4 (less than 6 mg/dL)

3 Grade 3 (less than 2 mg/dL); Grade 4 (less than 1 mg/dL)

4 Grade 3 (less than 0.8 mEq/L); Grade 4 (less than 0.5 mEq/L)

Injection Site Reactions

Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Ocular Adverse Events

Ocular inflammation such as uveitis and scleritis can occur with bisphosphonate use, including Zometa. No cases of iritis, scleritis or uveitis were reported during these clinical trials. However, cases have been seen in postmarketing use [*see Adverse Reactions (6.2)*].

Multiple Myeloma and Bone Metastases of Solid Tumors

The safety analysis includes patients treated in the core and extension phases of the trials. The analysis includes the 2,042 patients treated with Zometa 4 mg, pamidronate 90 mg, or placebo in the three controlled multicenter bone metastases trials, including 969 patients completing the efficacy phase of the trial, and 619 patients that continued in the safety extension phase. Only 347 patients completed the extension phases and were followed for 2 years (or 21 months for the other solid tumor patients). The median duration of exposure for safety analysis for Zometa 4 mg (core plus extension phases) was 12.8 months for breast cancer and multiple myeloma, 10.8 months for prostate cancer, and 4.0 months for other solid tumors.

Table 7 describes adverse events that were reported by 10% or more of patients. Adverse events are listed regardless of presumed causality to study drug.

Table 7: Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System

	Zometa 4 mg n (%)		Pamidronate 90 mg n (%)		Placebo n (%)	
Patients Studied						
Total No. of Patients	1031	(100)	556	(100)	455	(100)
Total No. of Patients with any AE	1015	(98)	548	(99)	445	(98)
Blood and Lymphatic						
Anemia	344	(33)	175	(32)	128	(28)
Neutropenia	124	(12)	83	(15)	35	(8)
Thrombocytopenia	102	(10)	53	(10)	20	(4)
Gastrointestinal						
Nausea	476	(46)	266	(48)	171	(38)
Vomiting	333	(32)	183	(33)	122	(27)
Constipation	320	(31)	162	(29)	174	(38)
Diarrhea	249	(24)	162	(29)	83	(18)
Abdominal Pain	143	(14)	81	(15)	48	(11)
Dyspepsia	105	(10)	74	(13)	31	(7)
Stomatitis	86	(8)	65	(12)	14	(3)

Sore Throat	82	(8)	61	(11)	17	(4)
General Disorders and Administration Site						
Fatigue	398	(39)	240	(43)	130	(29)
Pyrexia	328	(32)	172	(31)	89	(20)
Weakness	252	(24)	108	(19)	114	(25)
Edema Lower Limb	215	(21)	126	(23)	84	(19)
Rigors	112	(11)	62	(11)	28	(6)
Infections						
Urinary Tract Infection	124	(12)	50	(9)	41	(9)
Upper Respiratory Tract Infection	101	(10)	82	(15)	30	(7)
Metabolism						
Anorexia	231	(22)	81	(15)	105	(23)
Weight Decreased	164	(16)	50	(9)	61	(13)
Dehydration	145	(14)	60	(11)	59	(13)
Appetite Decreased	130	(13)	48	(9)	45	(10)
Musculoskeletal						
Bone Pain	569	(55)	316	(57)	284	(62)
Myalgia	239	(23)	143	(26)	74	(16)
Arthralgia	216	(21)	131	(24)	73	(16)
Back Pain	156	(15)	106	(19)	40	(9)
Pain in Limb	143	(14)	84	(15)	52	(11)
Neoplasms						
Malignant Neoplasm Aggravated	205	(20)	97	(17)	89	(20)
Nervous						
Headache	191	(19)	149	(27)	50	(11)
Dizziness (excluding vertigo)	180	(18)	91	(16)	58	(13)
Insomnia	166	(16)	111	(20)	73	(16)
Paresthesia	149	(15)	85	(15)	35	(8)
Hypoesthesia	127	(12)	65	(12)	43	(10)
Psychiatric						
Depression	146	(14)	95	(17)	49	(11)
Anxiety	112	(11)	73	(13)	37	(8)
Confusion	74	(7)	39	(7)	47	(10)
Respiratory						
Dyspnea	282	(27)	155	(28)	107	(24)
Cough	224	(22)	129	(23)	65	(14)
Skin						
Alopecia	125	(12)	80	(14)	36	(8)
Dermatitis	114	(11)	74	(13)	38	(8)

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in three clinical trials of Zometa in patients with bone metastases are shown in Tables 8 and 9.

Table 8: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

Laboratory Parameter	Zometa 4 mg	Grade 3 Pamidronate 90 mg	Placebo

	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1*]	7/529	(1%)	4/268	(2%)	4/241	(2%)
Hypocalcemia[2]	6/973	(<1%)	4/536	(<1%)	0/415	—
Hypophosphatemia[3]	115/973	(12%)	38/537	(7%)	14/415	(3%)
Hypermagnesemia[4]	19/971	(2%)	2/535	(<1%)	8/415	(2%)
Hypomagnesemia[5]	1/971	(<1%)	0/535	—	1/415	(<1%)

1 Grade 3 (greater than 3x Upper Limit of Normal); Grade 4 (greater than 6x Upper Limit of Normal)

* Serum creatinine data for all patients randomized after the 15-minute infusion amendment

2 Grade 3 (less than 7 mg/dL); Grade 4 (less than 6 mg/dL)

3 Grade 3 (less than 2 mg/dL), Grade 4 (less than 1 mg/dL)

4 Grade 3 (greater than 3 mEq/L); Grade 4 (greater than 8 mEq/L)

5 Grade 3 (less than 0.9 mEq/L); Grade 4 (less than 0.7 mEq/L)

Table 9: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

Laboratory Parameter	Zometa 4 mg		Grade 4 Pamidronate 90 mg		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1*]	2/529	(<1%)	1/268	(<1%)	0/241	—
Hypocalcemia[2]	7/973	(<1%)	3/536	(<1%)	2/415	(<1%)
Hypophosphatemia[3]	5/973	(<1%)	0/537	—	1/415	(<1%)
Hypermagnesemia[4]	0/971	—	0/535	—	2/415	(<1%)
Hypomagnesemia[5]	2/971	(<1%)	1/535	(<1%)	0/415	—

1 Grade 3 (greater than 3x Upper Limit of Normal); Grade 4 (greater than 6x Upper Limit of Normal)

* Serum creatinine data for all patients randomized after the 15-minute infusion amendment

2 Grade 3 (less than 7 mg/dL); Grade 4 (less than 6 mg/dL)

3 Grade 3 (less than 2 mg/dL); Grade 4 (less than 1 mg/dL)

4 Grade 3 (greater than 3 mEq/L); Grade 4 (greater than 8 mEq/L)

5 Grade 3 (less than 0.9 mEq/L); Grade 4 (less than 0.7 mEq/L)

Among the less frequently occurring adverse events (less than 15% of patients), rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zometa 4 mg and pamidronate groups) compared to the placebo group.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 16% of patients in the Zometa 4 mg group compared with 9% in the pamidronate group. Decreased appetite was reported in slightly more patients in the Zometa 4 mg group (13%) compared with the pamidronate (9%) and placebo (10%) groups, but the clinical significance of these small differences is not clear.

Renal Toxicity

In the bone metastases trials, renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (less than 1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (greater than or equal to1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials (see Table 10).

Table 10: Percentage of Patients with Treatment Emergent Renal Function Deterioration by Baseline Serum Creatinine*

Patient Population/Baseline Creatinine		
Multiple Myeloma and Breast Cancer	**Zometa 4 mg**	**Pamidronate 90 mg**

	n/N	(%)	n/N	(%)
Normal	27/246	(11%)	23/246	(9%)
Abnormal	2/26	(8%)	2/22	(9%)
Total	29/272	(11%)	25/268	(9%)
Solid Tumors	**Zometa 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9%)	1/20	(5%)
Total	18/165	(11%)	11/163	(7%)
Prostate Cancer	**Zometa 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	12/82	(15%)	8/68	(12%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	16/92	(17%)	10/78	(13%)

*Table includes only patients who were randomized to the trial after a protocol amendment that lengthened the infusion duration of Zometa to 15 minutes.

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving Zometa (4 mg over 15 minutes), placebo, or pamidronate.

In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal function, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial Zometa dose.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of Zometa. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Osteonecrosis of the Jaw

Cases of osteonecrosis (primarily involving the jaws) have been reported predominantly in cancer patients treated with intravenous bisphosphonates including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be a risk factor for ONJ. Data suggests a greater frequency of reports of ONJ in certain cancers, such as advanced breast cancer and multiple myeloma. The majority of the reported cases are in cancer patients following invasive dental procedures, such as tooth extraction. It is therefore prudent to avoid invasive dental procedures as recovery may be prolonged [*see Warnings And Precautions (5)*].

Musculoskeletal Pain

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported with bisphosphonate use [*see Warnings And Precautions (5)*].

Atypical subtrochanteric and diaphyseal femoral fractures

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including Zometa [*see Warnings and Precautions (5.6)*].

Ocular Adverse Events

Cases of uveitis, scleritis, episcleritis, conjunctivitis, iritis, and orbital inflammation including orbital edema have been reported during postmarketing use. In some cases, symptoms resolved with topical steroids.

Hypersensitivity Reactions

There have been rare reports of allergic reaction with intravenous zoledronic acid including angioedema, and bronchoconstriction. Very rare cases of anaphylactic reaction/shock have also been reported.

Additional adverse reactions reported in postmarketing use include:

CNS: taste disturbance, hyperesthesia, tremor; ***Special Senses:*** blurred vision; ***Gastrointestinal:*** dry mouth; ***Skin:*** Increased sweating; ***Musculoskeletal:*** muscle cramps; ***Cardiovascular:*** hypertension, bradycardia, hypotension (associated with syncope or circulatory collapse primarily in patients with underlying risk factors); ***Respiratory:*** bronchoconstriction; ***Renal:*** hematuria, proteinuria; ***General Disorders and Administration Site:*** weight increase, influenza-like illness (pyrexia, asthenia, fatigue or malaise) persisting for greater than 30 days; ***Laboratory Abnormalities:*** hyperkalemia, hypernatremia.

7 DRUG INTERACTIONS

In-vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. *In-vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In-vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

7.1 Aminoglycosides

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in Zometa clinical trials.

7.2 Loop Diuretics

Caution should also be exercised when Zometa is used in combination with loop diuretics due to an increased risk of hypocalcemia.

7.3 Nephrotoxic Drugs

Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.

7.4 Thalidomide

No dose adjustment for Zometa 4 mg is needed when co-administered with thalidomide. In a pharmacokinetic study of 24 patients with multiple myeloma, Zometa 4 mg given as a 15 minute infusion was administered either alone or with thalidomide (100 mg once daily on days 1-14 and 200 mg once daily on days 15-28). Co-administration of thalidomide with Zometa did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precaution (5.9)]*

There are no adequate and well-controlled studies of Zometa in pregnant women. Zometa may cause fetal harm when administered to a pregnant woman. Bisphosphonates, such as Zometa, are incorporated into the bone matrix and are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been

established. If this drug is used during pregnancy or if the patient becomes pregnant while taking or after taking this drug, the patient should be apprised of the potential hazard to the fetus.

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of ≥0.07 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate-class effect.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and postimplantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≤0.5 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥0.05 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

8.3 Nursing Mothers

It is not known whether zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Zometa, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Zoledronic acid binds to bone long term and may be released over weeks to years

8.4 Pediatric Use

Zometa is not indicated for use in children.

The safety and effectiveness of zoledronic acid was studied in a one-year active-controlled trial of 152 pediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1-17 years, 55% male, 84% Caucasian, with a mean lumbar spine BMD of 0.431 gm/cm^2, which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of -2.7). At one year, increases in BMD were observed in the zoledronic acid treatment group. However, changes in BMD in individual patients with severe osteogenesis imperfecta did not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain. The adverse events observed with Zometa use in children did not raise any new safety findings beyond those previously seen in adults treated for hypercalcemia of malignancy or bone metastases. However, adverse reactions seen more commonly in pediatric patients included pyrexia (61%), arthralgia (26%), hypocalcemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within 3 days after the first infusion and became less common with repeat dosing. Because of

long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk.

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with 0.05 mg/kg dose over 30 min. Mean C_{max} and $AUC_{(0\text{-last})}$ was 167 ng/mL and 220 ng.h/mL, respectively. The plasma concentration time profile of zoledronic acid in pediatric patients represent a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

8.5 Geriatric Use

Clinical studies of Zometa in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zometa as compared to younger patients. Controlled clinical studies of Zometa in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

10 OVERDOSAGE

Clinical experience with acute overdosage of Zometa is limited. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

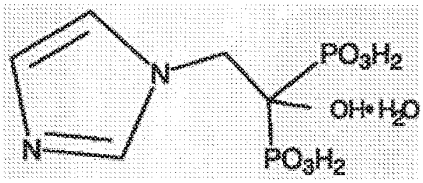
In an open-label study of zoledronic acid 4 mg in breast cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose, the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100U/L, each value unknown). The outcome of this case is not known.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy [*see Dosage And Administration (2.4)*].

11 DESCRIPTION

Zometa contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1g/Mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.
Zometa is available in 100-mL bottles as a sterile liquid ready-to-use solution for intravenous infusion and in 5-mL vials as a sterile liquid concentrate solution for intravenous infusion.

- Each 100 mL ready-to-use bottle contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 5100 mg of mannitol, USP, water for injection, and 24 mg of sodium citrate, USP.
- Each 5 mL concentrate vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection, and 24 mg of sodium citrate, USP.

Inactive Ingredients: mannitol, USP, as bulking agent, water for injection and sodium citrate, USP, as buffering agent.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

12.2 Pharmacodynamics

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into two groups according to the pathophysiologic mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous cell malignancies of the lung or head and neck or in genitourinary tumors such as renal cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation [*see Dosage And Administration (2)*].

12.3 Pharmacokinetics

Pharmacokinetic data in patients with hypercalcemia are not available.

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa were given to 64 patients with cancer and bone metastases. The postinfusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end of infusion to less than 1% of C_{max} 24 hours postinfusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 postinfusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 2-16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In-vitro and *ex-vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro*, mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, less than 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases, on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post-Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL versus 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL versus 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pediatrics

Zometa is not indicated for use in children [*see Pediatric Use (8.4)*].

Geriatrics

The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.

Race

Population pharmacokinetic analyses did not indicate any differences in pharmacokinetics among Japanese and North American (Caucasian and African American) patients with cancer and bone metastases.

Hepatic Insufficiency

No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency

The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 mL/min. Creatinine clearance is calculated by the Cockcroft-Gault formula:

$$CrCl = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=$6.5(CL_{cr}/90)^{0.4}$. These formulae can be used to predict the Zometa AUC in patients, where CL = Dose/$AUC_{0-\infty}$. The average AUC_{0-24} in patients with normal renal function was 0.42 mg•h/L and the calculated $AUC_{0-\infty}$ for a patient with creatinine clearance of 75 mL/min was 0.66 mg•h/L following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed [*see Warnings And Precautions (5.2)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥0.002 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in-vivo* rat micronucleus assay.

Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group (with systemic exposure of 0.2 times the human systemic exposure following an

intravenous dose of 4 mg, based on an AUC comparison) and high-dose group included an increase in preimplantation losses and a decrease in the number of implantations and live fetuses.

14 CLINICAL STUDIES

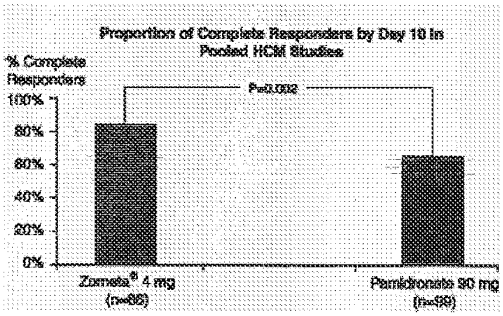
14.1 Hypercalcemia of Malignancy

Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). NOTE: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes [*see Warnings And Precautions (5.1, 5.2) and Dosage And Administration (2.4)*]. The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were Black, and 4% were of other races. 60% of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of greater than or equal to 12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to less than or equal to 10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion.

To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a preplanned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (P=0.002) (see Figure 1). In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.

Figure 1



Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of corrected serum calcium (CSC) by Day 4; the proportion of patients who had normalization of CSC by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value less than 11.6 mg/dL (less than 2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≤10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 11.

Table 11: Secondary Efficacy Variables in Pooled HCM Studies

		Zometa 4 mg		Pamidronate 90 mg
Complete Response	**N**	**Response Rate**	**N**	**Response Rate**
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
Duration of Response	**N**	**Median Duration (Days)**	**N**	**Median Duration (Days)**
Time to Relapse	86	30*	99	17
Duration of Complete Response	76	32	69	18

* P less than 0.05 versus pamidronate 90 mg.

14.2 Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors

Table 12 describes an overview of the efficacy population in three randomized Zometa trials in patients with multiple myeloma and bone metastases of solid tumors. These trials included a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in prostate cancer, and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, including NSCLC, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer, GI/genitourinary cancer, head and neck cancer, and others. These trials were comprised of a core phase and an extension phase. In the solid tumor, breast cancer and multiple myeloma trials, only the core phase was evaluated for efficacy as a high percentage of patients did not choose to participate in the extension phase. In the prostate cancer trials, both the core and extension phases were evaluated for efficacy showing the Zometa effect during the first 15 months was maintained without decrement or improvement for another 9 months. The design of these clinical trials does not permit assessment of whether more than one-year administration of Zometa is beneficial. The optimal duration of Zometa administration is not known.

The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8 mg Zometa treatment arm were switched to 4 mg due to toxicity. Patients who were randomized to the Zometa 8 mg group are not included in these analyses.

Table 12: Overview of Efficacy Population for Phase III Studies

Patient Population	No. of Patients	Zometa Dose	Control	Median Duration (Planned Duration) Zometa 4 mg
Multiple myeloma or metastatic breast cancer	1,648	4 and 8* mg Q3-4 weeks	Pamidronate 90 mg Q3-4 weeks	12.0 months (13 months)
Metastatic prostate cancer	643	4 and 8* mg Q3 weeks	Placebo	10.5 months (15 months)
Metastatic solid tumor other than breast or prostate cancer	773	4 and 8* mg Q3 weeks	Placebo	3.8 months (9 months)

* Patients who were randomized to the 8 mg Zometa group are not included in any of the analyses in this package insert

Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was a SRE in the prostate cancer study only. Planned analyses included the proportion of patients with a SRE during the study and time to the first SRE. Results for the two Zometa placebo-controlled studies are given in Table 13.

Table 13: Zometa Compared to Placebo in Patients with Bone Metastases from Prostate Cancer or Other Solid Tumors

	I. Analysis of Proportion of Patients with a SRE[1]				II. Analysis of Time to the First SRE		
Study	Study Arm & Patient Number	Proportion	Difference[2] & 95% CI	P-value	Median (Days)	Hazard Ratio[3] & 95% CI	P-value
Prostate Cancer	Zometa 4 mg (n=214)	33%	-11% (-20%, -1%)	0.02	Not Reached	0.67 (0.49, 0.91)	0.011
	Placebo (n=208)	44%			321		
Solid Tumors	Zometa 4 mg (n=257)	38%	-7% (-15%, 2%)	0.13	230	0.73 (0.55, 0.96)	0.023
	Placebo (n=250)	44%			163		

1SRE=Skeletal-Related Event
2Difference for the proportion of patients with a SRE of Zometa 4 mg versus placebo.
3Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus placebo

In the breast cancer and myeloma trial, efficacy was determined by a noninferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with a SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1,128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with a SRE by 13.1% (95% CI = 7.3%, 18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 14.

Table 14: Zometa Compared to Pamidronate in Patients with Multiple Myeloma or Bone Metastases from Breast Cancer

	I. Analysis of Proportion of Patients with a SRE[1]				II. Analysis of Time to the First SRE		
Study	Study Arm & Patient Number	Proportion	Difference[2] & 95% CI	P-value	Median (Days)	Hazard Ratio[3] & 95% CI	P-value
Multiple Myeloma & Breast Cancer	Zometa 4 mg (n=561)	44%	-2% (-7.9%, 3.7%)	0.46	373	0.92 (0.77, 1.09)	0.32
	Pamidronate (n=555)	46%			363		

1SRE=Skeletal-Related Event
2Difference for the proportion of patients with a SRE of Zometa 4 mg versus pamidronate 90 mg.
3Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus pamidronate 90 mg.

16 HOW SUPPLIED/STORAGE AND HANDLING

4 mg/100 mL single-use ready-to-use bottle

Carton of 1 bottle.....NDC 0078-0590-61

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

4 mg/5 mL single-use vial of concentrate

Carton of 1 vial.....NDC 0078-0387-25

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

- Patients should be instructed to tell their doctor if they have kidney problems before being given Zometa.

- Patients should be informed of the importance of getting their blood tests (serum creatinine) during the course of their Zometa therapy.
- Zometa should not be given if the patient is pregnant or plans to become pregnant, or if she is breast-feeding.
- Patients should be advised to have a dental examination prior to treatment with Zometa and should avoid invasive dental procedures during treatment.
- Patients should be informed of the importance of good dental hygiene and routine dental care.
- Patients with multiple myeloma and bone metastasis of solid tumors should be advised to take an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.
- Patients should be advised to report any thigh, hip or groin pain. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.
- Patients should be aware of the most common side effects including: anemia, nausea, vomiting, constipation, diarrhea, fatigue, pyrexia, weakness, lower limb edema, anorexia, decreased weight, bone pain, myalgia, arthralgia, back pain, malignant neoplasm aggravated, headache, dizziness, insomnia, paresthesia, dyspnea, cough, and abdominal pain.
- There have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates, including zoledronic acid. Before being given zoledronic acid, patients should tell their doctor if they are aspirin-sensitive.

Manufactured by
Novartis Pharma Stein AG
Stein, Switzerland for
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2012-11

24. Declaration of Herriot Tabuteau submitted in U.S. Application No. 13/894,252 on March 28, 2014.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**5890**
Appln. No.	:	**13/894,252**
Applicant	:	**Herriot Tabuteau**
Filed	:	**May 14, 2013**
TC/A.U.	:	**1627**
Examiner	:	**Svetlana M. Ivanova**
Docket No.	:	**1958603.00019**
Customer No.	:	**45200**
Title	:	**COMPOSITIONS COMPRISING ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR RELIEVING PAIN ASSOCIATED WITH ARTHRITIS**

DECLARATION UNDER 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. I am the inventor of the present application.

2. I have an M.D. degree from Yale University School of Medicine.

3. I have carefully reviewed US 2004/0063670 (Fox).

4. I have also read and understand the Office Action of February 7, 2014 for the present application.

5. Fox actually contains no evidence that oral zoledronic acid is effective in the treatment of any condition. Instead, all of the experiments in Fox related to zoledronic acid for treating any condition were carried out with subcutaneous administration.

6. With respect to Example 2 of the specification of the present application, which describes a test of oral zoledronic acid in a rat model of arthritis, zoledronic acid 54 mg/m^2 (or 9 mg/kg), divided in three equal daily doses, was tolerated.

7. An Oral Repeat Dose Toxicity Study with Zoledronic Acid in Dogs was carried out at my request. The study is described in the following paragraphs.

Objective

8. The purpose of the study was to evaluate the toxicity of zoledronic acid in Beagle dogs when administered orally once daily for up to 14 days. However, due to toxicity resulting in death or necessitating euthanization during the first few days of the study, dosing was stopped in all groups of animals after no more than 5 days.

Methods

9. Groups of 8 dogs (4/sex) were either left untreated to serve as a control group (Group 1) or given daily oral doses of zoledronic acid at 50 or 100 mg (Groups 2 and 3, respectively) or at 150 mg (Groups 4 and 5). At the start of dosing, body weight averaged 8.9 kg for males and 6.7 kg for females, so the zoledronic acid dose levels were approximately 5.6, 11.2, and 16.9 mg/kg, respectively, for males and 7.5, 14.9, and 22.4 mg/kg, respectively, for females.

10. In life, dogs were observed for clinical signs of toxicity and changes in body weight, food consumption, and hematology, coagulation, clinical chemistry, and urinalysis parameters. A complete necropsy was performed on all animals.

Results and Conclusions

11. Dogs did not tolerate daily oral doses of zoledronic acid at 50, 100, or 150 mg/day, which were approximately 5.6, 11.2, and 16.9 mg/kg, respectively, for males and 7.5, 14.9, and 22.4 mg/kg, respectively, for females. Clinical signs of ill health occurred within a few days at all dose levels, which resulted in the death of one dog, the euthanasia of several more dogs in moribund condition or for humane reasons, and the early termination of the study. Other in life findings included emesis, decreased activity, rigidity or stiffness, abnormal gait and posture, muscle tremors and/or twitching.

12. One Group 5 animal was found dead on the morning of Day 4. Based on the mortality and morbidity observed at a dose level of 150 mg/day and the numerous adverse clinical signs seen in almost all animals at this dose level, all Groups 4 and 5 animals were sacrificed early in moribund condition or for humane reasons. In addition, one Group 2 animal and several Group 3 animals were also sacrificed in moribund condition, due to adverse clinical signs of toxicity. Because of the onset of clinical signs similar to the ones seen in the animals sacrificed moribund before, the remaining study animals were sacrificed early for humane

reasons on Day 5 (male Groups 1-3) and Day 4 (female Groups 1-3). This decision was made independently by the contract research laboratory that conducted the study, with the recommendation of their Director of Laboratory Animal Medicine.

13. At necropsy, at all dose levels, most animals dosed with zoledronic acid had test article related visible lesions. Findings included, but were not limited to red to dark red mucosa of the stomach, duodenum, jejunum, colon and pancreas, stomach mucosa with lesions, masses and/or multiple foci of various colorations, and thickened edematous mucosa of the pylorus. No gross necropsy findings were noted for Group 1 (control group) animals.

14. This demonstrates that the upper end of the range "from 0.002-20.0 mg/kg" in ¶ 0075 of Fox must refer to bisphosphonates that are less toxic than zoledronic acid.

15. As a person signing below:

I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

SIGNATURE(S)

Full Name: Herriot Tabuteau, M.D.

Signature: _____ Date: 3/28/2014

25. Henry McQuay, *Opioids in pain management*, 353 LANCET 2229 (1999).

Pain

Opioids in pain management

Henry McQuay

Opioids are our most powerful analgesics, but politics, prejudice, and our continuing ignorance still impede optimum prescribing. Just over 100 years ago, opium poppies were still grown on the Cambridgeshire fens in the UK to provide oblivion for the working man and his family, but the brewing lobby argued on thin evidence that their potions were less dangerous. The restriction of opioid availability to protect society and the individual continues in many countries. In this review I focus on chronic and cancer pain, but many of the principles apply in acute pain. The justification for this focus is that patients with chronic pain may suffer longer and unnecessarily if we prescribe and legislate badly.

Dose titration and differences between clinical and laboratory pharmacology

The clinical use of opioids shows a difference between their clinical pharmacology and their laboratory pharmacology. What happens when opioids are given to someone in pain is different from what happens when they are given to someone not in pain. The respiratory depression that results from the acute use of opioids is seen in studies of volunteers who are not in pain. But respiratory depression is kept to a minimum when appropriate regular doses of opioid are given to patients with chronic pain. Patients maintained on oral morphine without respiratory depression who then receive successful nerve blocks must have their morphine dose reduced. Failure to reduce the dose will result in respiratory depression.[1,2] One explanation is that the respiratory centre receives nociceptive input[3] which counterbalances the respiratory depressant potential of the opioid. Absence of this pain input, for example because of a successful nerve block, leaves the respiratory depressant effect of the opioid unopposed.

The clinical message is that opioids need to be titrated against pain. Excessive doses, doses greater than needed to relieve pain, or doses given when there is no pain, will cause respiratory depression. However, concern about respiratory depression should not inhibit the appropriate use of opioids—ie, to provide analgesia when the pain is deemed to be opioid sensitive. A postoperative patient who complains of pain when the previous dose has had time to be absorbed needs more drug. The titration, size of doses, timing of doses, and use of escape doses has to be well organised.[4]

The difference in opioid pharmacology between individuals with and without pain also applies to addiction. The drug-seeking behaviour synonymous with drug addiction does not occur in patients after pain relief with opioids in childbirth, operations, or after myocardial infarction.[5] Drug addicts are not in pain. The political message is that the medical use of opioids does not create drug addicts, and restrictions on this medical use hurt patients.

Lancet 1999; **353:** 2229–32

Pain Research, Nuffield Department of Anaesthetics, University of Oxford, The Churchill, Oxford Radcliffe Hospital, Headington, Oxford OX3 7LJ, UK (H McQuay DM)
(e-mail: henry.mcquay@pru.ox.ac.uk)

Common opioids

Morphine
Diamorphine (UK)
Pethidine/meperidine
Methadone
Hydromorphone
Oxycodone
Fentanyl (lollipop/transdermal)
Buprenorphine

Clinical issues

Unresolved issues in clinical opioid use include the choice of opioid (panel), tolerance, pain sensitivity to opioids, and whether to change the drug or change the route of administration when things go badly. Cloning of opioid receptors has revealed many receptor subtypes, doubtless with more to come. The irony is that, because clinically we titrate opioids to effect, we cannot logically expect to see much difference in efficacy between opioids. This expectation is based on the assumption that all types of pain respond equally well to all opioids. This assumption may be wrong, particularly if differences in receptor selectivity between opioids can be exploited to manage different types of pain. However, there is no available clinical evidence of such differential efficacy. Similarly, although in some patients a change of opioids (at the same level of analgesia) can reduce adverse effects, we have no data on which to make policy.

Choice of opioid

Morphine is the standard opioid against which others are judged. Beliefs that other drugs act faster, last longer, or have a better balance between effect and adverse effect for a particular patient often have little empirical credibility. Political decisions limit medical availability and hence choice of opioids in many countries. Particular agonists and mixed agonist-antagonists may be the only permissible opioids in some countries, because of perceived lower dependence liability. Partial agonists may not relieve severe pain if the ceiling to their effect occurs at low doses.

Efficacy differences: speed of onset and duration of effect

There is little difference between different opioids in speed of onset and duration of effect; faster onset and longer effect are achieved by changing the route of administration

or formulation. Fast onset of effect is not a critical factor if the patient is receiving continual analgesics for chronic pain, but may be relevant in patients taking the drug on an as-needed basis for acute or chronic pain. With the intravenous route, there is little difference in onset time (2 min) between different opioids. With intramuscular injection, the more lipophilic the drug, the faster the onset time (20 min). Normal-release oral formulations take 1 h to work, whereas sustained-release formulations may take 2–4 h.[6] Fast-onset, fast-offset opioids would be highly desirable in childbirth or for chronic movement-related pain. Sustained-release oral formulations, subcutaneous or intravenous infusions, or spinal injections are used to achieve duration of effect of longer than 4–6 h.

Toxic and active metabolites and differences in adverse effects

Pethidine has a toxic metabolite, norpethidine.[7] Norpethidine causes tremor, twitching, agitation, and convulsions, and these effects increase with multiple dosing and in the presence of impaired renal function. Since use of pethidine is not associated with any specific advantage, it is a poor choice if multiple doses are needed.

Morphine has an active metabolite, morphine-6-glucuronide (M6G), which is a major metabolite in man and is more potent than morphine. Intrathecal M6G is 10–20 times more potent than morphine,[8] and it may also contribute to the analgesic effect of morphine by its action through a different receptor subtype.[9]

Unexpected degree and duration of effect of M6G can occur in patients with severely impaired renal function given morphine or derivatives in whom there is a cumulation of M6G.[10] The glucuronidation of morphine is not affected significantly in cirrhosis,[11] but in precoma states, the kinetics[12] and dynamics[13] of morphine metabolism are altered.

Difficulties arise with morphine only if a fixed-dose schedule is used without taking account of renal function, or without adequate titration against pain intensity. Drug doses should be decreased substantially if creatinine clearance is less than 30 mL/min per 1·73 m^2. With less severe renal dysfunction, careful titration is needed, but it should always be remembered that renal function deteriorates with older age.

Adverse effects

Any opioid that produced fewer adverse effects than morphine, at a dose which provided the same degree of analgesia, would be an improvement. For most clinically important adverse effects, there are no comparative data at equianalgesic doses to allow recommendation of any of the alternatives. The key factor is equianalgesic dosing. If the adverse effect is mediated via opioid receptors, then similar effects should occur at equianalgesic doses of different opioids that act through the same receptors. A common claim is that a drug has fewer adverse effects than morphine, but only because the comparison was made at a much less effective dose than the morphine dose. Some idea of the adverse effects that may be expected within 6 weeks on oral morphine comes from a randomised study by Moulin and colleagues[14]—13 of 46 chronic non-cancer patients had dose-limiting adverse effects, 18 reported nausea, 17 dizziness, and 19 constipation.

Differences in the rate of adverse effects between opioids are apparent in randomised single-dose postoperative studies of dysphoria; Houde[15] reported a rate of 20% with pentazocine and butorphanol versus 3% with other opioids. Rigorous 3-day multiple-dose comparison of oxycodone and morphine at equianalgesic doses also showed differences in the rate of adverse effects in a few patients.[16] If the adverse effect is mediated by opioid receptors, then these differences may be explained by differences in receptor binding; if such events are not mediated via opioid receptors then some other explanation must be sought.

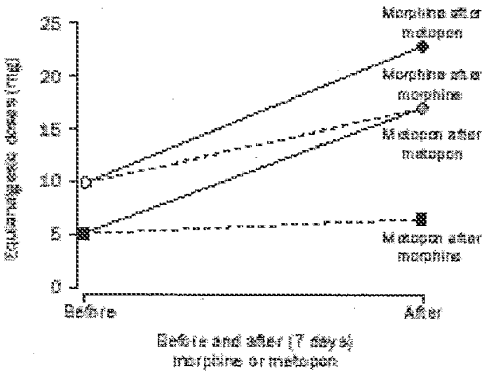
Constipation is a side-effect of all opioids, and is opioid-receptor mediated with both central and peripheral mechanisms; tolerance to this effect develops slowly if at all. Moulin and colleagues[14] reported that about 40% of patients on oral morphine were constipated. This proportion may be increased among patients with severe illness. Claims that other opioids cause less constipation than oral morphine are open to the challenge that the comparison was not made at equianalgesic doses.

The extent to which nausea and vomiting are mediated by opioid receptors is arguable. Some of the effect may come from stimulation of opioid receptors at the chemoreceptor trigger zone in the medulla. If the effect is receptor-related, equianalgesic doses of different opioids would be expected to produce the same amount of nausea. For most patients tolerance develops quickly, but some patients have nausea with all opioids at effective doses. Pain itself can also cause nausea.[16] Moulin and colleagues[14] showed that 40% of patients on oral morphine may have nausea. Kalso and Vainio's comparison[17] of morphine and oxycodone showed that there may be differences between individual patients with different opioids.

Pethidine is said to be the opioid of choice for biliary colic because its atropine-like effect will counteract the opioid action on smooth muscle. Topical atropine, however, does not relax a contracted gall bladder and there is no good evidence to suggest that pethidine has any clinically significant advantage at equianalgesic doses over other opioids for biliary or renal colic. The interaction between pethidine and inhibitors of monoamine oxidase is another reason why pethidine is not the first choice of opioid for the management of severe chronic pain.

Tolerance

Tolerance is the need for a higher dose (or increased plasma concentration) to achieve the same pharmacological effect. Clinicians argue that the need for a greater dose is driven by worsening disease rather than by pharmacological tolerance, and cite the fact that many patients are maintained satisfactorily on the same oral morphine dose for months. It is ingenuous to argue that opioid tolerance does not occur in man. Two classic experiments showed chronic tolerance when patients' analgesic response to a test dose was measured before and after chronic dosing.[18,19] Houde and colleagues[18] found that in ten patients challenged with a single dose of morphine, before and after 2 weeks of regular morphine injections, the response to the second challenge was less than to the first. Houde[19] also showed that in 13 patients challenged with single doses of morphine or metopon (no longer in use), before and after 1 week of regular injections of either drug, the dose-response curve was again shifted to the right after the regular injections; to complicate matters, this change was greater for the drug that was given repeatedly after the first challenge (figure). The two studies show tolerance, less effect from the same dose after repeated



Dose required to achieve same degree of pain relief when rechallenged after 1 week of chronic dosing

13 patients had a controlled relative potency assay to compare morphine and metopon after 1 week of regular dosing with either drug. Reproduced with permission from Houde.[18]

injections, and, because the slopes of the four lines in the figure differ, incomplete cross-tolerance is evident from the second study.

The pragmatic issues are whether the escalation of dose that some patients require, and which produces different adverse effects, can be avoided by changing opioid or route of administration, or by blocking tolerance.

Oral morphine: success and failure

In patients with chronic pain opioids are usually given by mouth. The dose is calculated by titration over a few days, and then the drug is given regularly, without waiting for the pain to come back. The initial reactions of nausea or dizziness commonly abate. If constipation is likely laxatives are given. If a patient's pain starts to increase the dose is increased. Audits of cancer pain report that the use of analgesics according to the WHO ladder can relieve pain for 80% of patients;[20] for most of the 80% the relief will be good, for a few patients it will be only moderate.

Oral opioids will "fail" in patients who are unable to swallow, and then the route of administration needs to be changed to sublingual, transdermal, or suppository. In patients who are able to swallow, oral morphine can fail because of intolerable or unmanageable adverse effects, opioid-insensitive pain, and movement-related pain. These situations present particular clinical difficulties for diagnosis and management, and the controversy between proponents of change of drug or change of route of administration but same drug is unresolved.

Intolerable or unmanageable adverse effects due to opioid action via opioid receptors will not be improved by changing to an equianalgesic dose of a different opioid that acts on the same receptors. For this approach to work would require different dose-response curve slopes for the effect and adverse effects for different opioids, and we have limited evidence for such differences. The case reports of changing opioid to reduce the adverse effects and maintain analgesia commonly describe complex cases that defy simple interpretation, but Kalso and Vainio's randomised study[17] indicates that there may be exploitable differences. In that double-blind crossover study, morphine and oxycodone hydrochloride were given to 20 patients with severe cancer pain and equal analgesia was achieved with morphine and oxycodone, but morphine caused more nausea than oxycodone and hallucinations occurred only with morphine.[17] Whether changing the route of administration (same drug) can improve the balance between efficacy and adverse effect is unclear. The necessary evidence would come from a randomised comparison of oral and injected dosing with the same drug.[17]

Opioid-insensitive pain

Chronic cancer pain and non-cancer pain are not always relieved by opioids. Opioid-insensitive pain can be defined as pain that does not respond progressively to increasing opioid dose. The most common causes of this type of pain are nerve compression and nerve destruction. Controversy has arisen about whether the opioid insensitivity is absolute or relative; if it is relative (dose-response curve shifted to the right) then giving greater doses would produce analgesia. The academic answer is that the insensitivity is usually relative, but increasing the opioid dose provokes intolerable or unmanageable adverse effects. A working rule is that if the pain is in a numb area—as a marker for a damaged nervous system—we should be less confident that opioids will work, except at doses that give troublesome adverse effects, and our threshold for considering other strategies (change of route or drug) should be lower. We have no simple way to test for opioid sensitivity other than time-consuming titration.

The usual pharmacological solutions for neuropathic pain include oral antidepressants, anticonvulsants, and local anaesthetics,[21] with spinal infusions of local anaesthetic and opioid mixtures as the last resort. There is still no quality evidence that changing from oral morphine to another oral opioid, methadone, or ketabemidone, with different opioid-receptor binding profiles, makes a difference. Differences in opioid sensitivity need to be assessed in efficacy comparisons of changing opioid or route of administration in chronic pain. The same drug by a different route must act on the same receptors. The issue is whether changing the route allows for a dose increase and effective analgesia without an increase in adverse effects.

Movement-related pain

Movement-related pain is difficult to manage. The doses of oral opioid required to control movement-related pain may be excessive when the pain stops (no movement). Two audits show that pain on movement is a major problem for half of those whose pain is controlled at rest.[22,23] Fast-onset, fast-offset opioids administered by injection might improve management of pain on movement.

Changing drug (opioid rotation) or changing route of administration

Oral morphine is the standard oral opioid, but the clinical dilemma is what should be done when oral morphine does not work—should the oral opioid or the route of administration be changed? There is limited quality evidence to guide the clinician. Physicians who can change the route of administration do so, while those who cannot change the drug. Until we have more hard evidence that there is genuine advantage in changing the drug, such as a differential rate of adverse effects or evidence from a randomised comparison of the two strategies, this question remains unresolved. Kalso and colleagues' small randomised study[24] showed that changing from oral morphine to subcutaneous or epidural morphine improved

pain relief and reduced adverse effects. Until there is a well-controlled randomised trial of adequate size, we can all continue with our beliefs unchallenged. My vote is to change route of administration not drug, but I am in the privileged position of being able to do this.

This dilemma also raises other issues. When changing drugs and not route of administration, comparisons must be made at equianalgesic doses. By contrast, when changing route of administration and not drug, the dose of the drug must be adjusted, particularly between oral and parenteral routes if the opioid undergoes extensive first-pass metabolism. Endless argument can result. For morphine, the effect of a single injected dose was six times that of a single oral dose.[35] In the multiple-dose context of chronic pain, ratios of two to one or three to one are used successfully. The active metabolite may contribute more to the analgesic effect with repeated doses than with a single dose.[10] Moreover, the basis on which such decisions are made constantly changes. The original spinal (generic for intrathecal and extradural) opioid question was whether spinal opioid alone was better than simpler injection routes. Randomised comparison of subcutaneous and epidural morphine showed little difference between the two routes in efficacy and adverse effects.[24] Currently it is the use of spinal combinations of local anaesthetic and opioid that promises the greatest clinical benefit.

Continuous spinal infusions of a combination of local anaesthetic and opioid exploit the synergy between local anaesthetic and opioid.[26,27] Low doses of both components can provide analgesia with little loss of mobility. Although there are many randomised trials of these combinations in postoperative pain, there are few in chronic pain.[28] Such spinal infusions can succeed in neuropathic and movement-related pain when oral opioid has failed, and the addition of clonidine may provide additional benefit in neuropathic pain.[29] Technical debate continues over the relative advantages of epidural versus intrathecal and high-cost implant versus simple percutaneous catheters and external syringe drivers. In my experience, the epidural with external syringe driver works well.

Opioids in non-cancer pain

In 1999, opioids are used for cancer pain, but we still argue over the use of opioids in non-cancer pain. Medical proponents of opioid use in non-cancer pain argue that when there is no other effective remedy and opioids are effective then they should be used. Some oppose this view on the basis of harm to the individual, and yet there is no evidence that long-term opioid use creates irreversible physical change. Lurking behind such opposition is the view that increased opioid availability is bad for society. The issue of opioids in non-cancer pain cannot, however, be properly addressed by such polarised positions. A bedridden patient with multiple sclerosis and opioid-sensitive pain has to be seen in a different light from a 25-year-old with back pain. The danger is that legislation that denies opioid access to the latter also forbids it to the former. Common sense dictates that not all patients with non-cancer pain should be treated with opioids. However, that small number of patients for whom opioids are the only effective remedy have the right to receive effective relief, as do their doctors to prescribe such relief for them.

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26. Declaration of Herriot Tabuteau submitted in U.S. Application. No. 13/894,262 on June 6, 2014.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**5890**
Appln. No.	:	**13/894,252**
Applicant	:	**Herriot Tabuteau**
Filed	:	**May 14, 2013**
TC/A.U.	:	**1627**
Examiner	:	**Svetlana M. Ivanova**
Docket No.	:	**1958603.00019**
Customer No.	:	**45200**
Title	:	**COMPOSITIONS COMPRISING ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR RELIEVING PAIN ASSOCIATED WITH ARTHRITIS**

DECLARATION UNDER 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. I am the inventor of the present application.

2. I have an M.D. degree from Yale University School of Medicine.

3. Example 1 of the present application describes a study that was carried out to determine the effect of orally administered zoledronic acid in a rat model of inflammatory pain.

4. Table 1 below shows the mean paw compression thresholds, in grams, measured for the rats in the vehicle group, and the rats in the group receiving 18 mg/m^2 (3 mg/kg) for three days.

	Pre-CFA	Day 1 BL	Day 1 (0.5hr)	Day 1 (1hr)	Day 1 (3hr)	Day 2 BL	Day 2 (1hr)	Day 3 BL	Day 3 (1hr)	Day 4
Vehicle	241	90	102	102	94	99	87	106	110	107
Zoledronate 18 mg/m^2	243	90	91	114	107	110	104	124	134	130

Table 1

5. From these values, reversal of inflammatory pain was calculated as described in paragraph 116 of the specification.

6. Total Pain Relief (TOTPAR), for the 24 hours following drug administration, was calculated as the area under the pain relief versus time curve, as described in US20140107210, using the linear trapezoidal rule. TOTPAR values were quantified as %•hr, or the product of reversal of hyperalgesia (%) and time (hr).

7. TOTPAR values for morphine were also calculated based on results reported in Whiteside et al., *The Journal of Pharmacology and Experimental Therapeutics*, 310:793-799, 2004.

8. I have carefully reviewed US 2004/0063670 (Fox). TOTPAR values for Fox were also calculated based upon the statement "[i]n a model of inflammatory hyperalgesia induced by unilateral hindpaw injection of complete Freund's adjuvant Zoledronate (0.003-0.1 $mgkg^{-1}$ s.c.) produced a dose-dependent reversal of mechanical hyperalgesia. The effect was rapid in onset, with a maximal reversal of 100% within 30 min, and of short duration with no significant activity 3 h following administration" found in paragraph 102 of Fox. The 0.1 mg/kg dose was used. Based upon this statement, pain relief at 30 minutes was taken to be 100%, and pain relief at 3 hours was assumed to be 0%.

9. Table 2 shows the total pain relief over 24 hours calculated as described above for Fox; day 1, day 2, and day 3, for the rats in Example 2 of the present application; and for morphine.

Total Pain Relief 0-24 hrs	Reversal of hyperalgesia
Fox	150%
Example 2 - Day 1	283%
Example 2 - Day 2	370%
Example 2 - Day 3	652%
Morphine	540%

Table 2

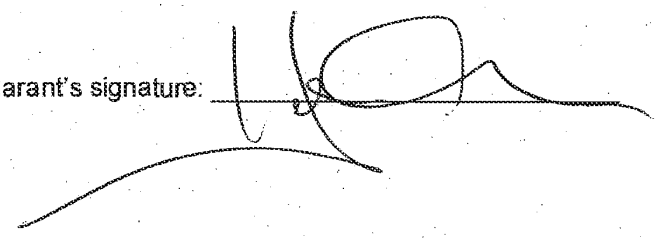
10. As a person signing below:

I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

SIGNATURE(S)

Full Name: HERRIOT TABUTEAU

Declarant's signature:  Date: June 6, 2014

27. U.S. Publication No. 2014/0107210.

US 20140107210A1

(19) **United States**

(12) **Patent Application Publication**

Kowalski et al.

(10) **Pub. No.: US 2014/0107210 A1**

(43) **Pub. Date: Apr. 17, 2014**

(54) **METHOD OF TREATING POST-SURGICAL ACUTE PAIN**

(71) Applicant: **Depomed, Inc.**, Newark, CA (US)

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(73) Assignee: **Depomed, Inc.**, Newark, CA (US)

(21) Appl. No.: **14/137,605**

(22) Filed: **Dec. 20, 2013**

Related U.S. Application Data

(63) Continuation of application No. 13/205,033, filed on Aug. 8, 2011, now Pat. No. 8,623,920, which is a continuation of application No. 12/706,117, filed on Feb. 16, 2010, now Pat. No. 8,110,606, which is a continuation of application No. 12/391,434, filed on Feb. 24, 2009, now Pat. No. 7,662,858.

(60) Provisional application No. 61/055,581, filed on May 23, 2008.

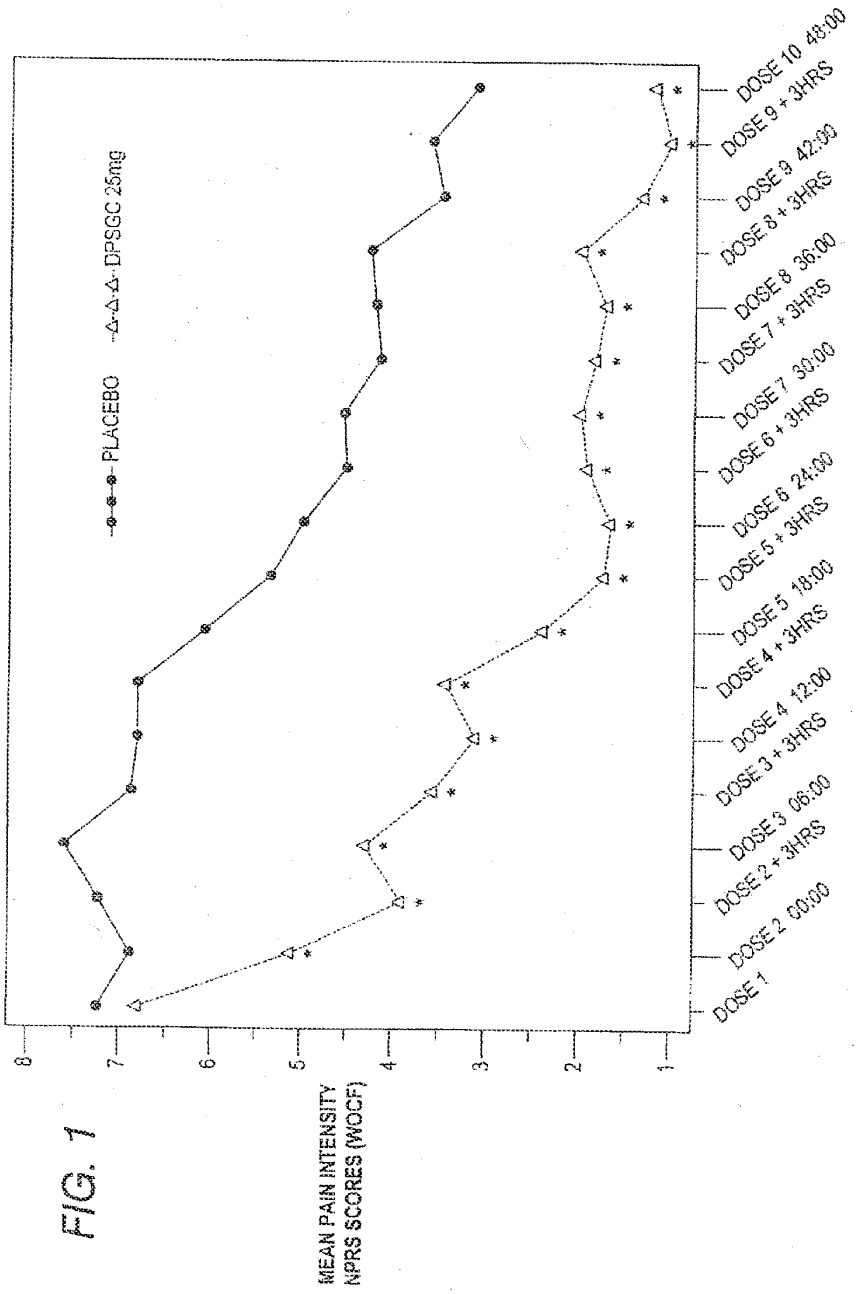
Publication Classification

(51) **Int. Cl.**
A61K 31/196 (2006.01)

(52) **U.S. Cl.**
CPC *A61K 31/196* (2013.01)
USPC **514/567**

(57) **ABSTRACT**

A method is provided for treating pain in patients recovering from post-surgical trauma by administering between about 13 to about 30 mg of diclofenac potassium in a liquid dispersible formulation over a period of at least 24 hours, wherein the daily total amount of diclofenac potassium administered is less than or equal to about 100 mg. The method is particularly useful in treating acute pain in bunionectomy patients.


PLACEBO
DPSGC 25mg
MEAN PAIN INTENSITY
NPRS SCORES (WOCF)
8
7
6
5
4
3
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1
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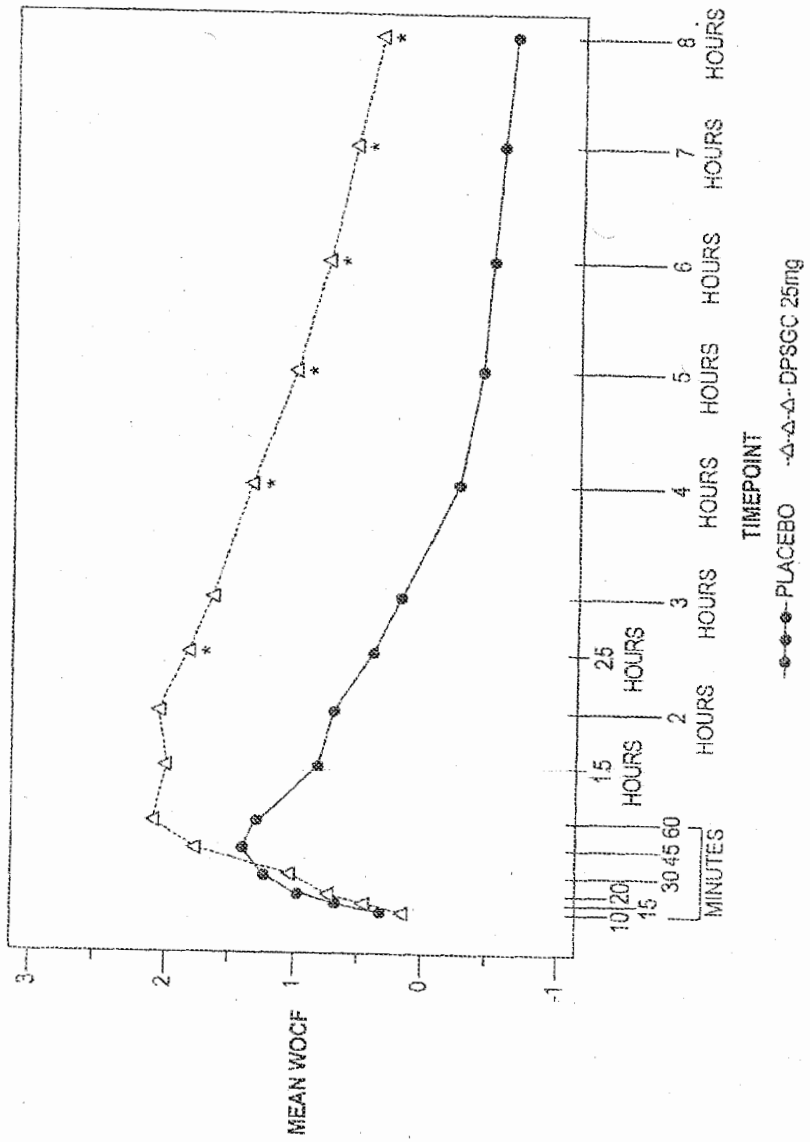
DOSE 9 + 3HRS
DOSE 10 48:00

FIG. 1

FIG. 2


MEAN WOCF
3
2
1
0
-1
MINUTES
10 15 20 30 45 60
1.5 HOURS
2 HOURS
25 HOURS
3 HOURS
4 HOURS
5 HOURS
6 HOURS
7 HOURS
8 HOURS
TIMEPOINT
PLACEBO
DPSGC 25mg

METHOD OF TREATING POST-SURGICAL ACUTE PAIN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of pending U.S. Ser. No. 13/205,033, filed Aug. 8, 2011, which is a continuation of U.S. Ser. No. 12/706,117, filed Feb. 16, 2010, now U.S. Pat. No. 8,110,606, issued Feb. 7, 2012, which is a continuation of U.S. Ser. No. 12/391,434, filed Feb. 24, 2009, now U.S. Pat. No. 7,662,858, issued Feb. 16, 2010, which in turn claims the benefit of priority from U.S. Provisional Application Ser. No. 61/055,581, filed May 23, 2008, which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to a method for treating acute pain in a patient recovering from post-surgical trauma which employs an orally administered low dose amount of diclofenac potassium in a dispersible liquid formulation. Specifically, the present invention relates to a method for treating acute pain in patients recovering from a bunionectomy which utilizes an orally administered low dose amount of diclofenac potassium in a dispersible liquid formulation.

BACKGROUND OF THE INVENTION

[0003] Pain is an unpleasant sensory and emotional experience arising from actual or potential tissue damage. Pain is highly subjective to the individual experiencing it, but medical diagnosis is based on characterising it in various ways such as the duration, severity, type (dull, burning or stabbing), and location in body. Experiencing pain is influenced by a number of dynamic, changing and interacting physical, mental, biochemical, physiological, psychological, social, cultural and emotional factors. Thus, pain perceived as intense at one time may at another time be perceived as less intense although all other factors appear to be constant.

[0004] Pain management divides symptoms into acute or chronic pain. Acute pain is distinguished from chronic pain. Acute pain warns the patient that something is wrong, and may result from a variety of causes including tissue damage, infection and/or inflammation. Chronic pain, on the other hand, may have no apparent cause or may be caused by a developing illness or imbalance. Sometimes chronic pain can have a psychosomatic or psychogenic cause.

[0005] Surgical procedures often result in some form of acute pain. Surgical pain may include nociceptive, neuropathic or psychological components. Nociceptive pain is a pain experienced as a result of nociception, which is detection of a stimulus by a pain receptor (nociceptor) and transmission of the information to the brain along nerves. Nociceptive pain is caused by tissue damage and inflammation in response to trauma. The resulting pain is usually not well localized and is opioid responsive.

[0006] The goal of post-surgical pain management is two-fold: i) to provide a quick onset of analgesic or pain relief and ii) to reduce or modulate the quality and intensity of pain a patient experiences in the post-surgical period. The improvement in minimally invasive surgical techniques has resulted in a reduction in patient time in a hospital and has shifted many procedures to the physician's office. Outpatient surgery has become a procedure of choice for many simple to complex procedures, such as bunionectomy, knee surgery, hernia repair, tonsillectomy, carpel tunnel release, cataract removal, hysterectomy and prostatectomy. The patient must now be made comfortable enough in a short period of time to return home and safely manage his or her own pain. Medications that provide gradual but extended response to acute pain situation are often inappropriate in this situation.

[0007] Treatment for acute pain after bunionectomy surgery typically consists of opioid and/or NSAIDs/COX-2 inhibitors. In some cases, opioids are given for several days and then the subject is treated with an NSAID or COX-2 Inhibitor. However, interest in the cardiovascular risk associated with the use of COX-2 inhibitors has become intense, especially in regard to rofecoxib and celecoxib. While current treatments for management of post-surgical acute pain are useful, there is a need for improved methods for treating post-surgical acute pain, particularly following bunionectomy, which provides immediate relief of acute pain with little or no risk of a cardiovascular event.

BRIEF DESCRIPTION OF DRAWINGS

[0008] FIG. 1 depicts mean NPRS pain intensity scores over time during the 48-hour multiple dose period (Full Analysis Population).

[0009] FIG. 2 depicts Day 1 mean PID scores over time (Full Analysis Population).

SUMMARY OF THE INVENTION

[0010] In a first aspect, the invention provides a method of treating acute post-surgical pain, e.g., osteotomy pain, in a patient in need of such treatment, said method comprising the step of orally administering to the patient a dose of between about 13 to about 30 mg of diclofenac potassium in an liquid dispersible formulation every 4 hours to 8 hours over a period of at least 24 hours, wherein the daily total amount of diclofenac potassium administered is less than or equal to about 100 mg.

[0011] In one embodiment of the first aspect, the pain results from a bunionectomy.

[0012] In another embodiment of the first aspect, internal fixation may be performed during the bunionectomy.

[0013] In a second aspect, the invention provides a method of treating acute post-bunionectomy pain in a patient in need of such treatment, said method comprising orally administering to the patient a dose of between about 13 to about 30 mg of diclofenac potassium in a dispersible liquid formulation every 4 hours to 8 hours over a period of at least 24 hours, wherein the daily total amount of diclofenac potassium administered is less than or equal to about 100 mg.

[0014] In one embodiment of the second aspect, internal fixation may be performed during the bunionectomy.

[0015] In one embodiment of either aspect, the diclofenac potassium in the dispersible liquid formulation is administered about every 5 hours to about 8 hours.

[0016] In another embodiment of either aspect, the diclofenac potassium in the dispersible liquid formulation is administered about every 6 hours.

[0017] [In another embodiment of either aspect, the diclofenac potassium in the dispersible liquid formulation is administered over a period of at least about 30 hours.

[0018] In another embodiment of either aspect, the diclofenac potassium in the dispersible liquid formulation is

administered over a period of at least about 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 168 hours or seven days.

[0019] In another embodiment of either aspect, the amount of the diclofenac potassium in the dispersible liquid formulation comprises at least about 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 28 mg, or 30 mg of diclofenac potassium.

[0020] In another embodiment of either aspect, the administered amount of diclofenac potassium in the dispersible liquid formulation is effective for treating the pain for about 6 to about 8 hours.

[0021] In another embodiment of either aspect, the plasma concentration of diclofenac in a patient ranges between about 670 to about 1500 ng/ml in less than 30 minutes with the concomitant onset of relief of acute pain.

[0022] In another embodiment of either aspect, the administration of diclofenac potassium in the dispersible liquid formulation results in immediate increase in plasma concentration of diclofenac characterized by T(max) of 0.47 hours.

[0023] In another embodiment of either aspect, diclofenac is substantially eliminated from plasma in the first 2 hours following administration.

[0024] In another embodiment of either aspect, the amount of the diclofenac potassium in the dispersible liquid formulation comprises about 25 mg of diclofenac potassium.

[0025] In another embodiment of either aspect, the administration of diclofenac potassium in the dispersible liquid formulation results in an average 48 hour NPRS pain score of about 2.49.

[0026] In another embodiment of either aspect, the administration of diclofenac potassium in the dispersible liquid formulation results in a median time to onset of greater than or equal to 30% pain reduction of about 60 minutes in a 6 to 8 hour initial dosing period.

[0027] In another embodiment of either aspect, the administration of diclofenac potassium in the dispersible liquid formulation provides a median time to onset of meaningful pain relief of about 70 minutes in a 6 to 8 hour initial dosing period.

[0028] In another embodiment of either aspect, the administration of diclofenac potassium in the dispersible liquid formulation provides clinically significant analgesic efficacy for about 6 hours.

[0029] In another embodiment of either aspect, 25 mg of diclofenac potassium in the dispersible liquid formulation is administered four times over a period of about 24 hours.

[0030] In another embodiment of either aspect, the diclofenac potassium in the dispersible liquid formulation is contained in a capsule such as a soft or hard gelatin capsule.

[0031] In another embodiment of either aspect, no opioid is co-administered with the diclofenac potassium in the dispersible liquid formulation.

[0032] In another embodiment of either aspect, the acute pain comprises mild to moderate pain, moderate to moderately severe pain, or moderate to severe pain.

[0033] These and other embodiments of the invention will become apparent in light of the detailed description below.

DETAILED DESCRIPTION OF THE INVENTION

[0034] The present invention provides a method for treating acute pain in patients recovering from post-surgical trauma such as that resulting from osteotomy. The method is particularly useful in treating acute pain in patients that have undergone outpatient surgical procedures such as bunionectomy. The method comprises orally administering between about 13 to about 30 mg, e.g., about 25 mg, of diclofenac potassium in a dispersible liquid formulation about every four hours to 8 hours for a period of at least 24 hours, wherein the daily total amount of diclofenac potassium administered is less than or equal to about 100 mg.

[0035] The method is based on the surprising discovery that post-surgical analgesia, particularly post-osteotomy analgesia, can be achieved, without the need for opioids, with a relatively low oral dose (e.g., between about 13 mg to about 30 mg) of diclofenac potassium in a dispersible liquid formulation. Surgical procedures, such as bunionectomy, that are typically performed as an outpatient procedure have a preferential need for post-surgical analgesic methods that can be administered without substantial patient overview. Consequently, use of analgesics that affect, inter alia, motor functions, such as opioids, are not desirable for management of post-surgical pain after an outpatient surgical procedure. The post-surgical analgesia achieved with a low oral dose dispersant liquid diclofenac potassium preparation provides sufficient analgesia to delay or suspend the use of an opioid in the treatment of acute post-surgical pain, and is, therefore, an effective method of pain management after an outpatient surgical procedure. The method of the invention surprisingly provided effective pain relief for patients who had undergone osteotomy, e.g., bunionectomy surgery, without an increased risk of a treatment related adverse event relative to the control.

[0036] All publications, patent applications, patents and other references mentioned herein, if not otherwise indicated, are explicitly incorporated by reference herein in their entirety for all purposes as if fully set forth.

[0037] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control.

[0038] Except where expressly noted, trademarks are shown in upper case.

[0039] Unless stated otherwise, all percentages, parts, ratios, etc., are by weight.

[0040] When an amount, concentration, or other value or parameter is given as a range, or a list of upper and lower values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper and lower range limits, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the present invention be limited to the specific values recited when defining a range.

[0041] When the term "about" is used in describing a value or an end-point of a range, the invention should be understood to include the specific value or end-point referred to.

[0042] As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having" or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but can include other elements not expressly listed or inherent to such process, method, article, or apparatus. Further, unless expressly stated to the contrary, "or" refers to an inclusive or and not to an exclusive or. For

example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and Bare true (or present).

[0043] The use of "a" or "an" to describe the various elements and components herein is merely for convenience and to give a general sense of the invention. This description should be read to include one or at least one and the singular also includes the plural unless it is obvious that it is meant otherwise.

Diclofenac Potassium in a Dispersible Liquid Formulation:

[0044] The present invention relates to a method for treating acute pain such as that resulting from an osteotomy, e.g., a bunionectomy, based on use of an oral dispersible liquid formulation comprising diclofenac potassium and at least one pharmaceutically acceptable, non-toxic dispersing agent. A particularly useful dispersible liquid formulation of diclofenac potassium is described in U.S. Pat. No. 6,365,180, which is hereby incorporated by reference in its entirety. Another useful orally administered dispersible liquid formulation of diclofenac potassium, based on the use of a bicarbonate dispersing agent, is described in U.S. Pat. No. 6,974,595 (i.e., Examples 6 and 7), which is incorporated by reference in its entirety. Diclofenac (potassium [2-(2,6-dichlorophenyl) amino]-phenyl]acetate), is a potent nonsteroidal anti-inflammatory (NASID) drug therapeutically used in inflammatory conditions and as an analgesic. Like other NASIDs, diclofenac interacts with the arachidonic acid cascade at the level of cyclo-oxygenase. Diclofenac inhibits cyclo-oxygenase at micromolar concentrations and as a consequence the formation of thromboxanes, prostaglandins and prostacyclin is inhibited under various clinical and experimental conditions. As used herein, the term "pharmaceutically acceptable," when referring to any or all components of the present compositions, means that such component(s) are compatible with other components therein, and not deleterious to the recipient thereof.

[0045] A dispersing agent is a surface-active substance added to a suspension, usually a colloid, to improve the separation of particles and to prevent settling or clumping in the gastrointestinal tract by facilitating distribution of particles or droplets throughout the gastrointestinal tract. Any pharmaceutically acceptable dispersing agents may be used, including, for example, alkali metal bicarbonates or mixtures thereof, such as potassium bicarbonate in amount 20-80% by weight of the weight of diclofenac; the polymer-based dispersing agents which include, for example, polyvinylpyrrolidone (PVP; commercially known as Plasdone™); and the carbohydrate-based dispersing agents such as, for example, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), and the cyclodextrins. Useful dispersing agents include PVP K29-32, dextrins, starch, derivatized starch and dextrans, while of the dextrins, derivatized cyclodextrins are especially useful. Of such cyclodextrins, hydroxypropyl beta-cyclodextrin and gamma-cyclodextrin are especially preferred. The numbers relate to the molecular weight of the polymer wherein, for example, PVP K-30 has an average molecular weight of about 30,000, with attendant viscosity characteristics.

[0046] The dispersible liquid formulation further comprises at least one pharmaceutically acceptable non-toxic solubilizing agent. Such readily available solubilizing agents are well known in the art and is typically represented by the family of compounds known as polyethylene glycols (PEG) having molecular weights from about 200 to about 8,000. For liquid formulations used for filling soft capsules such as soft gelatin capsules, suitable molecular weights range from about 200 to about 600 with PEG 400 being especially useful. Another example of suitable solubilizing agent includes sorbitol.

[0047] Optionally, another solubilizing agent which may be utilized in compositions of the present invention is water, especially purified and deionized water. For such compositions, the concentration of water is from about zero percent to about ninety-nine percent (w/w). More particularly for compositions of the present invention to be filled into soft capsules, a maximum water concentration from about 0% to about 5% is preferred, although the concentration of total solubilizing agent may be the full concentration range taught herein.

[0048] As used in the present compositions, the concentration of the sum of solubilizing agent utilized, wherein more than one solubilizing agent can be utilized, is from about 0 percent to about 99 percent (w/w). The preferred concentration of solubilizing agent in the present compositions is from about 60 percent to about 90 percent (w/w).

[0049] If the dispersible liquid formulations are to be filled in soft gelatin capsules, is at least one optional pharmaceutically acceptable, non-toxic plasticizing agent may be used. Such plasticizing agents, which are well known in the pharmaceutical formulation art, include, for example, glycerin, propylene glycol, and sorbitol. Such commercially available plasticizers can be prepared to include more than one plasticizing agent component, but the preferred plasticizing agent for the present compositions is glycerin. In addition to its use as a plasticizing agent, propylene glycol can be used as a solubilizing agent when used alone or in combination with another solubilizing agent as taught herein.

[0050] As used in the present invention, the concentration of the sum of plasticizing agent utilized, wherein more than one plasticizing agent can be utilized, is from about zero percent to about 75 percent (w/w). The preferred of plasticizing agent is from about zero percent (0%) to about fifty percent (50%), and an especially preferred concentration in a range from about one percent (1%) to about thirty percent (30%). When the compositions of the present invention are used to fill soft gelatin capsules, the general concentration of such plasticizing agent ranges from about 5 percent to about 10 percent (w/w). Such plasticizers are especially useful with soft gelatin capsule preparations because, without which, such capsules tend to harden and lose their beneficial properties by, potentially, cracking or becoming brittle.

[0051] Another optional component of the present compositions, which is a preferred component, is at least one pharmaceutically acceptable, non-toxic, surfactant, preferably a non-ionic surfactant. Such surfactants are well known in the pharmaceutical formulation art and include readily available surfactants having a concentration from about zero percent to about 90 percent such as, for example, macro gel esters (Labrafils), Tandem 522™, Span 80™, Gelucieres™, such as, for example, tocopherol polyethylene glycol 1000 succinate, polysorbate 20, and polysorbate 80. Of these, polysorbate 20 and polysorbate 80 are particularly useful. The addition of at least one surfactant, particularly a non-ionic as described above, to the liquid compositions of the present invention, improves the dispersion properties of diclofenac potassium relative to compositions not containing such non-ionic sur-

factant. This in turn provides a more rapid onset of the therapeutic benefits provided by diclofenac potassium with reduced gastroirritation in a mammal relative to compositions not containing the surfactant.

[0052] As used in the present invention, the concentration of the sum of non-ionic surfactant utilized, wherein more than one such surfactant can be utilized, generally ranges from about zero percent to about 10 percent (w/w), with a range from about 1 percent to about 5 percent (w/w) being preferred. A particularly useful concentration is about 3 percent (w/w).

[0053] Typically, the order of addition of the various components comprising the present invention will not affect the formation of a solution, when desired, of the present invention. However, when such a surfactant is used, it may be best to add the surfactant or surfactants following addition of diclofenac active ingredient and dispersing agent.

[0054] It should be understood that each component comprising the compositions of the present invention must be pharmaceutically acceptable and utilized in a non-toxic concentration. Other pharmaceutically acceptable, non-toxic pharmaceutical additives may be included in the compositions of the present invention and include, for example, sweetening agents, local anesthetics, antibacterials, a lower alkyl alcohol such as ethanol, and the like.

[0055] Commonly used pharmaceutical agents, such as, for example, about 0.1 N to 6N hydrochloric acid, are used in the liquid formulation as a stabilizing agent for softgel capsule. A preferred pH range of the present compositions when used for filling soft gelatin capsules is from about 4.0 to about 9.0.

[0056] The resulting oral administrable composition compromising diclofenac potassium in a dispersible liquid formulation exhibits improved dispersing properties of the diclofenac potassium upon contact with stomach acid, which results in faster, reproducible, and a more uniform absorption rate than conventional pharmaceutical compositions. A more rapid, uniform absorption of the diclofenac potassium generally provides a more rapid onset of the therapeutic benefits.

[0057] The oral dispersible liquid formulations of the present invention are usually formulated to deliver a dosage level of between about 13 to about 30 mg, usually between about 14 mg to about 25 mg, of diclofenac potassium for total dosage amount of up to about 100 mg per day. This formulation may also be used to fill capsules such as hard or soft gelatin capsules. The preparation of such capsules is well known in the pharmaceutical art [see, e.g. Modern Pharmaceutics, Third Edition, (G. S. Banker and C. T. Rhodes, ed.; 1996); and The Theory and Practice of Industrial Pharmacy, Third Edition, (L. Lachman, H. A. Lieberman, and J. L. Kanig, ed.; 1986)].

Pain Management After Bunionectomy:

[0058] A bunion or hallux valgus is an inflammation or thickening of the joint capsule of the great toe. This inflammation causes injury and deformity to the joint due to abnormal bone growth. The great toe is forced in toward the rest of the toes, causing the head of the first metatarsal bone to jut out and rub against the side of the shoe; the underlying tissue becomes inflamed and a painful growth forms. As this bony growth develops, the bunion is formed as the big toe is forced to grow at an increasing angle towards the rest of the toes. A bunion may also develop in the fifth metatarsal bone, in which case it is known as a bunionette or tailor's bunion. Bunions often develop from wearing narrow, high-heeled shoes with pointed toes, which puts enormous pressure on the front of the foot and causes the foot and toes to rest at unnatural angles. Injury in the joint may also cause a bunion to develop over time. Genetics play a factor in 10% to 15% of all bunion problems; one inherited deformity, hallux valgus, causes the bone and joint of the big toe to shift and grow inward, so that the second toe crosses over it. Flat feet, gout, and arthritis increase the risk for bunions.

[0059] Bunion surgery, usually called a bunionectomy, is almost always done as an outpatient procedure. The procedure itself varies depending on the type and severity of the deformity. Although the procedure varies, the recovery is the same for all. Some of the bunionectomy procedures are named Akin, Austin Akin, Keller, Silver, Silver Akin, and Kalish depending on which area of the bone is cut and the type of cut that is made. Once the subject is in the operating room and after anesthesia has been started, a tourniquet is applied to either the thigh or ankle depending on the type of anesthesia. The tourniquet is used to prevent bleeding during surgery. After the tourniquet is applied, the foot and lower leg are washed in a sterile fashion to help prevent infection. The surgeon then makes an incision at the top of the great toe into the joint capsule.

[0060] Once the bone is exposed, the surgeon makes a cut in the bone in order to correct the deformity. This is called an "osteotomy". As defined herein, an osteotomy is a surgical procedure in which a bone is cut to shorten, lengthen or change its alignment. It is used for example to straighten a bone that has healed crookedly following a fracture. Bone is defined herein as a connective tissue consisting of bone-building osteoblasts, stationary osteocytes, and bone-destroying osteoclasts, embedded in a mineralized matrix infused with spaces and canals. In the case of the hallux valgus, a small piece of bone is removed and the bone realigned to correct the deformity. Tendon and other soft tissue correction may also be required in order to assure full correction is made.

[0061] Depending on the type of bunionectomy, fixation may be required. Fixation may be internal, percutaneous or by external means such as a cast or splint, surgical shoe, adhesive form or a dressing. In the bunionectomy the fixation is often internal. This is usually done with either screws or wire. Once the bone is realigned, the wound is irrigated with warm sterile saline and then sutured closed and a dressing applied. Recovery varies according to extent of the surgical procedure and each individual's rate of healing.

[0062] Usual post-operative care consists of rest, elevation, and ice for the first 3-5 days. Depending on the procedure performed some walking may be done in a special shoe during this time. A check-up is performed in the office and the bandage is changed. Often subjects will return to work after 3-7 days, depending on the requirements of the job. Skin usually heals in two weeks and at this time the stitches are removed. Bone takes 6-8 weeks to heal. Taking X-rays at regular intervals can assess the rate of bone healing. Any bunion surgery results in some stiffness. Physical therapy starts at the second or third week to minimize this stiffness, usually home exercises are sufficient. If these exercises are not performed, a poor result may occur due to excessive stiffness. Swelling gradually decreases and, at two months, providing sufficient healing of the bone has occurred, regular shoes may be worn. Regular activities can often be resumed at two to three months as tolerated. Some swelling may be present for six months or more. The recovery period varies

according to procedure and each individual's rate of healing. Some factors such as circulation, smoking, bone quality, and general health can also have an effect.

[0063] Treatment for pain after bunionectomy surgery typically consists of opioid and/or NSAIDs/COX-2 inhibitors. In some cases, opioid are given for the first 3-5 days and then the subject is treated with an NSAID or COX-2 Inhibitor. However, interest in the cardiovascular risk associated with the use of NSAID/COX-2 inhibitors has become intense, raising serious questions regarding the use of such agents. It has been discovered that an oral administrable composition comprising low dosages (e.g. between about 13 mg to about 30 mg) of diclofenac potassium, in a dispersible liquid formulation (relative to conventional dosage amounts of 50 mg or more) is surprisingly effective in providing immediate effective relief of moderate to severe acute pain to patients following post-surgical procedures, particularly outpatient post-surgical procedures such as bunionectomy, such that the need for opioids can be delayed, reduced or eliminated altogether. Furthermore, the reduction of the unit dosage amount of diclofenac potassium can lead to a substantial reduction or elimination of the risk of a cardiovascular event.

[0064] The term "acute pain" as used herein means pain that has a sudden onset and commonly declines over a short time (days, hours, minutes) and follows injury to the body and which generally disappears when the bodily injury heals. The intensity of the acute pain following a bunionectomy can be mild to moderate, moderate to moderately severe, or moderate to severe.

[0065] Pain rating scales are used in daily clinical practice to measure pain intensity. The commonly used measurement scales include the Visual Analog Scale (VAS), the Graphic Rating Scale (GRS), the Simple Descriptor Scale (SDS), the Numerical Rating Scale (NRS), and the Faces Rating Scale (FRS). All of these scales have been documented as being valid measures of pain intensity. The three scales most commonly used in the U.S. are the numerical, word and faces scales.

[0066] The visual analog scale (VAS) is a 10 cm. vertical or horizontal line with word anchors at the extremes, such as "no pain" on one end and "pain as bad as it could be" at the other. The patient is asked to make a mark along the line to represent pain intensity.

[0067] The graphic rating scale (GRS) is a variation of the visual scale which adds words or numbers between the extremes. Wording added might include "no pain", "mild", "severe".

[0068] The descriptor scale (SDS) is a list of adjectives describing different levels of pain intensity. For example pain intensity may be described as "no pain", "mild", "moderate" or "severe".

[0069] The numerical pain rating scale (NPRS) refers to a numerical rating of 0 to 10 or 0 to 5 or to a visual scale with both words and numbers. The patient is asked to rate the pain with 0 being no pain and 10 being the worst possible pain. The faces scale was developed for use with children. This scale exists in several variations but relies on a series of facial expressions to convey pain intensity.

[0070] Grouping patients' rating of pain intensity as measured with a numerical scale ranging from 0 to 10 into categories of mild, moderate, and severe pain is useful for informing treatment decisions, and interpreting study outcomes. In 1995, Serlin and colleagues (Pain, 1995, 277-84) developed a technique to establish the cut points for mild, moderate, and severe pain by grading pain intensity and functional inference. Since then, a number of studies have been conducted to correlate the numerical scales, for example the NPRS, with cutpoints related to levels of pain intensity. Common severity cutpoints are (1 to 4) for mild pain, (5 to 6) for moderate pain, and (7 to 10) for severe pain.

[0071] The term "patient" as used herein refers to a warm blooded animal such as a mammal which is the subject of surgical trauma. It is understood that at least dogs, cats, mice and humans are within the scope of the meaning of the term.

[0072] As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of acute pain, when a composition of the present invention is administered following the onset of acute pain.

[0073] In one embodiment, a method is provided for treatment of acute pain following a post-surgical procedure, particularly following an osteotomy such as a bunionectomy. The method comprising orally administering to the patient between about 13 to about 30 mg, usually about 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 28 mg or 30 mg of diclofenac potassium in a dispersible liquid formulation. Suitable oral dispersible liquid formulations are described, for instance, in U.S. Pat. Nos. 5,183,829 and 6,365,180, which are incorporated by reference in their entirety.

[0074] The diclofenac potassium in the dispersible liquid formulation can be administered about every 4 hours to 8 hours for a period of at least about 24 hours, at least about 36 hours, at least about 48 hours, at least about 72 hours, at least about 96 hours, at least about 120 hours, or at least about 144 hours or at least about seven (7) days, wherein the daily total amount of diclofenac potassium administered is less than or equal to about 100 mg.

[0075] In a specific embodiment, a dosage amount of about 25 mg diclofenac potassium in a dispersible liquid formulation has been found to be suitable for treating acute pain, e.g., mild to moderate, moderate to moderately severe, or moderate to severe, resulting from post-surgical trauma, e.g., such as that resulting from an osteotomy. A dosage amount of 25 mg diclofenac has been found to be particularly effectively for treating post-bunionectomy acute pain.

[0076] In a specific embodiment, diclofenac potassium salt in a dispersible liquid formulation in the dosage amounts discussed above can be administered at an interval of at least about 4 hours, at least about 5 hours, at least about 6 hours, or at least about 8 hours. The administered amount of diclofenac potassium salt can be effective in providing acute pain relief for about 4 to about 8 hours, preferentially for about 6 to about 8 hours, after administration.

[0077] In a specific embodiment, the method of the invention utilizes about 25 mg of diclofenac potassium contained in a dispersible liquid formulation contained in a liquid-filled, soft gelatin capsule. The formulation includes a combination of polyethylene glycol 400, glycerin, sorbitol, povidone, polysorbate 80, and hydrochloric acid, isopropyl alcohol, and mineral oil.

[0078] In a specific embodiment, the diclofenac potassium composition useful in the inventive method can provide a plasma concentration of diclofenac in a patient ranges between about 670 to about 1500 ng/ml in less than 30 minutes with the concomitant onset of relief of acute pain.

[0079] In a specific embodiment, the administration of diclofenac potassium composition in accordance with the

inventive method can result in immediate increase in plasma concentration of diclofenac characterized by T(max) of about 0.47.

[0080] In a specific embodiment, the diclofenac potassium composition useful in the method of the invention provides the following mean pharmacokinetic characteristics of: a terminal half-life (hr) of 1.07+0.29; a Cmax (ng/mL) of 1087+419; and an AUC (0 to infinity) (ng·h/mL) of 597+151.

[0081] In another embodiment, diclofenac is substantially eliminated from plasma in the first 2 hours following administration. As defined herein, the phrase "substantially eliminated" means at least about 75%, 80%, 85%, 90% or 95% of diclofenac is eliminated from plasma in the first 2 hours or after about the first 2 to 3 hours.

[0082] The following examples provide a representative composition comprising diclofenac potassium in a dispersible liquid formulation (Example 1) and method of treating post-bunionectomy acute pain using diclofenac potassium in a dispersible liquid formulation (Example 2). The materials, methods, and examples herein are illustrative only and, except as specifically stated, are not intended to be limiting.

EXAMPLES

Example 1

Preparation of Liquid Diclofenac Potassium Formulation

[0083] A typical formulation used in pain treatment is summarized in Table 1:

TABLE 1

Ingredient	Description	A % w/w	B % w/w	C % w/w
Diclofenac Potassium (25 mg)	Active	6.25	6.25	6.25
PEG 400NF	Dispersing agent; Solubilizing agent	70.12	69.70	66.95
Glycerin	Co-solvent; Plasticizing agent	10.0	10.0	10.0
Sorbitol Solution 70%	Solubilizing agent; Stabilizing agent; Plasticizing agent	5.0	5.0	5.0
Povidone USP (PVP K-30)	Dispersing agent;	6.3	6.3	6.3
Polysorbate 80	Emulsifying agent; Surfactant	1.5	1.5	3.0
6NHCl	Softgel Stabilizing agent	0.832	1.25	NA
2NHCl	Softgel Stabilizing agent	NA	NA	2.5
Nitrogen Gas (if stored prior to filling)		Overlay	Overlay	Overlay

[0084] PEG 400 was heated to about 45° C. in a cowls mixer. One half of Polysorbate 80 was then added to the heated PEG 400 and mixed while maintaining the temperature at about 45° C. Diclofenac potassium was then added and mixed to dissolve while maintaining the temperature, followed by addition of Povidone to the mixture. The contents were mixed to dissolve new additions at each step while maintaining the temperature at 45° C. The mixture was cooled to about 25-30° C. while continuing to mix. 6NHCL was subsequently added and mixed followed by mixing remaining Polysorbate 80 into the mixture. Glycerin and Sorbitol were then added and mixed while continuing to maintain the temperature at about 25-30° C. The final pH to about 6. The solution was filtered and filled into 25 mg soft gelatin capsules (400 mg fill weight).

Example 2

Method for Treatment of Post-Surgical Acute Pain Using Liquid Diclofenac Potassium Formulation

[0085] Clinical studies were conducted to determine the analgesic efficacy of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) 25 mg in acute surgical pain. The study was a placebo controlled study in subjects recovering from bunionectomy surgery. A total of 201 subjects, 102 in the DPSGC group and 99 in the placebo group, were enrolled, randomized and received at least one dose of study drug. Three subjects, 1 in the DPSGC and 2 in the placebo group discontinued.

[0086] The primary efficacy variable was the average pain intensity over a 48-hour multiple dose period calculated using an 11-point Numerical Pain Rating Scale (NPRS).

[0087] Other variables analyzed to evaluate analgesic effect of Diclofenac Potassium Soft Gelatin Capsules included:

(1) Evaluation of the analgesic efficacy of a single dose of DPSGC (during the initial dosing period) with individual pain intensity assessments as compared to placebo;

(2) Evaluation of the time needed to re-medication (during the initial dosing period) of a single dose of DPSGC as compared to placebo;

(3) Evaluation of the frequency and timing (defined as time of meaningful pain relief) of obtaining clinically significant analgesic efficacy (defined as a 30% reduction in pain intensity) as compared to placebo in acute pain;

(4) Evaluation of the use of rescue medication during the multiple dose period;

(5) Evaluation of the time to onset of obtaining a 30% reduction in pain intensity, as compared to placebo, and its duration in acute pain; and

(6) Evaluation of the safety and tolerability of DPSGC 25 mg when used for the treatment of acute surgical pain.

[0088] The efficacy measures in the study included the NPRS, the Pain Relief Rating Scale, and the Time to Meaningful, Perceptible Pain Relief, and a Global Assessment of Study Medication.

Numerical Pain Rating Intensity Scale (NPRS):

[0089] The 11-point NPRS was utilized to assess the primary endpoint. At each time point, subjects evaluated their current pain intensity relative to an 11-point numerical rating scale. A score of zero represented no pain and a score of 10 represented worst possible pain.

[0090] Subjects were instructed to: "Rate your pain by recording the one number that best describes the amount of pain you have at this time."

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

[0091] Pain Relief Rating Scale:

[0092] Subjects assessed their level of pain relief using a 5-point Pain Relief Rating Scale. A worksheet with a list of adjectives was provided to the subject, and the subject was asked to respond to the following question: "How much relief do you have from your starting pain?"

0	No pain relief
1	A little pain relief
2	Some pain relief
3	A lot of pain relief
4	Complete pain relief

Time to Meaningful and Perceptible Pain Relief:

[0093] When the subject received study medication, the Study Coordinator started 2 stopwatches and covered the time displays. To determine the exact moment that the subject began to obtain first perceptible relief, the subject was given the stopwatch 3-4 minutes after dosing and was instructed as follows: "Stop the stopwatch when you have perceptible pain relief, that is, when the relief from pain is first noticeable to you."

[0094] Determination of the exact moment that the subject began to obtain meaningful relief was attained similarly, except that the question was: "Stop the stopwatch when you have meaningful pain relief, that is, when the relief from pain is meaningful to you."

[0095] The elapsed time for each of these determinations was recorded.

Subject Global Assessment of Study Medication:

[0096] The subject provided an overall (global) evaluation of the study medication on a 5-point categorical scale. A worksheet with ratings was given to the subject, and the subject was asked to respond to the following question: "How would you rate this study medication as a pain reliever?"

1 Poor

2 Fair

3 Good

[0097] 4 Very good

5 Excellent

Secondary Efficacy Endpoints

[0098] Secondary efficacy endpoints were onset of perceptible and meaningful pain relief during the single-dose period on Day 1, TOTPAR during the single-dose period on Day 1, and onset of 30% reduction from baseline in pain intensity during the single-dose period on Day 1. Further descriptions of these endpoints follow.

[0099] Onset of perceptible and meaningful pain relief was based on double stopwatch method and measured on Day 1. Subjects who discontinued the study before onset were censored at the time of the last on-study NPRS evaluation. Subjects who received rescue medication or study drug re-medication before onset were censored at the time that rescue medication or study drug was administered. Total Pain Relief (TOTPAR) was calculated with the trapezoidal rule for the pain relief at 10, 15, 20, 30, 45, and 60 minutes and at 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose on Day 1 or until the time of re-medication. The calculation was similar to that for the SPID (described below). Imputation of missing values before re-medication was performed with the WOCF (worst observation carried forward) approach as defined for the primary efficacy endpoint.

[0100] The onset of a ≥30% reduction in pain intensity after the administration of the first dose of the study drug on Day 1 was measured. Subjects who discontinued the study before onset were censored at the time of the last on-study NPRS evaluation. Subjects who received rescue medication or study drug re-medication before onset were censored at the time that rescue medication or study drug was administered.

[0101] The sum of Pain Intensity Differences (SPID) over the 48-hour multiple dose period was measured. Differences were calculated from the pre-Dose 1 pain assessment on Day 1. Imputation of missing scheduled observations and of pain assessments following rescue medication was performed with the same method used for the primary efficacy endpoint. Pain assessments at the time of rescue medication and scheduled pain assessments (imputed or observed) were included in the calculation. The calculation method for the Day 1 SPID (described below) was used.

[0102] Sum of Pain Intensity Differences (SPID) was calculated with the trapezoidal rule for the pain intensity differences at 10, 15, 20, 30, 45, and 60 minutes and at 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose on Day 1 or until the time of re-medication. The area between 2 consecutive time points was calculated as ([time 2−time 1]×[pain intensity difference at time 2+pain intensity difference at time 1])/2. Imputation of missing values before re-medication was performed with the WOOF approach as defined for the primary efficacy endpoint.

[0103] Pain intensity, pain intensity difference, and pain relief were measured at 10, 15, 20, 30, 45, and 60 minutes and at 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the initial dose on Day 1 or until the time of re-medication. Pain intensity was assessed using the NPRS and the pain intensity difference was calculated as the change in pain intensity from baseline to the time point. Pain intensity at pre-Dose 1 was considered baseline. Pain relief was assessed using a 5-point relief rating scale (0=no relief, 4=complete pain relief). Imputation of missing values before re-medication was performed with the WOCF approach as defined for the primary efficacy endpoint.

[0104] Proportion of subjects requiring rescue medication, total number of rescues on each postoperative day, and quantity of rescue medication on each postoperative day was measured. Postoperative day was the same as calendar day. If no rescue medication was required for a subject, the total number of rescues and quantity of rescue medication were counted as zero. Otherwise, missing data were not imputed.

[0105] Mean rescue interval during the multiple dose period (Days 1-4) was measured. The mean rescue interval was calculated from the rescue intervals during each 6-hour dosing interval for postoperative Days 1-4. The rescue interval was defined as the difference between the dosing time and either the time that a rescue medication was taken (if any) or the time of the next study drug administration, whichever was less.

[0106] Proportion of subjects discontinuing due to inadequate pain relief, was recorded on the Day 5 completion

CRF (case report form). This included subjects who discontinued due to inadequate pain relief during the single-dose portion of the study.

[0107] Subjects' global assessment of study drug at discharge and on Day 5 or early termination was measured.

[0108] Time to re-medication following the initial dose on Day 1 was measured. Subjects who discontinued the study before study drug re-medication were censored at the time of the last on-study NPRS evaluation. Subjects who received rescue medication before study drug re-medication were censored at the time that rescue medication was administered.

[0109] The duration of obtaining a ≥30% reduction in pain intensity after the administration of the first dose of the study drug on Day 1 was measured.

[0110] Proportion of subjects achieving clinically significant analgesic efficacy after the administration of the first dose of the study drug on Day 1 was monitored. Clinically significant analgesic efficacy was defined as both ≥30% reduction from baseline pain intensity using NPRS and meaningful relief as indicated by the stopwatch method. The events may have occurred at any time after dosing on Day 1 and the 2 events may have occurred at different times on Day 1. Subjects were considered failures for this endpoint if they discontinued the study or received study drug re-medication before the last event occurred.

[0111] Proportion of subjects experiencing mild to no pain (NPRS ≤2) after the administration of the first dose of study drug on Day 1. Subjects were considered failures for this endpoint if they discontinued the study, received rescue medication, or received study drug re-medication before experiencing mild to no pain.

[0112] SPID and TOTPAR were analyzed with an analysis of covariance or ANCOVA model having factors for treatment and site and with the baseline value (pain intensity NPRS Score) as covariate. The 2-way ANOVA with factors for treatment and site was used to analyze average rescue interval and duration of a ≥30% reduction in pain intensity. The number of rescues on each day and the amount of rescue medication on each day were analyzed for treatment differences with the Wilcoxon test.

[0113] The treatment-by-site interaction was assessed in a supportive ANCOVA model for the primary endpoint. If the treatment-by-site interaction was statistically significant, exploratory data analysis could have been performed to provide an adequate description of the interaction. If a quantitative interaction was present, the overall treatment effect was to be estimated over sites based on the final model with the interaction effect and all other statistically significant effects. If a qualitative interaction was present, the potential cause of the interaction (such as subject characteristics, clinic management, data/CRF handling) was to be explored.

[0114] Least squares means (LS-means) for each treatment, differences in the LS-means between the treatments, and 95% confidence intervals for the treatment difference in LS-means were also provided for endpoints analyzed with the 2-way analysis of variance, ANOVA, or analysis of covariance, ANCOVA.

[0115] Categorical efficacy endpoints were analyzed with the Cochran-Mantel-Haenszel test with site as the stratification factor. Endpoints included the proportion of subjects achieving clinically significant analgesic efficacy, proportion of subjects requiring rescue medication, proportion of subjects discontinuing due to inadequate pain relief, global assessment of study drug, proportion of subjects achieving no or mild pain, pain intensity at each time point, pain intensity difference at each time point, and pain relief at each time point.

[0116] All time-to-event efficacy endpoints were summarized for each treatment group using Kaplan-Meier survival curves. This method estimated the median and 95% confidence limits for the time-to-event in each treatment group. Treatment groups were compared using a log-rank test. In addition, a Cox proportional hazard model was used with effects for treatment, baseline pain intensity score (based on the Pain Intensity NPRS score), and any demographic characteristic that was found to be statistically significantly different between treatment groups (if any) ($p \leq 0.05$). The treatment factor was parameterized using reference cell parameterization with placebo as the reference group such that the parameter estimate for the DPSGC 25 mg product represented the adjusted treatment effect and the Wald Chi-Square statistic provided a test of the DPSGC 25 mg product vs. placebo effect.

Treatment Regimen:

[0117] This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study in subjects recovering from bunionectomy surgery. The study consisted of 2 dosing periods: an initial dosing period (on Day 1) followed by a multiple dose period (through Day 4).

[0118] Subjects were provided 1-2 tablets of hydrocodone/acetaminophen (APAP) (5 mg/500 mg) every 4 to 6 hours as needed for pain, not to exceed 8 tablets daily during the day of surgery and up until 4 hours before the treatment study began. Analgesic use was recorded. If subjects required pain medication other than that specified per protocol, they were discontinued. The use of ice packs was allowed on Day 0 and on Day 1 up to 3 hours after the last analgesic dose taken prior to randomization (study medication dose 1) but not after randomization during Days 1-4.

[0119] Upon awakening at 4 am or later on the morning of Day 1 (initial dosing period), subjects who complained of having increased pain assessed their pain intensity at rest (no activity of the affected toe for at least 10 minutes prior to pain assessments) using the 11-point NPRS (0=no pain, 10=worst pain imaginable). When subjects first reported a pain intensity score of at least 4 between 4 am and 10 am, they were randomly allocated to 1 of 2 blinded treatment arms: Arm A (placebo) or Arm B (25 mg DPSGC). All pain medication (i.e., hydrocodone/APAP) was to have been discontinued at least 4 hours before the initial dose of study medication.

[0120] After taking the first dose, subjects were provided 2 stopwatches to record the time to onset of perceptible pain relief and the time to onset of meaningful pain relief. Pain intensity and pain relief assessments and vital signs were measured at various time points after the initial dose or until the time of re-medication.

[0121] The second dose (re-medication) was given to the subject when the subject requested the second dose to treat his/her pain. If the subject did not indicate a need for re-medication within 8 hours of taking the first dose of study medication, he/she was given the second dose of study medication at 8 hours.

[0122] There-medication dose was the second dose of the study and marked the start of the 48-hour assessment period, during which subjects took their study medication every 6 hours. Following the re-medication dose, subsequent doses while in the study unit occurred every 6 hours (+/−1 hour from

the 6-hour schedule established at the time of re-medication). Study medication use was not to exceed 4 doses in one 24-hour period. Subjects were discharged after the 48-hour period was completed and were instructed to take their medication on an outpatient basis at 6 am, 12 pm, 6 pm and 12 am. The last dose of study medication was taken at 12 midnight on Day 4.

[0123] Rescue medication consisting of hydrocodone/APAP (5 mg/500 mg) was available for the subjects after the re-medication dose. However, subjects were encouraged to delay taking rescue medication until at least 1 hour after receiving study medication. Subjects who took rescue medication recorded a pain assessment at the time of rescue and took the subsequent doses of study medication on schedule. They continued the remaining pain assessments.

[0124] The primary efficacy endpoint of the average of pain intensity over 48 hours was analyzed using an analysis of covariance (ANCOVA) model with factors for treatment and site and baseline pain intensity score (using the pain intensity NPRS Score; 0=no pain, 10=worst pain imaginable) as a covariate.

[0125] SPID and TOTPAR were analyzed with an ANCOVA model having factors for treatment and site and with the baseline value (pain intensity NPRS Score) as covariate. The 2-way analysis of variance (ANOVA) with factors for treatment and site was used to analyze average rescue interval and duration of a ≥30% reduction from baseline in pain intensity. The number of rescues on each day and the amount of rescue medication on each day were analyzed for treatment differences with the Wilcoxon test. The treatment-by-site interaction was assessed in a supportive ANCOVA model for the primary endpoint. Least squares means (LS-means) for each treatment, differences in the LS-means between the treatments, and 95% confidence intervals for the treatment difference in LS-means were also provided for endpoints analyzed with the 2-way ANOVA or ANCOVA.

[0126] Categorical efficacy endpoints were analyzed with the Cochran-Mantel-Haenszel test with site as the stratification factor. All time-to-event efficacy endpoints were summarized for each treatment group using Kaplan-Meier survival curves. In addition, a Cox proportional hazard model was used with effects for treatment and baseline pain intensity score (based on the Pain Intensity NPRS Score). Pain measures taken after re-medication or use of rescue medication were considered missing and replaced using worst observation carried forward (WOCF) methodology.

Evaluation of Efficacy of Analgesic Effect of Liquid Formulation of Diclofenac Potassium:

[0127] The primary efficacy assessment endpoint was the average pain intensity over the 48-hour multiple dose period. Pain intensity was measured using a NPRS of 0 to 10 (0=no pain, 10=worst possible pain).

[0128] All observed, scheduled NPRS pain assessments were averaged for each subject over the 48-hour multiple dose period, unless rescue medication was administered. If rescue medication was administered, scheduled pain assessments were considered missing for 6 hours following administration of rescue medication and the pain assessment at the time of rescue medication was carried forward. If rescue medication was administered more than once within 6 hours, the pain assessment at the first rescue was carried forward until there had been at least 6 hours since the use of last rescue. Pain assessments at the time of rescue medication and scheduled pain assessments (imputed or observed) were included in the average pain intensity over the 48-hour multiple dose period. Missing scheduled pain assessments for subjects who did not prematurely discontinue from the study were imputed with the worst observation carried forward (whether it was the baseline or some other value) up to the time of the missing observation (regardless of whether the worst value occurred in association with rescue medication). For subjects who prematurely discontinued from the study, the worst observation (whether it was the baseline or some other value) was carried forward for the remainder of the 48-hour multiple dose period (regardless of whether the worst value occurred in association with rescue medication).

[0129] The primary efficacy endpoint of the average of pain intensity over 48 hours was analyzed using an ANCOVA model with factors for treatment and site and baseline pain intensity score (using the pain intensity NPRS Score) as a covariate. The baseline pain intensity score was the last pain intensity score obtained before study drug dosing on Day 1.

[0130] The 3-hour post-dose pain assessment was not required if it fell between midnight and 5 am. If these values were not obtained, they were not considered missing data points and were not imputed.

[0131] Subjects recorded their pain intensity post-operatively on a 0-10 numerical pain rating scale (NPRS). A clinically significant difference was felt to be 1.5 units on the NPRS for the average pain intensity over 48 hours with the NPRS. If the common standard deviation was 3.0, then a sample size of 86 subjects per group would provide over 90% power to detect as significant a difference of 1.5 units between the placebo and active groups using a two-sample t-test with a significance level of 0.05 two-sided.

[0132] No statistically significant difference was observed between the DPSGC 25 mg and placebo groups for the mean NPRS pain intensity score at baseline (6.89 and 7.29, respectively). The difference between the treatment groups in average pain intensity over the 48-hour multiple dose period, calculated using the 11-point NPRS, was statistically significant in the full analysis population (Table 2).

TABLE 2

Primary Endpoint	Placebo	DPSGC 25 mg	p-value
Average 48-Hour Pain Intensity NPRS Score	5.56	2.49	<0.0001

[0133] In the full analysis population, the difference between the treatment groups in average pain intensity over the 48-hour multiple dose period, calculated using the 11-point NPRS was statistically significant using the WOOF methodology ($p<0.0001$). A lower average pain score was observed in the DPSGC 25 mg group compared to the placebo group (2.49 vs. 5.56). This substantial difference (greater than 2 points) in average pain intensity would be expected to provide a significant clinical benefit to subjects. Results were similar in the evaluable population and when LOCF (last observation carried forward) and observed cases methodologies were used. A summary of average pain intensity over the 48-hour multiple dose period for the full analysis and evaluable populations is presented in Table 3.