CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-575

PHARMACOLOGY REVIEW

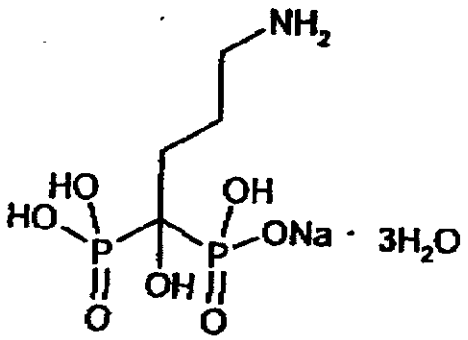
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-575
Sequence number/date/type of submission:11/15/02; once weekly Fosamax (alendronate) 70 mg
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Merck Research Laboratories
Manufacturer for drug substance : Merck

Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: DMEDP
HFD #: 510
Review completion date: 3/13/03

Drug:

Trade name: fosamax
Generic name (list alphabetically): alendronate
Code name: MK-0217; L-670452
Chemical name: 4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate
Molecular formula/molecular weight: 325.12
Structure:



Relevant INDs/NDAs/DMFs: 20-560 (alendronate) also other approved bisphosphonates
Drug class: bisphosphonate

Indication: prevention/treatment of osteoporosis previously NDA 20-560 (S-021 & S-022) was approved for a 35 mg (prevention) and 70 mg (treatment) once weekly tablet.

Clinical formulation: 70 mg oral [redacted] solution [redacted]

Alendronate Sodium Oral [redacted] Solution, 70 mg - Market Composition

Ingredients	Reference	Function	mg/mL[4]
Alendronate Sodium[5]	Ph. Eur.	[redacted]	1.218
(as anhydrous free acid equivalent)			(0.933)
Sodium Citrate Dihydrate	USP/Ph. Eur.		[redacted]
Citric Acid Anhydrous	USP/Ph. Eur.		[redacted]
Sodium Butylparaben[3, 5]	BP		0.07500
Sodium Propylparaben[4, 5]	NF/Ph. Eur.		0.2250
Saccharin Sodium	USP/Ph. Eur.		[redacted]
Artificial Raspberry Flavor			[redacted]
Purified Water	USP/Ph. Eur.		[redacted]

[redacted]
[4] Fill volume is targeted to [redacted]
[5] The product is provided as a unit dose. Each bottle contains 91.35 mg of Alendronate Sodium, which is equivalent to 70 mg as an anhydrous free acid.
[3] Alternatively, this antimicrobial preservative may be referred to as Sodium Butyl Hydroxybenzoate.
[4] Alternatively, this antimicrobial preservative may be referred to as Sodium Propyl Hydroxybenzoate.

Route of administration: oral solution

Proposed use: once weekly (70 mg) oral [redacted] solution formulation (75 ml) for the indicated uses

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Fosamax (NDA 20-560) is approved for the treatment and prevention of osteoporosis in men and postmenopausal women, ——— in a daily tablet and once weekly formulation. NDA 21-575 seeks approval for a once weekly oral ——— solution ——— of 70 mg. Local esophageal irritation studies have been performed in dogs given weekly administration for up to one-month duration to support safety of this new formulation. Based on the results of these studies in conjunction with those submitted in NDA 20-560 for the active drug substance (alendronate) Pharmacology/Toxicology recommends approval of NDA 21-575.

B. Recommendation for Nonclinical Studies-none

C. Recommendations on Labeling: none, the pertinent Pharmacology/Toxicology sections of the product label have not been revised since the last approved product labeling, further revision is not needed at this time.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: submitted toxicity studies to NDA 20-560 included:1) *in vitro* and *in vivo* genotoxicity studies; 2) single and multiple dose toxicity studies in rats, mice and dogs; 3) developmental and reproductive toxicity in rats and rabbits; 4) carcinogenicity studies in rats and mice and 5) special toxicity studies to evaluate esophageal irritation potential of alendronate. These studies have been submitted in previously approved marketing applications/supplements of alendronate. Additional studies reviewed in NDA 21-575 are four esophageal irritation studies with a once weekly oral ——— alendronate formulation.

Daily exposure to an alendronate solution (0.2 mg/ml) at pH 2 resulted in esophageal irritation in dogs. Exposure of the esophagus once weekly for one month to alendronate 0.8 mg/ml at pH 2 was not irritating to the esophageal mucosa. Increasing the alendronate concentration to 3.73 mg/ml pH 6.8 resulted in no morphologic evidence of esophageal irritation. Together these studies suggest that weekly dosing of an oral ——— formulation (pH 6.8) is not irritating to the esophagus despite a higher concentration (3.73mg/ml) than used in a once-a-day dosing solution (0.2 mg/ml) in the dog. Significant esophageal irritation (ulceration/erosion) was observed with 7.47 mg/ml given once weekly for four weeks, however this represents a significantly higher exposure multiple (17X) compared to the proposed MRHD (70 mg). Lower doses tested in the dog model (3.73 and 0.93 mg/ml) did not show significant irritation which represents exposures ≤10X the MRHD.

B. Pharmacologic Activity: alendronate is a bisphosphonate which acts as a specific inhibitor of osteoclast mediated bone resorption.

C. Nonclinical Safety Issues Relevant to Clinical Use: none

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. **PHARMACOLOGY:** See NDA 20-560 S021/S022 efficacy supplement review for once weekly dosing

Primary pharmacodynamics: Alendronate is a bisphosphonate which acts as specific inhibitors of osteoclast mediated bone resorption.

III. **SAFETY PHARMACOLOGY:** See NDA 20-560 review

III. PHARMACOKINETICS/TOXICOKINETICS: See NDA 20-560 review (9/1/95) and efficacy supplement S021/S022 from 9/22/00

IV. GENERAL TOXICOLOGY: See NDA 20-560 review (9/1/95) and efficacy supplement S021/S022 from 9/22/00

V. GENETIC TOXICOLOGY: See NDA 20-560 review (9/1/95) and efficacy supplement S021/S022 from 9/22/00

VI. CARCINOGENICITY: See NDA 20-560 review (9/1/95)

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY: See NDA 20-560 review (9/1/95)

VIII. **SPECIAL TOXICOLOGY STUDIES:** See NDA 20-560 review (9/1/95) and efficacy supplement S021/S022 from 9/22/00

Single Dose Esophageal Irritation Study in Dogs (TT#00-048-1)
GLP/QA report in 2/sex/group dogs aged 54-62 weeks following a single dose of 0.93 mg/ml oral ——— formulation (———) of alendronate (50 ml for 30 min. infusion) or vehicle control. Physical exam, body weight, necrospy and esophageal histopathology were performed on the day following dosing. The incidence of minimal lymphoid cellular infiltration in the esophagus was ¼ vehicle controls and ¾ dogs given alendronate.

5-Week (Single Weekly Dose) Esophageal Irritation Study in Dogs (TT #00-048-0)

Key study findings: In dogs given once weekly gavage dosing of alendronate (—) 0.93 mg/ml (50 ml), ¼ had slight esophageal submucosal lymphoid hyperplasia.

Volume #, and page #: 1.2 pg.Q-31
Conducting laboratory/location: Merck Institute for Therapeutic Research; West Point, PA
Date of study initiation: 7/6/2000
GLP compliance: yes

QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: not specified
Formulation/vehicle: oral ——— formulation ——— containing sodium citrate dihydrate, citric acid, sodium propyl hydroxybenzoate, sodium butylhydroxybenzoate, saccharin, sodium, raspberry flavor and water; pH —

Methods:
Dosing:

Species/strain: beagle
#/sex/group or time point (main study): 2/sex/group
Satellite groups used for toxicokinetics or recovery: N/A
Age: 40-61 weeks at initiation
Weight: 7.4-12.4 kg
Doses in administered units: 0, 0.93 mg/ml; 50 ml for 30 min. infusion or 46.5 mg/dog given once weekly for 5 weeks
Route, form, volume, and infusion rate: oral gavage, 50 ml over 30 minutes

Observations and times: timing of observations was not specified except necropsy 1 week post last dose.

Procedures Performed	Yes	No	Procedures Performed	Yes	No
Physical examinations	✓		Ophthalmology		✓
Body weights	✓		Electrocardiogram		✓
Food consumption	✓		Organ weights		✓
Water consumption		✓	Necropsy	✓	
Hematology		✓	Histology[a]	✓	
Clinical chemistry		✓	Toxicokinetics		✓
Urinalysis		✓			

[a] Histological examination was limited to the esophagus on all animals.

Animals were dosed under thiopental sodium (2.5%), and maintained throughout the procedure using isoflurane gas with an in place endotracheal tube.

Results:

Mortality: none
Clinical signs: none
Body weights: unremarkable
Food consumption: unremarkable
Ophthalmoscopy: N/A
Electrocardiography: N/A
Hematology: N/A
Clinical chemistry: N/A
Urinalysis: N/A
Organ weights: esophagus is unremarkable

Gross pathology: esophagus is unremarkable

Histopathology:Esophagus	Vehicle	Alendronate 0.93 mg/ml

Lymphoid cell infiltration	¾ (minimal)	¾ (minimal)
Submucosa lymphoid hyperplasia	--	¼ (slight)

Individual animal data is not provided, data from both genders has been combined.
Toxicokinetics: N/A

Summary of individual study findings: In dogs given once weekly gavage dosing of alendronate ——, 0.93 mg/ml (50 ml), ¼ had slight esophageal submucosal lymphoid hyperplasia compared to vehicle which was without incidence. Both vehicle and alendronate treatment resulted in minimal esophageal lymphoid cellular infiltration in ¾ dogs. The sponsor concludes that the alendronate —is not irritating to the esophageal mucosa of dogs.

Single-Dose Esophageal Irritation Study in Dogs (TT #01-053-0)

GLP/QA report in 2/sex/group dogs aged 33-76 weeks following a single dose of 3.73 mg/ml or 7.47 mg/ml oral ——— formulation (—; pH 6.8) of alendronate (50 ml for 30 min. infusion) or vehicle control. Physical exam, body weight, necropsy and esophageal histopathology were performed one day following dosing. The necropsy/histopathology findings were unremarkable in contrast to study TT #00-048-1 where the incidence of minimal lymphoid cellular infiltration in the esophagus was ¼ vehicle controls and ¾ dogs given alendronate at a lower dose of 0.93 mg/ml. The sponsor concludes that alendronate is not irritating to the esophageal mucosa of dogs.

5-Week (Once Weekly Dosing) Esophageal Irritation Study in Dogs

Key study findings:

- **Alendronate —given once weekly by gavage for 4 weeks at 3.73 mg/ml is not irritating to the esophageal mucosa of dogs**
- **Alendronate —given once weekly by gavage for 4 weeks at 7.47 mg/ml resulted in erosive (slight) or ulcerative (moderate) esophagitis in all treated dogs**

Study no: TT #01-048-0
Volume #, and page #: 1.2; Q-72
Conducting laboratory/location: Merck Institute for Therapeutic Research; West Point, PA
Date of study initiation: 7/6/2000
GLP compliance: yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: not specified
Formulation/vehicle: oral ——— formulation ——, containing sodium citrate dihydrate, citric acid, sodium propyl hydroxybenzoate, sodium butylhydroxybenzoate, saccharin sodium raspberry flavor and water; pH —

Methods:

Dosing:

Species/strain: beagle
#/sex/group or time point (main study): 2/sex/group
Satellite groups used for toxicokinetics or recovery: N/A
Age: 39-70 weeks at initiation
Weight: 7.2-13.3 kg
Doses in administered units: 0, 3.73, 7.47 mg/ml; 50 ml for 30 min. infusion or 46.5 mg/dog given once weekly for 5 weeks
Route, form, volume, and infusion rate: oral gavage, 50 ml over 30 minutes

Observations and times: timing of observations was not specified except necropsy 1 week post last dose.

Procedures Performed	Yes	No	Procedures Performed	Yes	No
Physical examinations	✓		Ophthalmology		✓
Body weights	✓		Electrocardiogram		✓
Food consumption	✓		Organ weights		✓
Water consumption		✓	Necropsy	✓	
Hematology		✓	Histology[a]	✓	
Clinical chemistry		✓	Toxicokinetics		✓
Urinalysis		✓			

[a] Histological examination was limited to the esophagus on all animals.

Animals were dosed under thiopental sodium (2.5%), and maintained throughout the procedure using isoflurane gas, with an in place endotracheal tube.

Results:

Mortality: none

Clinical signs: emesis was seen in some drug-treated dogs during recovery from anesthesia, the sponsor does not consider this to be drug-related

Body weights: unremarkable

Food consumption: unremarkable

Ophthalmoscopy: N/A

Electrocardiography: N/A

Hematology: N/A

Clinical chemistry: N/A

Urinalysis: N/A

Organ weights: N/A

Gross pathology: esophageal irritation at 7.47 mg/ml consisting of focal reddening of the distal esophageal mucosa

Histopathology esophagus	Vehicle	3.73 mg/ml	7.47 mg/ml
Erosive esophagitis			2/4 min-slight
Ulcerative esophagitis			2/4 moderate

Necropsy followed one week post dose

Toxicokinetics: N/A

Summary of individual study findings:

Oral ——— formulation of alendronate at 3.73 mg/ml was not irritating to the esophagus of dogs when given once weekly for 4 weeks by gavage. However higher doses (7.47 mg/ml) resulted in minimal to slight erosive or moderate ulcerative esophagitis in treated dogs, one week following weekly exposure for 4 weeks.

Toxicology summary:

Nonclinical Toxicology Summary - List of Studies

Type of Study	Study No. [Reference No.]†	Species/ Sex	Route	Duration of Treatment	Dose
Single Dose	TT #00-048-1 [H-1]	Dog/ F & M	Esophageal	1 day	50 mL of 0.93 mg/mL
Multiple Dose	TT #00-048-0 [H-2]	Dog/ F & M	Esophageal	4 weeks 1 dose/week	50 mL of 0.93 mg/mL
Single Dose	TT #01-053-0 [H-3]	Dog/ F & M	Esophageal	1 day	50 mL of 3.73 mg/mL or 7.47 mg/mL
Multiple Dose	TT #01-048-0 [H-4]	Dog/ F & M	Esophageal	4 weeks 1 dose/week	50 mL of 3.73 mg/mL or 7.47 mg/mL

† [ ] All studies listed in the Table of Investigations will be found in Nonclinical Pharmacology and Toxicology Documentation, References.
M = Male.
F = Female.
[H-1 to H-4]

The dog was selected since there was a considerable amount of safety data available in that species. Esophageal mucosa were exposed for 30 minutes in a single daily dose or once weekly for 4 weeks to assess the local irritation potential of alendronate ——. Beagle dogs were immobilized under general anesthesia induced by thiopental sodium and thereafter an endotracheal tube was placed. Anesthesia was maintained using isoflurane gas. Dogs were placed in a 30^0 incline with their head elevated. A total of 50 ml was infused using an infusion pump. The irritation potential was evaluated by gross and histopathology of the esophagus.

Earlier studies showed no evidence of esophageal irritation in dogs, infused (50 ml) once a week for 4 weeks with 0.8 mg/ml of alendronate at pH 2. This was in contrast to animals dosed daily at a lower concentration (0.2 mg/ml). A once weekly dosing regimen provides an adequate interval between doses to avert esophageal irritation seen with daily dosing. Studies using a single dose of an oral ——— formulation (pH 6.8) at concentrations ranging from 0.93-7.47 mg/ml; concentrations corresponding to 1-8 times the intended clinical dose was not irritating to the esophageal mucosa. Weekly infusion for one month of the same formulation at 0.93-3.73 mg/ml resulted in no adverse effects on esophageal histomorphology. Increasing the concentration to 7.47 mg/ml resulted in erosive/ulcerative esophagitis. These studies support the earlier findings that the irritation potential of alendroante is dependent on dose, pH, concentration and dosing frequency.

Toxicology conclusions: The sponsor submitted a publication (Digestive Diseases and Sciences 1998; 43(9):1998-2002 Peter CP, Handt LK, Smith SM; Esophageal irritation due to alendronate sodium tablets: possible mechanisms) which suggest that multiple factors contribute to the development of clinical esophagitis including prolonged contact of the tablet with the mucosa, reflux of acidic gastric contents containing alendronate and preexisting esophageal damage from a low pH environment (gastric reflux damage). Under acid conditions (pH <3) alendronate exists in the free acid form (>67%) which is more irritating than the sodium salt form. It has been suggested that an excipient within the tablet may lead to local dehydration and irritation conditions when transit time of the tablet has been reduced for various reasons. The sponsor suggests that most of the clinical cases of esophagitis are associated with deviations from proper dosing. Irritation can be minimized by proper dosing and avoidance of conditions known to exacerbate gastric acid reflux. The development of an oral [redacted] formulation of alendronate (70 mg) is designed to avoid these complications and is according to Merck bioequivalent to the 70 mg tablet. Alendronate [redacted] was evaluated in dogs using once weekly oral gavage dosing with a 30 minute infusion under anesthesia at various doses. Significant esophageal irritation (ulceration/erosion) was observed with 7.47 mg/ml repeated dose which represents a significantly higher exposure multiple (17X) compared to the proposed MRHD (70 mg). Lower doses tested in the dog model (3.73 and 0.93 mg/ml) did not show significant irritation.

Weekly Dose (Mg/ml)	Weekly Dose (mg/kg)*	Weekly Dose (mg/M^2)	Exposure Multiple#	Esophagitis
0.93	4.65	93	2X	-
3.73	18.65	373	9X	-
7.47	37.35	747	17X	Minimal-slight erosive 2/4 Moderate ulcerative 2/4

*dog body weight=10 kg; # exposure multiple based on MRHD=70 mg/60 kg or 43 mg/M^2

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: see Toxicology Conclusions

General Toxicology Issues: none

Recommendations: Approval (AP)

Labeling with basis for findings: revisions to the currently approved product label are not needed at this time based on the new Pharmacology/Toxicology information in this submission.

X. APPENDIX/ATTACHMENTS:

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/s/

Karen Davis-Bruno.
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PHARMACOLOGIST

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