CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-575

MEDICAL REVIEW

CLINICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: N21-575
Sponsor: Merck

Pharmaceutical Category: Bisphosphonate
Indication: Treatment of postmenopausal osteoporosis and treatment to increase bone mass in men with osteoporosis
Reviewer: Theresa Kehoe, MD

Application Type:
Proprietary Name: Fosamax
Route of Administration: Oral ——— Solution
Dosage: 70mg / 75mL once weekly

Date Review Completed: August 21, 2003

Chemistry Reviewer: Elsbeth Chikhale, Ph.D.
Pharmacology Reviewer: Karen Davis-Bruno, Ph.D.
Biopharmaceutics Reviewer: S.W. Johnny Lau, Ph.D.
Statistical Reviewer: N/A

REVIEW SUMMARY: This application is submitted as a supplemental new drug application documenting the clinical bioavailability, bioequivalence and safety of the 70mg/75mL alendronate oral ——— solution compared to the 70mg once weekly tablet of alendronate. This program consisted of 4 clinical pharmacology studies: 2 bioavailability studies using a 70-mg/75-mL oral ———solution, 1 pivotal bioequivalence study, and an earlier pilot bioavailability study using multiple 10-mg dose formulations. The 70 mg alendronate/75 mL oral solution was equally bioavailable to the 70 mg alendronate oral tablet. However, the maximum alendronate urinary excretion rate could not be reliably assessed due to the long sampling interval used (i.e., 8 hours). No new clinical efficacy data are presented. A safety review of data from the clinical pharmacology studies was performed. A total of 157 subjects received at least one dose of alendronate during the conduct of the three trials that utilized alendronate doses of at least 35mg. When compared with the 70mg tablet, there were similar patterns of adverse events reported with the oral solution. In the one trial that utilized a placebo group, gastrointestinal adverse events were higher in the alendronate groups compared with placebo. This finding is consistent with prior alendronate trials. Overall, adverse events including gastrointestinal events did not appear to increase in frequency with the escalating doses (up to 375mg) of alendronate ——— solution. Based on the safety data evaluation, this reviewer recommends approval of the weekly 70mg oral alendronate ———solution.

OUTSTANDING ISSUE: none

RECOMMENDED REGULATORY ACTION:

N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**
NDA, Efficacy/Label supplement: _____ **Approvable** _____ **Not Approvable**
Approve

SIGNATURES: **Medical Reviewer:** Theresa Kehoe, M.D. **Date:** _____.

Medical Team Leader: Eric Colman, M.D. **Date:** _____.

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Clinical Review for NDA 21-575

Executive Summary

I. Recommendations

A. Recommendation on Approvability: APPROVE

B. Recommendation on Phase 4 Studies and/or Risk Management Steps: None

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program: This application is submitted as a supplemental new drug application documenting the clinical bioavailability, bioequivalence and safety of the 70mg/75mL alendronate oral ——— solution compared to the 70mg once weekly tablet of alendronate. This program consisted of 4 clinical pharmacology studies: 2 bioavailability studies [P163; P204] using a 70-mg/75-mL oral ——— solution, 1 bioequivalence study [P177], and an earlier bioavailability pilot study [P110] using multiple 10-mg dose formulations. The 10mg pilot study provided the basis for the development of the 70-mg oral ——— solution. Daily alendronate was initially approved for treatment of postmenopausal osteoporosis in August, 1995 (NDA 20-560). Once weekly alendronate was approved for the treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis in October 2000, based on BMD comparability studies. This new formulation was developed to provide an alternative for individuals who have difficulty swallowing a tablet or prefer a solution.

B. Efficacy: The focus of this application is on the bioavailability and bioequivalence of the 70-mg alendronate oral ——— solution compared to the 70-mg marketed tablet. No new clinical efficacy data are presented.

C. Safety: A total of 157 subjects received at least one dose of alendronate solution during the conduct of the three bioavailability and bioequivalence trials that utilized alendronate doses of at least 35mg. When compared with the 70mg tablet, there were similar patterns of adverse events reported. In the one trial that included a placebo group (trial 204), gastrointestinal adverse events were higher in the alendronate oral ——— solution groups (placebo - 1 event, 70mg – 8 events, 140mg – 3 events, 280mg – 3 events, 375mg – 5 events). This finding is

consistent with prior alendronate trials. Overall, adverse events including gastrointestinal events did not appear to increase in frequency with the escalating doses (up to 375mg) of alendronate ——— solution.

D. Dosing: No dosing adjustment is needed for the oral ——— solution.

E. Special Populations: Postmenopausal osteoporosis and male osteoporosis are diseases of predominantly older individuals. This age predominance is appropriately reflected in the populations of the studies reviewed. The gender distribution of the study participants is appropriate. The ethnic composition of the study population is diverse. ———

Clinical Review

I. Introduction and Background

I.A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups: Merck Research Laboratories, Inc. has submitted this new drug application for alendronate sodium [(4-amino-1- hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate] oral ——— solution, trade name Fosamax. Alendronate is a member of the bisphosphonate class of medications. Merck proposes to market this new formulation, a once weekly oral ——— solution, as an alternative for those individuals who have difficulty swallowing a tablet or prefer a solution.

I.B. State of Armamentarium for Indication(s): In addition to alendronate sodium, other medications currently approved for the treatment of postmenopausal osteoporosis include the bisphosphonates risedronate sodium (Actonel) and ibandronate sodium (Boniva) as well as raloxifene hydrochloride (Evista), salmon calcitonin (Miacalcin nasal spray) and teriparatide acetate (Forteo).

I.C. Important Milestones in Product Development: The alendronate oral ——— solution development program consists of 4 esophageal irritation studies in dogs and 4 clinical pharmacology studies: 2 bioavailability studies [P163; P204] using a 70-mg/75-mL oral ——— solution, 1 pivotal bioequivalence study [P177], and one pilot bioavailability study [P110] using several 10-mg dose formulations.

I.D. Other Relevant Information: Alendronate sodium 10mg daily was initially approved for the treatment of postmenopausal osteoporosis in September, 1995 (NDA 20-560). Other indications subsequently approved include the prevention of osteoporosis in postmenopausal women (5mg daily dose) in April 1997, the treatment of glucocorticoid-induced osteoporosis in women (5mg daily or 10mg daily for postmenopausal women not on estrogen) and men (5mg daily) receiving glucocorticoids in June 1999 and to increase bone mass in men with osteoporosis in September of 2000. A once weekly tablet formulation (35mg for prevention

of postmenopausal osteoporosis and 70mg for treatment of postmenopausal osteoporosis and to increase bone mass in men with osteoporosis) was approved in October 2000.

I.E. Important Issues with Pharmacologically Related Agents: Bisphosphonate are used in the prevention and treatment of postmenopausal and corticosteroid-induced osteoporosis, Paget's disease, hypercalcemia of malignancy, and bony metastases. Safety concerns with oral bisphosphonates include esophageal and gastric irritation and ulceration. Recently the Division has raised concern regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug. The Division is currently discussing these issues with the various bisphosphonate manufacturers.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

II.A. Chemistry: Please see Dr. Chikhale's review for complete details.

II.B. Animal Pharmacology and Toxicology: Please see Dr. Davis-Bruno's review for complete details. In addition to the toxicity studies previously submitted under NDA 20-560, four esophageal irritation studies with a once weekly oral ——— alendronate formulation have been submitted with this NDA. Daily exposure to an alendronate solution (0.2 mg/ml) resulted in esophageal irritation in dogs. Exposure to once weekly alendronate 0.8 mg/ml, for one month was not irritating to the esophageal mucosa of dogs. Increasing the alendronate concentration to 3.73mg/ml resulted in no evidence of esophageal irritation in the dog. This suggests that weekly dosing of an oral ——— formulation ——— is not irritating to the esophagus in the dog. Significant esophageal irritation did occur with once weekly alendronate at a significantly higher exposure multiple (17X) compared to the proposed MRHD (70 mg). The lower doses tested (3.73 and 0.93 mg/ml) did not show significant irritation (exposures ≤ 10X the MRHD).

III. Human Pharmacokinetics and Pharmacodynamics

III.A. Pharmacokinetics: Please see Dr. Lau's review for complete details. Study P177 is the pivotal bioequivalence study submitted with this NDA. The geometric mean ratio for the cumulative alendronate urinary excretion of the 70 mg solution to the 70 mg tablet was 0.99 (90% CI 0.90, 1.10) (95% CI 0.88, 1.12). Based on these observations, the 70 mg alendronate/75 mL oral solution is equally bioavailable to the 70 mg alendronate oral tablet. The tested solution formulation in Study P177 was identical to the to-be-marketed solution formulation.

Study P204 was conducted to examine the single dose tolerability and dose linearity of alendronate oral ——— solution over a dose range of 70 mg to 375 mg. The cumulative alendronate urinary excretion 36 hours post-dose was determined upon administration at each of the 4 doses: 70 mg/75 mL, 140 mg/75 mL, 280 mg/75 mL, and 375 mg/100 mL. Dose linearity

does not exist between 70 mg and 375 mg alendronate doses. However, dose linearity appears to exist between 140 and 375 mg alendronate doses.

IV. Description of Clinical Data and Sources

IV.A. Overall Data: The focus of this application is on the bioavailability and bioequivalence of the 70-mg alendronate oral [redacted] solution to the 70-mg marketed tablet. No new clinical efficacy data were submitted. The safety data presented are from these bioavailability and bioequivalence studies.

IV.B. Tables Listing the Clinical Trials

NDA 21-575 Clinical Studies			
Study		**N**	**Dose/formulation**
P177*	An Open-Label, Randomized, 2-Stage, 3-Period, Crossover Study to Evaluate the Bioequivalence of 35-mg and 70-mg Oral [redacted] Alendronate Solutions to a 70-mg Alendronate Tablet in Healthy Adult Subjects	115	70mg tab, 70mg [redacted] solution
P110	An Open, Randomized, 5-Period, Crossover Study in Healthy Subjects to Determine the Bioavailability of Alternative Alendronate Oral Formulations Relative to the Marketed Tablet	21	10mg tab, 10mg effervescent tab, 3 different 10mg [redacted] solutions
P163	An Open Label, Randomized, 3-Period, Crossover Pilot Study to Examine the Relative Bioavailability of an Oral [redacted] Alendronate Solution in Healthy Adult Subjects	12	70mg tab, 35mg [redacted] solution, 70mg [redacted] solution
P204	A 5-Period, Partially-Blinded, Placebo-Controlled, Single-Rising-Dose Study to Measure the Safety, Tolerability, and Dose- Proportionality of Alendronate Oral Solution in Healthy Volunteers	30	[redacted] solutions -70mg, 140mg, 280mg, 375mg
* definitive bioequivalence study			

IV.C. Postmarketing Experience: The oral [redacted] solution formulation of alendronate is not approved in any country. Alendronate has been marketed in more than 90 countries and it is estimated that as of June 2002, the cumulative patient-years of experience exceeded 12.5 million.

IV.D. Literature Review: A MEDLINE review was conducted for alendronate. No articles relating to the oral buffered solution were found.

V. Clinical Review Methods

V.A. How the Review was Conducted: All bioavailability and bioequivalence studies were evaluated for safety. This review concentrates on the three studies (Protocols 163, 177, and 204) that used the higher doses and the final formulation of the alendronate oral [redacted] solution.

V.B. Overview of Materials Consulted in Review: The information reviewed was provided in an electronic format.

V.C. Overview of Methods Used to Evaluate Data Quality and Integrity: The Division of Scientific Investigation (DSI) was not consulted for this NDA.

V.D. Were Trials Conducted in Accordance with Accepted Ethical Standards: All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

V.E. Evaluation of Financial Disclosure: Financial disclosure information was provided by the sponsor and reviewed by this Reviewer. A total of 18 investigators/subinvestigators participated in the four studies submitted. Four investigators were no longer at the site of record and no information was obtained. There were no disclosures of financial interests noted.

VI. Integrated Review of Efficacy :

VI.A. Brief Statement of Conclusions: No new efficacy data were submitted. The primary objective of these studies was to determine the bioavailability and bioequivalence of the new formulation. A brief discussion of study results can be found in the Human Pharmacokinetics section of this review. For a full assessment of these studies, please see Dr. Lau's review.

VII. Integrated Review of Safety

VII.A. Brief Statement of Conclusions: A total of 157 subjects received at least one dose of alendronate oral ——— solution during the conduct of the three bioavailability and bioequivalence trials that utilized alendronate doses of at least 35mg. When compared with the 70mg tablet, there were similar patterns of adverse events reported for the alendronate solution. In the one trial that utilized a placebo group (trial 204), gastrointestinal adverse events were higher in the alendronate groups compared with placebo. The largest number of gastrointestinal events occurred in the 70mg group, which was the lowest dose used in the trial. Overall, adverse events, including GI tolerability, did not appear to increase in frequency with the escalating doses (up to 375mg) of alendronate ——— solution.

VII.B. Description of Patient Exposure: The formulation of alendronate oral ——— solution used in Protocols 163, 177, and 204, with doses of 35 to 375 mg, was similar and represents the final to-be-marketed formulation. In these studies, all participants received a single dose of alendronate in each period for up to 5 periods. These were crossover studies and the same subjects received more than one treatment. A washout of 7 to 14 days separated the doses. Patient disposition from the three studies combined is shown in the following table.

Patient Disposition: Combined Trials P163, P177, P204

	Tablet		Oral [redacted] Solution				
	70mg	35mg	70mg	140mg	280mg	375mg	Placebo
Single Dose Treatment	N	N	N	N	N	N	N
Randomized	127	127	157	30	30	30	30
Received Dose	123	120	152	27	25	25	25
Total Discontinuations	3	2	7	2	0	0	0
Discontinuations due to AE	1	0	1	0	0	0	0
Discontinuations - other	2	2	6	2	0	0	0

† Since these were crossover studies, the same subjects received more than one treatment.

VII.C. Methods and Specific Findings of Safety Review: The formulation of alendronate oral [redacted] solution used in Protocols 163, 177, and 204 was the final formulation. The design of Protocols 163, 177, and 204 were similar. Results were reviewed and are discussed below.

VII.C..1. Study 177: An Open-Label, Randomized, 2-Stage, 3-Period, Crossover Study to Evaluate the Bioequivalence of 35-mg and 70-mg Oral [redacted] Alendronate Solutions to a 70-mg Alendronate Tablet in Healthy Adult Subjects. Study 177 was a single center, open, randomized, 3-period, 2-stage, balanced, crossover study in 115 (55 men, 60 women) healthy adult subjects aged 18 – 79 years. The primary objective was to demonstrate bioequivalence of the 70-mg oral [redacted] solution and the 70-mg tablet and a secondary objective to demonstrate bioequivalence for the 35-mg oral [redacted] solution and the 70-mg tablet. Subjects received 3 single doses of alendronate: a 70-mg tablet, a 70-mg oral [redacted] solution, and a 35-mg oral [redacted] solution. Subjects were excluded from participation if they had a history of major gastrointestinal disease within the past year, had abnormalities of the esophagus or stomach which could delay emptying, had dyspepsia or other symptoms that required prescription anti-peptic medication, or were a regular user of any medication that had the potential for gastrointestinal irritation. Safety parameters assessed pre-study included physical examination, 12-lead electrocardiogram (ECG), vital signs and laboratory safety measurements (hematology/blood chemistry/urinalysis). Serum β hCG was measured pre and post study and a urine β hCG was assessed prior to each dosing period in women of child bearing age. A repeat 12-lead electrocardiogram was performed post study. Adverse experience reporting was continuous throughout the study.

Demographics: Of the 115 participants who were randomized, 48% were men (mean 36 years, range 18 – 79 years) and 52% women (mean 40 years, range 18 – 77 years). The racial/ethnic makeup of the study population was diverse: 66% Caucasian, 29% Black, 3% Hispanic and 2% Native American.

Exposure: Two subjects withdrew after receiving 2 doses of alendronate (each received the 70mg tablet in Period 1 and the 70mg solution in Period 2). Seven subjects withdrew after one dose of alendronate (3 received the 70mg tablet, 2 received the 70mg solution and 2 received the 35mg solution).

Deaths: No deaths occurred in the study population.

Serious Adverse Events: A serious adverse experience was reported in 1 subject. This individual suffered from flu-like symptoms several hours after receiving the alendronate 70-mg tablet. The symptoms progressed, and the subject received a diagnosis of viral gastroenteritis the next day. This subject was discontinued from the study.

Adverse Events Leading to Withdrawal: One subject, discussed above withdrew due to adverse events after receiving the 70mg tablet. One subject developed hives 4 days after receiving the 70mg ——— solution during Period 2 (this individual had received the 70mg tablet in Period 1). After appropriate medical intervention, the hives resolved and the patient was withdrawn from the study.

Medical Officer Comment: It is likely that this was an allergic reaction to alendronate. Hypersensitivity reactions, including urticaria and rarely angioedema, have been previously reported with oral alendronate (tablet formulation).

Adverse Events: A total of 247 adverse events were reported across all treatment groups (see Table below). The most common adverse events occurred in the following systems: nervous (79 events), digestive (53 events) and body as a whole (46 events). The most common adverse event was headache (77 of the 79 nervous system events) which was evenly distributed among the treatment groups.

Trial 177: Number of Adverse Events, by body system

	Total	70mg tablet	70mg solution	35mg solution	Other*
Subjects Receiving Dose		111	108	110	
Events:					
Body as a whole	46	18	11	14	3
Musculoskeletal	22	11	4	4	3
Nervous	79	21	19	26	13
Digestive	53	19	18	15	1
Respiratory	7	0	1	6	0
Skin and Appendages	5	2	3	0	0
Special Senses	32	9	6	14	3
Urogenital	3	0	1	1	1
Total Events	247	80	63	80	24

* all adverse events reported as prestudy, predose or post study

Gastrointestinal and Other Adverse Events of Special Interest: The most common gastrointestinal adverse events were nausea (19 events) and diarrhea (10 events). These events were evenly distributed among the treatment groups. Other adverse events of special interest include ocular symptoms. There were a total of 3 reports of ophthalmic burning and pain, all in the 35mg ——— solution group. All episodes resolved and did not recur with further dosing.

Laboratory: There were no post dose laboratory studies obtained in this study.

Medical Officer Conclusions: In general, adverse events were evenly distributed among all dose groups. Compared with the tablet, there was no increase in GI adverse events with the oral ——— solution.

VII.C..2. Study 163: An Open Label, Randomized, 3-Period, Crossover Pilot Study to Examine the Relative Bioavailability of an Oral ——— Alendronate Solution in Healthy Adult Subjects. Study 163 was a pilot study that sought to estimate the oral bioavailability of the 35-mg and 70-mg oral ——— solution relative to the 70-mg alendronate marketed tablet. This study was an open-label, randomized, 3-period, balanced, crossover study in 12 healthy adults age 18 to 85 years, including at least 4 of each gender. In each treatment period, subjects received a single dose of alendronate given as a 70-mg tablet, a 35- mg oral ——— solution, or a 70-mg oral ——— solution. A 13-day washout separated each dose. The primary objective was to examine the bioequivalence of the 70-mg oral ——— solution compared with the 70-mg marketed tablet and a secondary objective to examine the bioequivalence of the 35-mg oral ——— solution compared with the 70-mg tablet. Subjects were excluded from participation if they had a history of major gastrointestinal disease within the past year, had abnormalities of the esophagus or stomach which could delay emptying, had dyspepsia or other symptoms that required prescription anti-peptic medication, or were a regular user of any medication that had the potential for gastrointestinal irritation. Safety parameters were assessed throughout the study by physical examination, 12-lead electrocardiogram (ECG), vital signs, laboratory safety measurements (hematology/blood chemistry/urinalysis), and adverse experience reporting.

Demographics: Of the 12 participants who were randomized, seven were men (mean 56 years, range 35 – 73 years) and five were women (mean 42 years, range 30 – 62 years). Seven subjects (58%) were caucasian and 5 (42%) subjects were black. All subjects completed the study.

Exposure: All subjects completed the study and received a single oral dose of 35mg oral buffered solution, 70 mg oral ——— solution and 70mg tablet with a 13 day washout period between doses.

Deaths and Serious Adverse Events: There were no deaths or serious adverse events in this study.

Adverse Events Leading to Withdrawal: No subject withdrew from the study due to adverse events.

Adverse Events: Five subjects reported a total of 13 adverse events during the study. The most common event was headache (5 events), followed by abdominal pain (2 events). By dose group, two events occurred in the 35mg solution group, four events occurred in the 70mg solution group and seven events occurred in the 70mg tablet group.

Laboratory: There were no trends or adverse experiences in the laboratories of any subject.

Medical Officer Conclusions: Adverse events were equally distributed among all dose groups with the highest number of events occurring in the 70mg tablet group. There was no increase in GI adverse events with the oral ——— solution.

VII.C. 3. Study 204: A 5-Period, Partially-Blinded, Placebo-Controlled, Single-Rising-Dose Study to Measure the Safety, Tolerability, and Dose- Proportionality of Alendronate Oral Solution in Healthy Volunteers. Study 204 was conducted to examine the single dose safety and tolerability and dose proportionality of higher doses (up to 375 mg) of alendronate oral ——— solution. This study was a single center, 5-period, partially-blinded, placebo-controlled, single-rising-dose study in 25 healthy nonpregnant women and men age 18 to 65 years. Subjects received alendronate oral ——— solution in 4 periods and placebo in 1 period. In each period, 20 subjects received the active drug (at doses of 70 mg/75 mL, 140 mg/75 mL, 280 mg/75 mL, and 375 mg/100 mL oral ——— solution) and 5 subjects received placebo. At least a 2-week washout separated each period. The objective of the study was to determine the safety and tolerability of alendronate oral ——— solution at doses up to 375 mg and to examine the relative urinary excretion of alendronate following oral doses of 70, 140, 280, and 375 mg administered as an oral solution. Subjects were excluded from participation if they had a history of major gastrointestinal disease within the past year, had abnormalities of the esophagus or stomach which could delay emptying, had dyspepsia or other symptoms that required prescription anti-peptic medication, or were a regular user of any medication that had the potential for gastrointestinal irritation. Safety parameters were assessed throughout the study by physical examination, 12-lead electrocardiogram (ECG), vital signs, laboratory safety measurements (hematology/blood chemistry/urinalysis), and adverse experience reporting.

Demographics: Of the 30 enrolled subjects, 13 were men (mean 41 years, range 23 – 65 years) and 17 were women (mean 38 years, range 20 – 59years). The ethnic makeup of the study population was diverse: 67% Caucasian, 17% Black, 10% Hispanic, 3% Asian and 3% Native American.

Trial 204: Disposition, by dose group

	70mg	140mg	280mg	375mg	Placebo
	N (%)	N (%)	N (%)	N (%)	N (%)
Enrolled	30	27	25	25	25
One or more AE	13 (43.3)	8 (29.6)	9 (36.0)	9 (36.0)	6 (24.0)
Discontinued due to AE	0	0	0	0	0

Exposure: As shown in the table above, a total of 30 subjects were enrolled in the study, 5 (3 subjects received one dose of study drug and 2 subjects received two doses of study drug prior to discontinuation) of the original 25 subjects withdrew prematurely and were replaced. One subject was noted to have a positive pregnancy test at the post study evaluation.

Deaths and Serious Adverse Events: There were no deaths or serious adverse events in this study. One subject reported her pregnancy 31 days after the last dose of study drug and elected to terminate the pregnancy.

Adverse Events Leading to Withdrawal: No subject withdrew from the study due to adverse events.

Adverse Events: Ninety three adverse events were reported across all treatment groups (see Table below). The most common adverse events occurred in the following systems: body as a whole (21 events), digestive (20 events), nervous (18 events), and musculoskeletal (15 events). The largest number of events occurred in the 70mg group. There was no escalation in the number of events with increasing dose.

Trial 204: Number of Adverse Events, by body system						
	Total	70mg	140mg	280mg	375mg	Placebo
Subjects Enrolled	30	30	27	25	25	25
Events:						
Body as a whole	21	13	0	2	4	2
Musculoskeletal	15	10	1	1	2	1
Nervous	18	5	3	5	5	0
Digestive	20	8	3	3	5	1
Respiratory	2	0	0	0	0	2
Skin and Appendages	5	3	0	1	0	1
Special Senses	9	1	4	0	3	1
Urogenital	3	0	1	1	1	0

Gastrointestinal Adverse Events: Gastrointestinal adverse events were higher in the alendronate groups compared with placebo with the largest number of events occurring in the 70mg group.

Laboratory: There were no trends or adverse experiences in the laboratories of any subject. There was no decrease in serum calcium levels 24 and 48 hours post dose.

Medical Officer Conclusions: Adverse events, including GI intolerability, did not appear to increase in frequency with increasing doses of the oral alendronate solution.

VII.D. Adequacy of Safety Testing: The safety monitoring conducted during these bioavailability and bioequivalence trials appears to have been adequate.

VII.E. Summary of Critical Safety Findings and Limitations of Data: Most of the safety data are from the crossover trials using active study drug formulations. There is a paucity of placebo data to aid in this safety evaluation. Headache was a commonly reported adverse event. In study 204, 17 of the 18 nervous system adverse events were due to headache. All occurred in alendronate treated groups (0 events in the placebo group, 5 events in the 70mg alendronate group, 3 events in the 140mg alendronate group, 5 events in the 280mg alendronate group, and 4 events in the 375mg alendronate group). In study 177, 77 of the 79 nervous system events were headache. These events were equally distributed among the alendronate dose regimens. In prior alendronate studies, headache was also reported as an adverse event with equal distribution between placebo and active treatment groups. There were no unexpected safety findings uncovered during the review of this submission.

VIII. Dosing, Regimen, and Administration Issues

Alendronate 70mg weekly is currently available in a tablet formulation. This current submission proposes the same dosing regimen utilizing a new formulation – a ——— oral solution rather than a tablet. No significant safety issues were raised by the submitted data.

IX. Use in Special Populations

IX.A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation: Alendronate is currently approved for therapy in both men and women. The three submitted trials reviewed have enrolled 48% men and 52% women. No analyses of gender effects has been done in these studies evaluating bioequivalence.

IX.B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy: Alendronate is currently approved for treatment and prevention of postmenopausal osteoporosis and to increase bone mass in men with osteoporosis. The age range of study participants was 18 – 79 years. No specific age analyses have been done with this submission. Age analyses have previously been conducted for alendronate under NDA 20-560. The racial composition of the study populations was diverse: 66% Caucasian, 28% Black, 4% Hispanic and 2% Native American. No specific racial analyses regarding bioequivalence or safety have been done.

IX.C. Evaluation of Pediatric Program: The proposed indications in this NDA are restricted to postmenopausal women and men with osteoporosis. The efficacy and safety of alendronate oral ——— solution have not been evaluated in the pediatric population ———

X. Conclusions and Recommendations

X.A. Conclusions: Merck has submitted data indicating that the 70mg alendronate ——— solution is equally bioavailable to the 70mg tablet. Because urine samples were not collected hourly or bi-hourly, the maximal rate of urinary excretion could not be calculated. Lacking these data, the 70 mg solution cannot be deemed bioequivalent to the 70 mg tablet. However, given the extremely low bioavailablity and long terminal half-life of alendronate, comparative data on the extent of absorption of the two formulations are adequate for approval of the 70mg solution. No unexpected safety findings for the 70mg solution were noted in the application.

X.B. Recommendations: Based on safety data evaluation, this reviewer recommends approval of the weekly 70mg oral alendronate ——— solution.

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/s/

Theresa Kehoe
8/27/03 11:46:58 AM
MEDICAL OFFICER

Eric Colman
8/28/03 09:28:42 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL