

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-762

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-762
Submission Dates May 24, 2004, original; November 11, 2004, N-000-BC; January 19, 2005, N-000-BC; February 24, 2005, N-000-BZ; February 25, 2005, N-000-BC
Brand Name FOSAMAX™ PLUS
Generic Names Alendronate sodium and vitamin D₃ (cholecalciferol)
Reviewer S.W. Johnny Lau
Team Leader Hae-Young Ahn
OCPB Division DPE II (HFD-870)
ORM Division Metabolic and Endocrine Drug Products (HFD-510)
Sponsor Merck Research Laboratories
Relevant IND 32.033
Submission Type: Code Original: S
Formulation: Strength(s) 70 mg alendronate + 2800 IU vitamin D₃ combination oral tablet
Indication To treat osteoporosis, increase bone mass, —

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1 Executive Summary

The sponsor submitted NDA 21-762 for the weekly oral 70 mg alendronate + 2800 IU vitamin D₃ combination tablet to seek approval for the following indications:

- to treat osteoporosis in postmenopausal women
- to increase bone mass in men with osteoporosis

The sponsor markets the weekly oral 70 mg alendronate alone regimen as tablet and buffered solution, which have the same indications as the proposed indications above. The approved alendronate labeling recommends patients receiving alendronate to supplement calcium and vitamin D if they have inadequate dietary intake. Alendronate is a nitrogen containing bisphosphonate that inhibits osteoclast activity and reduces bone resorption as well as turnover.

The sponsor conducted a pivotal clinical efficacy and safety study (P227, submitted study report in the 4-month safety update) and conducted 3 clinical pharmacology and biopharmaceutics studies (P183, P220, and P226) for NDA 21-762. Study P227 evaluates the efficacy of the combination tablet to reduce the proportion of patients with serum 25 hydroxyvitamin D insufficiency and deficiency in men and postmenopausal women with osteoporosis compared to the 70 mg alone tablet after 15 weeks of treatment (See Dr. Theresa Kehoe's medical review). Studies P183 and P220 were not thoroughly reviewed since they were pilot studies to guide the combination tablet's development and to determine intrasubject variability for Study P226's sample size calculation, respectively.

Study P226 is the definitive relative bioavailability (RBA) study for alendronate between the 70 mg alendronate combination tablet to the 70 mg alendronate alone tablet. It also compares the RBA for vitamin D₃ between the combination tablet and the 2800 IU vitamin D₃ alone tablet.

In Studies P227 and P226, the sponsor used the marketed 70 mg alendronate alone tablet formulation (reference) and the to-be-marketed 70 mg alendronate + 2800 IU vitamin D₃ combination tablet formulation (test). In Study P226, the vitamin D₃ alone tablet formulation has similar excipients to the to-be-marketed combination tablet formulation.

The sponsor proposed the same in vitro dissolution method but different acceptance criterion for alendronate in the combination tablet as those to the alendronate alone tablet. The sponsor did not propose a vitamin D₃ in vitro dissolution method for the combination tablet.

The Division of Scientific Investigation (DSI) inspected the site for clinical conduct that had the most alendronate administration to subjects in Study P226. DSI also inspected the site that performed both alendronate and vitamin D₃ bioanalyses for Study P226.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) reviewed NDA 21-762's clinical pharmacology and biopharmaceutics information and finds it acceptable provided the sponsor agreed to our following recommendations:

- the clinical pharmacology labeling comments on pages 10 - 12 of this review.
- The recommended alendronate in vitro dissolution acceptance criterion for the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet should be "not less than (Q =

of the labeled alendronate sodium amount dissolved in 15 minutes.” However, OCPB/DPEII accepted (on April 5, 2005 after negotiation) the sponsor’s proposed alendronate in vitro dissolution acceptance criterion for the combination tablet to be “not less than — , (Q = — of the labeled alendronate sodium amount dissolved in 20 minutes.” because about 30% of the tested batches require S2 testing to pass the dissolution test if the criterion were set at 15 minutes.

- batches require S2 testing if we use the 15 minute timeframe
- The recommended interim vitamin D₃ in vitro dissolution method and acceptance criterion follows:

	Vitamin D ₃
Apparatus	USP Type 2 (paddle)
In vitro dissolution medium	— with 0.9% NaCl in USP water
Volume of dissolution medium	500 mL
Medium temperature	37 ± 0.5°C
Stirring speed	75 rpm
Sampling Time	15 minute
Acceptance criterion	Not less than — (Q = —) of labeled vitamin D ₃ amount dissolved in 15 minutes

1.2 Phase IV Commitments

The sponsor should develop an acceptable vitamin D₃ in vitro dissolution method and acceptance criteria for the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet because:

- Vitamin D₃ is a drug in the combination tablet and requires an in vitro dissolution method and acceptance criteria to support the product quality and stability testing.
- which may affect the vitamin D₃ in vitro dissolution from the combination tablet.
- A vitamin D analog oral product has an approved in vitro dissolution method and acceptance criteria.
- Alendronate in vitro dissolution is an inappropriate surrogate marker for vitamin D₃ in vitro dissolution since alendronate is polar and water-soluble, whereas vitamin D₃ is nonpolar and not water-soluble.

The sponsor should submit data for the effect of the dissolution medium’s — concentrations on the in vitro dissolution of vitamin D₃ from the combination tablet for 2 different production-scale batches and 1 clinical batch.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Per Study P226, the alendronate in the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet is equally bioavailable to that in the 70 mg alendronate alone tablet. Moreover, the presence of 2800 IU vitamin D₃ does not affect the bioavailability of 70 mg alendronate from the combination tablet.

Per the baseline corrected and baseline uncorrected vitamin D₃ C_{max} and AUC_{0-t} for Study P226, the bioavailability of vitamin D₃ from the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet is

similar to that from the 2800 IU vitamin D₃ alone tablet. Moreover, the presence of 70 mg alendronate does not appear to affect the bioavailability of 2800 IU vitamin D₃ from the combination tablet.

The proposed alendronate in vitro dissolution method for the combination tablet is acceptable but the proposed alendronate dissolution method's acceptance criterion is unacceptable. The absence of a proposed vitamin D₃ in vitro dissolution method and acceptance criteria are not acceptable due to the necessity to assure quality and stability of a drug product.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-762 was conducted on March 18, 2005; participants included D. Lewis, R. Hedin, T. Kehoe, T. Kihira, H. Malinowski, J. Hunt, H. Ahn, and J. Lau.

FT signed by Hae-Young Ahn, Ph.D., Team Leader _____ 4/ /05

**APPEARS THIS WAY
ON ORIGINAL**

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the to-be-marketed 70 mg alendronate + 2800 IU vitamin D₃ formulation?

Table 1 below details the oral to-be-marketed formulation as white to off-white modified capsule-shaped tablet:

Component	Reference	Function	mg/tablet
Alendronate Sodium	Ph. Eur.	Active	91.37 ¹
Vitamin D ₃	Ph. Eur.,	Active	/
Lactose Anhydrous	NF/Ph. Eur.	/	/
Microcrystalline Cellulose	NF/Ph. Eur.	/	/
Colloidal Silicon Dioxide	NF/Ph. Eur.	/	/
Croscarmellose Sodium	NF/Ph. Eur.	/	/
Magnesium Stearate	NF/Ph. Eur.	/	/
Total Weight	---	---	325
Equivalent to 70 mg anhydrous free acid.			
/			
* Equivalent to 70 µg cholecalciferol.			
/			

2.2 General Clinical Pharmacology

Alendronate's clinical pharmacology information is available in the following articles:

- M. Sharpe et al. Alendronate, an update of its use in osteoporosis. *Drugs* **61**:999-1039 (2001)
- A.G. Porras et al. Pharmacokinetics of alendronate. *Clin Pharmacokinet* **36**:315-28 (1999)
- J.H. Lin. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* **18**:75-85 (1996)

Vitamin D's clinical pharmacology information is available in the following articles:

- AHFS Drug Information 2004, pages 3510-21
- G. Jones et al. Current understanding of the molecular actions of vitamin D. *Physiol Rev* **78**:1193-231 (1996)

2.2.1 How are the alendronate and vitamin D₃ doses selected?

The proposed oral 70 mg alendronate weekly dosing via the combination tablet is consistent with the approved oral 70 mg alendronate alone tablet weekly dosing.

The proposed oral 2800 IU vitamin D₃ weekly dose via the combination tablet provides the same cumulative amount of oral vitamin D₃ as 7 daily doses of the Food and Nutrition Board's recommended 400 IU vitamin D per day (Recommended Dietary Allowances). A 50000 IU vitamin D₃ oral dose was monthly administered for at least 6 months to 2 men and 21 postmenopausal women

receiving hormone replacement therapy without major safety concerns (Goldzieher et al. Single-monthly-dose vitamin D supplementation in elderly patients. *Endocr Pract* 5:229-32 (1999)).

2.3 Intrinsic Factors

The sponsor studied the effects of intrinsic factors such as age, gender, and renal insufficiency on alendronate pharmacokinetics (PK) (see alendronate's product labeling).

2.4 Extrinsic Factors

The sponsor studied the effects of extrinsic factors such as food-drug interactions on alendronate PK (see alendronate's product labeling).

2.5 General Biopharmaceutics

2.5.1 Does difference exist between the to-be-marketed formulation and the tested formulation in the pivotal clinical study (P227) and definitive relative bioavailability (RBA) study (P226)?

No. For Study P227:

The formulation for the 70 mg alone tablet is identical to the US marketed 70 mg alendronate tablet and the batch size is —. The formulation for the 70 mg combination tablet is identical to the to-be-marketed 70 mg alendronate combination tablet and the batch size is —.

For Study P226:

The sponsor used marketed 70 mg alendronate alone tablet and the to-be-marketed 70 mg alendronate + 2800 IU vitamin D₃ combination tablet, and the vitamin D₃ alone tablet (similar excipients to the combination tablet). See Attachment for formulation details. The alendronate alone tablets and the alendronate + vitamin D₃ combination tablets were produced at — manufacturing scale.

2.5.2 Is assessment of RBA via cumulative alendronate urinary excretion data valid?

Per the Code of Federal Regulations 320.24 (b)(2), the alendronate urinary excretion data is an acceptable alternative to assess RBA since alendronate is not metabolized but renally eliminated.

2.5.3 Did the sponsor adequately assess the oral alendronate RBA between the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet and the 70 mg alendronate alone tablet and the oral vitamin D₃ RBA between the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet and the vitamin D₃ alone tablet?

Yes. Study P226 was a 2-part study with each part consisted of a 2-period, crossover study in 244 healthy men and nonpregnant women aged 18 - 65. Each subject participated either in Part I or II. Randomized subjects received single oral doses of Treatments A and B in Part I and 207 subjects completed both periods. Randomized subjects received single oral doses of Treatments A and C in Part II and 28 subjects completed both periods. The 3 treatments were as follow:

- A. 70 mg alendronate + 2800 IU vitamin D₃ combination tablet
- B. 70 mg alendronate alone tablet
- C. 2800 IU vitamin D₃ alone tablet

Subjects for both parts of the study received all doses with 240 mL of tap water after an overnight fast and remained fasted until 2 hours postdose then received a standard meal. At least 12 days of washout separated each treatment periods within each part of the study.

Part II's subjects were instructed to avoid all active vitamin D compounds and vitamin D containing foods as well as to avoid prolonged direct sunlight exposure at least 10 days prior to Period 1 and during washout prior to Period 2. Subjects stayed in the study unit and did not expose to direct sunlight for the duration of the 144 hours PK-sampling periods (24 hours predose to 120 hours postdose). Subjects wore sunblock (SPF 45) and limited sun exposure throughout the entire study including washout.

Urine samples for alendronate determination were collected at -2 to 0, 0 to 8, 8 to 24, 24 to 36 hours postdose on Days 1 and 2 for the study's Part I. Serial serum samples were collected for vitamin D₃ determination 24 hours predose until 120 hours postdose for the study's Part II.

Table 2. Total urinary recoveries of alendronate over the 36 hours after single-dose administrations of a 70 mg alendronate/2800 IU vitamin D₃ combination tablet and a 70 mg alendronate alone tablet (per the Bioequivalence Guidance).

Cumulative Alendronate Urinary Recovery	Point Estimate of Ratio	90% CI
Combination vs. Alone Tablet	0.9963	0.8876 – 1.1182

Alendronate bioequivalence could not be adequately assessed because the urine sampling intervals were not short enough (0 - 8, 8 - 24, and 24 - 36 h postdose) to determine the maximum alendronate excretion rate. Per the 36-hour cumulative alendronate urinary excretion, the alendronate in the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet is equally bioavailable to that in the 70 mg alendronate alone tablet. Moreover, the presence of 2800 IU vitamin D₃ does not affect the bioavailability of 70 mg alendronate from the combination tablet.

Figure 1. Mean serum concentration-time profiles (baseline-uncorrected) of vitamin D₃ (n=28) following administration of single oral doses of 2800 IU vitamin D₃ alone (▲) and the alendronate/2800 IU vitamin D₃ combination tablet (○).

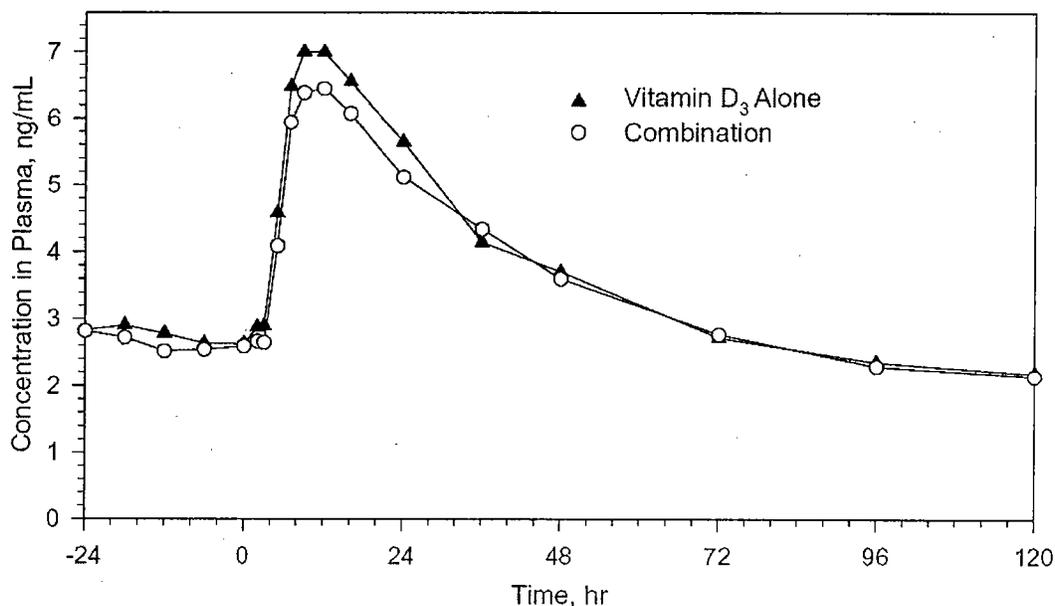


Table 3. Vitamin D₃ pharmacokinetic parameters (baseline-corrected and baseline-uncorrected) after single-dose administrations of a 70 mg alendronate + 2800 IU vitamin D₃ combination tablet and a 2800 IU vitamin D₃ alone tablet (per the Bioequivalence Guidance).

Baseline corrected	Point Estimate of Ratio	90% CI
Vitamin D ₃ C _{max}	0.8817	0.8302 – 0.9363
Vitamin D ₃ AUC _t	0.8718	0.7652 – 0.9931
Baseline uncorrected	Point Estimate of Ratio	90% CI
Vitamin D ₃ C _{max}	0.9099	0.8548 – 0.9686
Vitamin D ₃ AUC ₁₂₀	0.8923	0.8265 – 0.9633

Since vitamin D₃ is an endogenous substance, all postdose serum vitamin D₃ concentrations per subject per treatment period were subtracted from baseline (baseline corrected). Baseline was the average predose serum vitamin D₃ concentrations (-24 to 0 hours inclusive, usually 3 – 4 samples) per subject per treatment period. If a baseline corrected serum D₃ concentration was negative, its value was set to 0. The baseline corrected approach is consistent with recommendation for other sponsors' levothyroxine bioequivalence studies. This reviewer also analyzed the vitamin D₃ PK data via the baseline uncorrected approach but did not analyze the vitamin D₃ PK data via the ANCOVA and modeling approaches as the sponsor did.

Per the baseline corrected and baseline uncorrected vitamin D₃ C_{max} and AUC_{0-t}, the bioavailability of vitamin D₃ from the 70 mg alendronate combination tablet is similar to that from the 70 mg alendronate alone tablet. Moreover, the presence of 70 mg alendronate does not appear to affect the bioavailability of 2800 IU vitamin D₃ from the combination tablet.

The Division of Scientific Investigation (DSI) inspected the site for the clinical conduct that had the most alendronate participants in Study P226 and found no objectionable observation. DSI inspected the site that performed both alendronate and vitamin D₃ bioanalyses for Study P226 and found that 34 urine samples for alendronate determination (about 2% of the study samples) have decreased extraction recovery of the internal standard.

2.5.4 What are the proposed alendronate and vitamin D₃ in vitro dissolution methods and acceptance criteria for the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet?

The sponsor proposed the same in vitro dissolution method for alendronate in the combination tablet as that to alendronate alone tablet. The proposed acceptance criterion for alendronate in vitro dissolution from the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet is “not less than — (Q = — of labeled alendronate sodium amount dissolved in 20 minutes,” whereas the acceptance criterion for alendronate in vitro dissolution from the approved 70 mg alendronate alone tablet is “not less than — (Q = — of labeled alendronate sodium amount dissolved in 15 minutes.” Table 4 below details the proposed in vitro dissolution methods and acceptance criteria for alendronate and vitamin D₃ from the 70 mg alendronate + 2800 IU vitamin D₃ combination tablet.

	Alendronate	Vitamin D ₃
Apparatus	USP Type 2 (paddle)	pending
In vitro dissolution medium	Deaerated USP water	pending
Volume of dissolution medium	900 mL	pending
Medium temperature	37 ± 0.5°C	pending
Stirring speed	50 rpm	pending
Sampling Time	20 minute	pending
Acceptance criterion	Not less than — (Q = — of labeled alendronate sodium amount dissolved in 20 minutes	pending

The sponsor's proposed alendronate in vitro dissolution method for the combination tablet is acceptable because it is the same method as that for the 70 mg alendronate alone tablet. The sponsor submitted raw individual alendronate in vitro dissolution data from 6 batches of combination tablets (1 biobatch, 1 probe stability batch, 1 pre-engineering batch as 3 subbatches, and 1 engineering batch). Besides the biobatch and probe stability batch, the other 4 batches were produced at manufacturing scale.

At the 70 mg alendronate alone tablet's approved acceptance criterion of "not less than $Q = \frac{1}{2}$ of labeled alendronate sodium amount dissolved in 15 minutes," the combination tablet's biobatch has 3 out of 40 tablets $< \frac{1}{2}$ of labeled amount dissolved and other combination tablets' batches also show similar trend (1/12, 4/18, 2/18, 1/6, and 2/40 tablets have $< \frac{1}{2}$ labeled amount dissolved). Hence, these 6 batches do not pass Stage S₁ acceptance criterion per USP's 711 Dissolution Acceptance Table. However, these 6 batches do pass the USP Dissolution Stage S₂ acceptance criterion because each of the 6 batches' average are $\geq \frac{1}{2}$ labeled amount dissolved and no combination tablet is $< \frac{1}{2}$ of labeled amount dissolved in the 6 batches. Hence, the alendronate in vitro dissolution acceptance criterion for the combination tablet should be "not less than $Q = \frac{1}{2}$ of the labeled alendronate sodium amount dissolved in 15 minutes." The chemistry reviewer, Dr. David Lewis, confirmed that no individual combination tablet from all the stability testings showed in vitro dissolution of less than $\frac{1}{2}$ labeled alendronate sodium amount dissolved in 15 minutes.

Figure 2. Representative alendronate sodium dissolution profiles for 8 batches (initial timepoints only for stability batches)



The sponsor did not propose an in vitro vitamin D₃ dissolution method and acceptance criteria for the combination tablet because of the following reasons:

- vitamin D₃ in the combination tablet

The release of vitamin D₃ from the tablet is rapid and essentially complete within approximately 15 minutes.

- The absence of a dissolution requirement for vitamin D₃ is consistent with USP compendial requirements for solid dosage forms containing fat-soluble vitamins.
- The monitoring of alendronate sodium dissolution will serve as a surrogate marker for vitamin D₃ release.

However, the sponsor did develop an in vitro vitamin D₃ dissolution method to support the combination tablet's stability program (see Table 5 below).

OCPB/DPEII's response to the sponsor's reasons of not proposing an in vitro vitamin D₃ dissolution method and acceptance criteria for the combination tablet follows:

- Vitamin D₃ is a drug in the combination tablet per the General Council and requires an in vitro dissolution method and acceptance criteria to support the product quality and stability testing.
- _____
which may affect the vitamin D₃ in vitro dissolution from the combination tablet. Hence, an in vitro vitamin D₃ dissolution method and acceptance criteria are needed to assure the combination tablet's product quality.
- A vitamin D analog oral capsule, doxercalciferol (HECTOROL[®]), has an approved in vitro dissolution method and acceptance criteria.
- Alendronate in vitro dissolution is an inappropriate surrogate marker for vitamin D₃ in vitro dissolution because alendronate is polar and water-soluble, whereas vitamin D₃ is nonpolar and not water-soluble.

Table 5. Dissolution of vitamin D₃ from 70 mg alendronate + 2800 IU vitamin D₃ combination tablet.

Apparatus:	USP Apparatus II (paddles)
Rotation Speed:	75 rpm
Dissolution Medium:	— 0.9% NaCl in USP water
Medium Volume:	500 mL
Medium Temperature:	37°C
Sample Volume:	4 mL (1.5 mL for the blank samples)
Sampling Times:	10, 15, 20, 30, 45, and 60 minutes

The sponsor's in vitro vitamin D₃ dissolution method (Table 5) for 3 stability batches may not be discriminating enough so that at 15 minutes _____ of the vitamin D₃ content of the combination tablet are dissolved. The _____ may be too high and result in the fast dissolution of vitamin D₃ from the combination tablet. The sponsor should further study the effect of _____ concentrations on the in vitro dissolution of vitamin D₃ from the combination tablet for 2 different production-scale batches and 1 clinical batch.

2.6 Analytical Section

2.6.1 Are the bioanalytical methods for alendronate and vitamin D₃ properly validated?

The alendronate bioanalytical method in human urine samples follow:

- isolation, via precipitation and solid phase extraction of the analyte and internal standard from urine
- automated pre-column derivatization to form fluorescent products of the analytes
- high pressure liquid chromatography (HPLC) separation and fluorescence detection of the resulting derivatives.

The vitamin D₃ bioanalytical method in human serum samples follow:

- double liquid-liquid extraction of vitamin D₃ with internal standard
- derivatization of vitamin D₃ and internal standard in the extract
- separation of derivatized vitamin D₃ and internal standard and other components via HPLC

- quantitation via MS/MS with the heated nebulizer interface

The validation studies' results for alendronate and vitamin D₃ are acceptable and as follow (Table 6):

	Alendronate	Vitamin D ₃
Method	HPLC-fluorescent	HPLC/MS/MS
Lower Limit of Quantitation, ng/mL	1* or 5 [§] (urine)	0.5 (serum)
Recovery, %	95.8* or 70.7 [§]	82
Linearity, ng/mL	1 – 25* or 5 – 125 [§]	0.5 – 25
Accuracy		
intraday	<11%	<3%
interday	<6%	3%
Precision, % CV		
intraday	<10%	<7.2%
interday	<10%	<5.4%

MS = mass spectrometry; * = Protocol DM-177A; [§] = Protocol DM-177B

3 Detailed Labeling Recommendations

Only proposed clinical pharmacology information that is not in the approved alendronate labeling is presented below. The underlined text represents addition. The strikethrough text represents deletion. The italic text is internal notes and not to be communicated with the sponsor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Cholecalciferol

Vitamin D₃ is produced in the skin by photochemical conversion of 7-dehydrocholesterol to previtamin D₃ by ultraviolet light. This is followed by non-enzymatic isomerization to vitamin D₃. In the absence of adequate sunlight exposure, vitamin D₃ is an essential dietary nutrient. Vitamin D₃ in skin and dietary vitamin D₃ (absorbed into chylomicrons) is converted to 25 hydroxyvitamin D₃ in the liver. Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D₃ (calcitriol) in the kidney is stimulated by both parathyroid hormone and hypophosphatemia. The principal action of 1,25 dihydroxyvitamin D₃ is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

Vitamin D is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in hyperparathyroidism, hypophosphatemia, proximal muscle weakness and osteomalacia,

Vitamin D in general is required for bone formation *Other statements in the above 2 paragraphs are acceptable (Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press Washington D.C. 2000ed page 250; "Vitamin D: from photosynthesis, metabolism, and action to clinical application" in Endocrinology by DeGroot and Jameson).*

Pharmacokinetics

Absorption

Alendronate Sodium

The alendronate in the FOSAMAX PLUS tablet and the FOSAMAX (alendronate sodium) 70 mg tablet is equally bioavailable.

This statement is acceptable per the RBA results of Study P226.

Cholecalciferol

Following administration of FOSAMAX PLUS after an overnight fast and two hours before a standard meal, the baseline adjusted mean area under the serum-concentration-time curve (AUC_{0-120 hrs}) for vitamin D₃ was 120.7 ng-hr/mL. The mean maximal serum concentration (C_{max}) of vitamin D₃ was 4.0 ng/mL, and the mean time to maximal serum concentration (T_{max}) was 10.6 hrs. The bioavailability of the 2800 IU vitamin D₃ in FOSAMAX PLUS is similar to 2800 IU vitamin D₃ administered alone.

The AUC₀₋₁₂₀, C_{max} and T_{max} values are per RBA Study P226.

Distribution

Cholecalciferol

Following absorption, vitamin D₃ enters the blood as part of chylomicrons. Vitamin D₃ is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D₃, ~~the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D₃ at these sites for later release into the circulation.~~

The unstrikethrough part is acceptable (Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press Washington D.C. 2000ed page 253-4). This reviewer cannot find substantiation for the strikethrough part.

Circulating vitamin D₃ is bound to vitamin D-binding protein.

This statement is acceptable; "Vitamin D: from photosynthesis, metabolism, and action to clinical application" in Endocrinology by DeGroot and Jameson.

Metabolism

Cholecalciferol

Vitamin D₃ is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D₃, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D₃, which represents the biologically active form. Further hydroxylation occurs prior to elimination.

These statements are acceptable (Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press Washington D.C. 2000ed page 253).

A small percentage of vitamin D₃ undergoes glucuronidation prior to elimination.

This statement is acceptable; J Clin Investigation 46:983-92 (1967).

Excretion

Cholecalciferol

When radioactive vitamin D₃ was intravenously administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4% of the administered dose, and the mean fecal excretion of radioactivity after 48 hours was 4.9% of the administered dose. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of

_____ vitamin D₃ in the serum following an oral dose of FOSAMAX PLUS is approximately — 14 hours.

J Clin Investigation 46:983-92 (1967); mean _____ vitamin D₃ t_{1/2} per RBA Study P226.

Special Populations

Geriatric:

Cholecalciferol

Dietary requirements of vitamin D₃ _____ increased in the elderly.

This statement is acceptable because aging significantly decreases the capacity of human skin to produce vitamin D₃ (Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press Washington D.C. 2000ed page 255).

Renal Insufficiency:

Cholecalciferol

Patients with renal insufficiency will have decreased ability to form the active 1,25-dihydroxy vitamin D₃ metabolite.

Hepatic Insufficiency:

Cholecalciferol

Vitamin D₃ may not be adequately absorbed in patients who have malabsorption due to inadequate bile production.

This statement is acceptable because patients who are unable to secrete adequate amounts of bile are more prone to develop vitamin D deficiency (Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press Washington D.C. 2000ed page 255).

Drug Interactions (also see PRECAUTIONS, Drug Interactions)

Cholecalciferol

Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D.

This statement is acceptable because similar statements also appear in the labeling of doxercalciferol.

Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

This statement is acceptable (Exp Clin Endocrinol diabetes 108:37-43 (2000) for anticonvulsants; Digestion 46:61-4 (1990) for cimetidine; Metabolism 34:421-4 (1985) for thiazide).

PRECAUTIONS

Drug Interactions (also see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions)

Cholecalciferol

Drugs that may impair the absorption of cholecalciferol

Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D.

See comment on drug interactions of cholecalciferol and fats above.

Drugs that may increase the catabolism of cholecalciferol

Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

See comment on drug interactions of cholecalciferol above.

Attachment

70-mg Alendronate/2800-IU Vitamin D₃ Combination Tablet Formulation

70-mg Alendronate Market Tablet Formulation

Formulation No.	E-10129 ¹
Lot No.	WP-K969, WP-K972
Batch Size	—
Composition (per tablet):	
Alendronate sodium	91.37 mg ²
Microcrystalline Cellulose NF	/
Lactose Anhydrous NF	/
Croscarmellose Sodium NF	/
Magnesium Stearate NF	/
Content Assay (Alendronic Acid):	
Mean	/
Range	/
Manufactured by the Merck Manufacturing Division as commercial alendronate sodium 70-mg tablet product. Equivalent to 70.0-mg anhydrous free acid.	

Formulation No.	0217AOCT015B002
Lot No.	WP-K968, WP-K971
Batch Size	—
Composition (per tablet):	
Alendronate sodium	91.37 mg ²
Vitamin D ₃	/
Lactose Anhydrous NF	/
Microcrystalline Cellulose NF	/
Colloidal Silicon Dioxide NF	/
Croscarmellose Sodium NF	/
Magnesium Stearate NF	/
Content Assay (Alendronic Acid):	
Mean	/
RSD	/
Range	/
Content Assay (Vitamin D ₃):	
Mean	/
RSD	/
Range	/
Equivalent to 70.0-mg anhydrous free acid.	

2800 IU Vitamin D₃ Tablet Formulation

Formulation No.	0217AOCT502J001
Lot No.	WP-K970, WP-K973
Batch Size	—
Composition (per tablet):	
Vitamin D ₃	/
Microcrystalline Cellulose NF	/
Lactose Anhydrous NF	/
Croscarmellose Sodium NF	/
Colloidal Silicon Dioxide NF	/
Magnesium Stearate NF	/
Content Assay (Vitamin D ₃):	
Mean	/
RSD	/
Range	/
results in 2800 IU vitamin D ₃ per tablet.	

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	21-762	Brand Name	FASAMAX™ PLUS
OCPB Division	II	Generic Name	Alendronate + Vit D3
Medical Division	DMEDP, HFD-510	Drug Class	Bisphosphonate + vit
OCPB Reviewer	S.W. Johnny Lau	Indication(s)	Treat osteoporosis +
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Tablet
Date of Submission	24-MAY-2004	Dosing Regimen	1 tablet/weekly
Estimated Due Date of OCPB Review	28-JAN-2005	Route of Administration	Oral
Division Due Date	18-FEB-2005	Sponsor	Merck & Co., Inc.
PDUFA Due Date	24-MAR-2005	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if Included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug Interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
Bioequivalence studies -				

traditional design; multi dose:			
replicate design; single / multi dose:			
Food-drug interaction studies:			
Dissolution:			
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		3	
Filability and QBR comments			
	"X" if yes	Comments	
Application filable ?	X		
Comments sent to firm ?	X	The sponsor should submit individual in vitro dissolution data from the combination tablet, with descriptive statistics (mean, median, range, and standard deviation) and plots, for alendronate and vitamin D ₃ in 3 dissolution media to determine acceptable in vitro dissolution methods and acceptance criteria for alendronate and vitamin D ₃ .	
QBR questions (key issues to be considered)		The sponsor cannot claim Study P226 as a bioequivalence study, since this study only measured total alendronate urinary excretion and did not measure the alendronate urinary excretion rate.	
Other comments or information not included above		<p>No clinical safety and efficacy study supports NDA 21-762. Hence, a DS1 inspection on Study P226, definitive bioavailability study, is in order.</p> <p>Study P226 A 2-part, Open-Label, Randomized, Crossover Study to Evaluate the Bioequivalence of the 70-mg Alendronate/2800-IU Vitamin D₃ Final-Market Combination Tablet to a 70-mg Alendronate Marketed Tablet, and the Relative Bioavailability of Vitamin D₃</p> <p>Clinical Site (194 enrolled participants out of 214 total):</p> <p style="text-align: center;">/</p> <p>Bioanalytical site: Merck Research Laboratories West Point, PA 19486</p>	
Primary reviewer Signature and Date			
Secondary reviewer Signature and Date			

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/s/

S.W. Johnny Lau
7/7/04 04:25:06 PM
BIOPHARMACEUTICS

Hae-Young Ahn
7/12/04 05:30:41 PM
BIOPHARMACEUTICS

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA: 21-762
Compound: Alendronate sodium plus vitamin D₃ (FOSAMAX™ PLUS)
Sponsor: Merck & Co. Inc.
Submission Date: May 24, 2004
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submitted NDA 21-762 to seek approval for the weekly oral 70 mg alendronate + 2800 IU vitamin D₃ tablet to: 1) treat osteoporosis in postmenopausal women — increase bone mass in men with osteoporosis —. The sponsor markets the weekly oral 70 mg alendronate regimen as tablet and buffered solution, which have the same indications as the combination tablet's proposed indications —.

Findings

The sponsor:

- did not conduct any clinical safety and efficacy study to support NDA 21-672
- conducted 3 relative bioavailability (RBA) studies to support the Human Pharmacokinetics and Bioavailability section of NDA 21-672 (see Attachment). Studies P183 and 220 are pilot studies to guide the formulation development. Study P226 is the definitive study.
- used the marketed 70 mg alendronate tablet and the to-be-marketed 70 mg alendronate + 2800 IU vitamin D₃ tablet, and the vitamin D₃ tablet (same excipients as the combination tablet) in Study P226
- proposed the same in vitro dissolution acceptance criteria for alendronate in the combination tablet as that to alendronate alone tablet but did not propose in vitro dissolution method and acceptance criteria for vitamin D₃
- provided electronic data in SAS transport files, study reports, bioanalytical reports, and validation reports for all 3 RBA studies
- proposed labeling for review

Attachment

Study #	Protocol Description	Formulation	Formulation Number(s)	Bulk #	Code
183	An Open, Randomized, 2-Period, Crossover, Pilot Study to Investigate the Influence of Vitamin D ₃ on the Oral Absorption of Alendronate	Alendronate Sodium 70-mg Tablet	0217OCT001J011	ETA-100 57812	T2
		Vitamin D ₃ Powder for Reconstitution, —	C0217APFC001A002	#VT00030010)	P1
220	An Open-Label, Randomized, 3-Period, Crossover, Pilot Study to Examine the Relative Bioavailability of Alendronate and the Pharmacokinetics of Vitamin D ₃ in an Alendronate/Vitamin D ₃ Combination Tablet	Alendronate Sodium 70-mg/ Vitamin D ₃ 2800-I.U. Tablet	0217AOCT012B001	LTA-308/62039 #05883284)	T1
		Alendronate Sodium 70-mg Tablet	E-10129	JTA-249	T2
		Vitamin D ₃ 2800-I.U. Tablet	F0217AOCT502J001	62039 #05883284)	T3
226	A 2-Part, Open Label, Randomized, Crossover Study to Evaluate the Bioequivalence of the 70-mg Alendronate/2800-I.U. Vitamin D ₃ Final Market Combination Tablet to a 70-mg Alendronate Marketed Tablet, and the Relative Bioavailability of Vitamin D ₃ .	Alendronate Sodium 70-mg/ Vitamin D ₃ 2800-I.U. Tablet	0217AOCT015B002	LTA-308/64750 #00220895T0)	T1
		Alendronate Sodium 70-mg Tablet	E-10129	JTA-249	T2
		Vitamin D ₃ 2800-I.U. Tablet	F0217AOCT502J001	62039 #05883284)	T3

Post Filing Meeting (July 7, 2004) Notes

The review team decided to take the approach that vitamin D₃ is a drug for review purpose.

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/s/

S.W. Johnny Lau
4/5/05 05:39:40 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/5/05 06:04:03 PM
BIOPHARMACEUTICS