CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-762

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-762**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**5/24/04**
PRODUCT:	**Fosamax Plus**
INTENDED CLINICAL POPULATION:	**osteoporosis**
SPONSOR:	**Merck**
DOCUMENTS REVIEWED:	**eCTD NDA**
REVIEW DIVISION: **(HFD-510)**	**Division of Metabolic & Endocrine Drug Products**
PHARM/TOX REVIEWER:	**Davis-Bruno**
PHARM/TOX SUPERVISOR:	**Davis-Bruno**
DIVISION DIRECTOR:	**Orloff**
PROJECT MANAGER:	**Hedin**

Date of review submission to Division File System (DFS): 6/25/04

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability-Pharmacology/toxicology recommends approval based on previous determinations of safety and efficacy for alendronate and cholecalciferol products.

B. Recommendation for nonclinical studies- none

C. Recommendations on labeling: Modifications to the cholecalciferol portions of the label are suggested below.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Cholecalciferol

t. Ergocalciferol (vitamin D_2) at doses prior to mating resulted in altered estrous cycling and inhibition of pregnancy in female rats. The effect of cholecalciferol on male fertility

Pregnancy Category C:
Cholecalciferol

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

Nursing Mothers: human milk. Because many drugs are excreted in human milk caution should be exercised when Fosamax Plus is administered to nursing women.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings- Nonclinical safety and efficacy data is provided by inference based on prior Agency decisions of approval of 70 mg/week alendronate and vitamin D products. Vitamin D supplements (400

IU/day) have been utilized routinely during clinical studies with alendronate and constitute the standard of care for osteoporosis.

B. Pharmacologic activity-Fosamax Plus is consistent with the current dosing regimen for 70 mg alendronate once weekly and 400 IU recommended daily allowance of vitamin D or 2800 IU given weekly for osteoporosis. An open label bioequivalency clinical trial demonstrates that Fosamax Plus is bioequivalent to 70 mg Fosamax.

C. Nonclinical safety issues relevant to clinical use-none

Characterization of vitamin D toxicity is well established, occurring at doses ≥ 10,000 IU/day. Toxicity results primarily from deposition of calcium and phosphorus in soft tissues such as the heart, kidneys (stones) and blood vessels (e.g. calcification of renal arteries leading to renal hypertension) and also lung, tendons and ligaments. An upper limit of normal intake is considered 50 μg (2000 IU/day for adults, children > 1 yr and pregnant/lactating females. This limit is similar to the proposed total weekly dose (2800 IU/week). Vitamin D toxicity is characterized by nausea, vomiting, decreased food consumption, constipation, weakness, weight loss, increased serum calcium leading to possible confusion and arrhythmias. The GI side effects are self-limiting and serum calcium is clinically monitorable.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

Fosamax Plus is a fixed dose combination of 70 mg alendronate sodium (Fosamax) with 70 μg (2800 IU) of cholecalciferol (Vitamin D3) as a convenient once weekly treatment option in men and women with osteoporosis. Fosamax has been available in a dosing regimen of 70 mg once weekly since October 2000 (see Merck alendronate NDA 21-575). Supplementation with vitamin D is a recommended standard of care for patients with osteoporosis and routinely utilized in Fosamax clinical trials at 400 IU/day. Merck has provided information regarding vitamin D in a summary format from the Rocaltrol NDA (calcitriol, Hoffman-LaRoche) available through the FOIA (freedom of information act) and published literature. Rocaltrol is calcitriol or 9,10-seco(5Z,7E)-5,7,10(19)-cholestatriene-1(alpha), 3(beta), 25-triol. The other names frequently used for calcitriol are 1(alpha),25-dihydroxycholecalciferol, 1,25-dihydroxyvitamin D_3, 1,25-DHCC, 1,25$(OH)_2 D_3$ and 1,25-diOHC. The initial pathway in vitamin D3 synthesis is the reaction of 7-dehydrocholesterol with ultraviolet light in the skin to cholecalciferol. The first step in the metabolic activation of cholecalciferol is the carbon 25 hydroxylation through hepatic calciferol-25-hydroxylase yielding 25-hydroxycholecalciferol (calcifediol). This hydroxylase is located within the hepatic endoplasmic reticulum. The second step in activation involves the further hydroxylation of calcifediol to 1α,25-dihydroxycholecalciferol (calcitriol); the major biologically active form. The enzyme catalyzing this last step; 25-dihydroxycholecalciferol-1α-hydroxylase is located within the mitochondia of renal tubular epithelium. Calcitriol is transported via protein binding to the intestinal epithelium. Biosynthesis of calcitriol is upregulated with low serum calcium and high PTH.

NDA number: 21-762
Review number: 1
Sequence number/date/type of submission: 000, 5/24/04
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Merck
Manufacturer for drug substance: Merck (alendronate), — (vitamin D3)

Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: Div. Metabolic & Endocrine Drugs
HFD #: 510
Review completion date: 6/25/04

Drug:

Trade name: Fosamax Plus
Generic name: alendronate sodium + cholecalciferol (vitamin D3)
Code name: N/A
Chemical name: 4-amino-1-hydroxybutylidene see NDA 20-560 + cholecalciferol: [(3β, 5Z, &E)-9, 10-Secocholesta-5, 7, 10(19)-trien-3-ol]
CAS registry number: see NDA 20-560

Molecular formula/molecular weight: see NDA 20-560
Structure: see NDA 20-560

Relevant INDs/NDAs/DMFs: NDA 20-560 (Fosamax) AP 9/95, NDA 21-575 70 mg oral solution AP 9/03

Drug class: alendronate is a bisphosphonate

Intended clinical population: male and female osteoporosis patients

Clinical formulation:

Alendronate Sodium 70 mg/Vitamin D_3 2800 I.U.
Combination Tablets — Market Composition

Component	Reference	Function	mg/tablet
Alendronate Sodium	Ph. Eur.	Active	91.37†
Vitamin D_3	Ph. Eur.,	Active	
Lactose Anhydrous	NF/Ph. Eur.		
Microcrystalline Cellulose	NF/Ph. Eur.		
Collodial 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

The excipients are the same as used for alendronate tablets except for the colloidal silicon dioxide and magnesium stearate which are listed in the CDER Inactive ingredient guide at higher concentrations than proposed here.

Route of administration: a combination oral tablet containing 70 mg alendronate and 2800 IU/70 µg vitamin D3 given once weekly

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.
Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-762 are owned by Merck. Any

information or data necessary for approval of NDA 21-762 that Merck does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Merck does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-762.

Studies reviewed within this submission: none

Studies not reviewed within this submission: none

2.6.2 PHARMACOLOGY

See NDA 21-575 Fosamax/Merck for alendronate.

2.6.2 PHARMACOLOGY TABULATED SUMMARY

See NDA 21-575 Fosamax/Merck for alendronate.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

See NDA 21-575 Fosamax/Merck for alendronate.

2.6.6 TOXICOLOGY

See NDA 21-575 Fosamax/Merck for alendronate.

2.6.7 TOXICOLOGY TABULATED SUMMARY

See NDA 21-575 Fosamax/Merck for alendronate.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Pharmacology/Toxicology data has not been provided or needed for this application since approval is based on the prior decision of safety and efficacy in the approval of Fosamax (alendronate) 70 mg once weekly in Oct. 2000 and Rocaltrol (calcitriol) in 1978.

Recommendations: approval

Suggested Labeling: The proposed alendronate portions of the nonclinical sections of the label are acceptable. Modifications to the cholecalciferol portions of the label are suggested in the Executive Summary Labeling Section based on published literature provided by Merck with ergocalciferol (vitamin D_2).

	Ergocalciferol Doses Tested Based on Literature			Safety Margin[2]
	IU[1]	mg/kg	mg/m2	
Pregnant rabbit	10,000 q2d	0.069	0.83	120 X
Pregnant rat	40,000/day	6.7	40	5700 X
Rat	150,000/day	25	150	>20,000 X

[1]Based on 1 Unit =0.025 µg vitamin D2 or D3
[2]Clinical dose is 2800 IU/week or 400 IU/day or 10 µg/day or 0.007 mg/m2

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Pregnancy Category C:
Cholecalciferol

Reference to Rabbit Segment 2:
Chan GM et al. Pediat Res 1979;13:121-6
Friedman WF et al. Circulation 1966;34(1):77-86

Reference to Rat Segment 2:
Ornoy A, Nebel L, Menczel Y. Arch Pathol 1969;87:563-71
Ornoy A, Kaspi T, Nebel L. Isr J Med Sci 1972;8(7):943-9

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/s/

Karen Davis-Bruno
6/25/04 04:18:31 PM
PHARMACOLOGIST
P/T 1: AP, labeling comments to sponsor

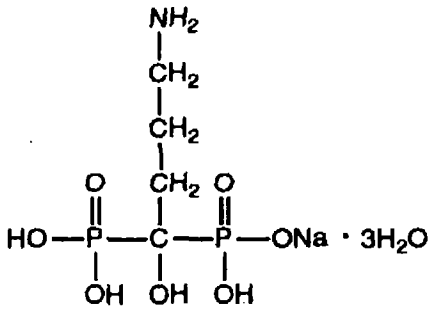
PHARMACOLOGY/TOXICOLOGY COVER SHEET

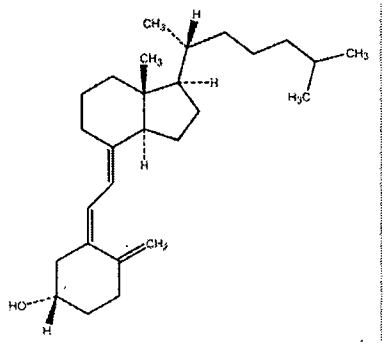
NDA number:	**21-762**
Compound:	**Fosamax™ Plus (Alendronate Sodium – 70 mg/2800 I.U. Vitamin D3 combination) Tablets**
Submission date:	May 24, 2004
Sequence number:	000
Type of submission:	N
Information to Sponsor:	Yes (x) (Labeling comments)
Sponsor:	Merck, NJ, USA
Manufacturer for drug substance:	Alendronate: Merck; Vitamin D3: [redacted]
Reviewer name:	Gemma Kuijpers
Division name:	Division of Metabolic and Endocrine Drug Products
HFD #:	510
Review completion date:	February 28, 2005

Drug:

Trade name:	Fosamax Plus
Generic name:	Alendronate sodium/VitaminD3
Code name:	Alendronate: MK-217
Chemical name:	Alendronate: (4-amino-1-hydroxybutylidene) bisphosphonic acid, monosodium salt, trihydrate Vitamin D3: [(3B, 5Z, 7E)-9, 10-secocholesta-5,7,10(19)-trien-3-ol]
USAN name:	VitD3: Cholecalciferol
Molecular formula:	Alendronate: $C_4H_{12}NNaO_7P_2.3H_2O$ Vitamin D3: $C_{27}H_{44}O$
Molecular weight:	Alendronate: 325.11.1 Vitamin D3: 384.6

Structure (Alendronate and Vitamin D3)





Relevant INDs/NDAs/DMFs:	IND 32,033 (alendronate); NDA 20-560 AP 1995 (alendronate 5 mg tablet); NDA-21575 AP 2003 (alendronate 70 mg oral solution)
Drug class:	Alendronate: Bisphosphonate (bone resorption inhibitor) Vitamin D3: hormone

Indication:	Treatment of postmenopausal osteoporosis Treatment to increase bone mass in men with osteoporosis
Clinical formulation:	Combination tablet, 70 mg/2800IU Fosamax/VitD3
Route of administration:	Oral (tablet)
Proposed use:	Tablet, orally, once weekly
Pivotal clinical study:	Bioequivalence study (Protocol 226) No efficacy studies
Disclaimer:	Tables and Figures from the electronic NDA submission have been copied for use in this review

Executive Summary

I. Recommendations

A. Recommendation on Approvability
Approval (AP)

Based on the results of nonclinical pharmacology and toxicology studies, Pharmacology/ Toxicology recommends approval of the NDA for Fosamax™ Plus for the indication of treatment of postmenopausal osteoporosis and increase of bone mass in men with osteoporosis.

B. Recommendation for Nonclinical Studies
No additional nonclinical studies are required.

C. Recommendations on Labeling
Recommmended labeling changes have been appended to this Review.

II. Summary of Nonclinical Findings

The current application (NDA #21-762) is for the use of alendronate in combination with vitamin D3 in the treatment of postmenopausal osteoporosis and to increase bone mass in men with osteoporosis. The intended dose is 70 mg (alendronate) and 2800 IU (VitD3), taken once weekly, as a tablet with a glass of water, at least 30 minutes before breakfast.

There were no studies in animals for evaluation of toxicity of the alendronate/Vitamin D3 combination. However, preclinical toxicity data on Vitamin D2 or D3 obtained through the Freedom of information Act (FOIA) (Rocaltrol NDA) and published scientific literature were described in the submission. Data in support of alendronate are provided by reference to NDA 20-560.

The studies described included general toxicology studies in rats and dogs with calcitriol (1,25-OH2Vitamin D3), genetic toxicology studies with calcitriol (1,25-OH2VitD3) and reproductive toxicity studies with ergocalciferol (Vitamin D2). Carcinogenicity studies have not been performed with Vitamin D.

Toxicity studies with i.v. doses of calcitriol, the active hormone metabolite of vitamin D3, of 13-52 week duration, in rats and dogs reflected the well known calcemic effect of calcitriol, and included hypercalcemia, urolithiases, increased kidney weight, decreased reproductive organ weight, parathyroid gland atrophy, parafollicular cell hyperplasia, and calcium deposition in various tissues. In a 26-week oral study in rats with Vitamin D3at doses 2x, 4x, 8x the intended human dose (2800IU/week) findings included hypercalcemia, tubule mineralization and nephrocalcinosis, and proliferative changes in adrenal medulla.

Mutagenicity studies with calcitriol (1,25-OH2VitD3) included a negative Ames test and a negative mouse micronucleus test.

There are no rodent carcinogenicity studies with Vitamin D3 reported in the literature.

Reprotoxicity studies with Vitamin D2 have been published in the literature. In rats, high doses of vitamin D2 before mating can cause persistent diestrus, suppress pregnancy and increase resorptions.

In rats dosed during gestation, high doses of Vitamin D2 cause decrease in fetal weight, femur weight and femur ash weight. Treatment also interfered with cartilage calcification, affected histologic structure of cartilage zones, and dia- and metaphyseal structure. In another rat study, gestational dosing with Vitamin D2 at high doses caused neonatal mortality, and impaired

PHARMACOLOGY/TOXICOLOGY REVIEW

INTRODUCTION

Alendronate is a nitrogen-containing bisphosphonate that has a high affinity for hydroxyapatite and inhibits osteoclast-mediated bone resorption. This inhibition indirectly suppresses bone formation and ultimately leads to an inhibition of bone turnover. In postmenopausal women bone loss is accelerated due to increased activation of basic multicellular units (BMU's) and a negative balance between bone formation and resorption in each remodeling cycle. Alendronate and other bisphosphonates prevent or reverse this bone loss because they reduce the size of the remodeling space at the tissue level, and they increase the degree of mineralization and increase focal bone balance in each newly formed bone unit. This results in an increase in bone volume and bone mass as reflected by an increase in bone mineral density (BMD). Alendronate (ALN) inhibits bone resorption and increases BMD in osteoporotic women and men, and can suppress the risk of fracture.

Cholecalciferol (Vitamin D3) is generated in the skin upon exposure to sunlight. It is a prehormoone, and is converted to 1-OH-VitD3 in the liver (enzyme: 25-hydroxylase) and to the active metabolite 1,25-OH2-VitD3 (calcitriol) in the kidney (enzyme: 1-a-hydroxylase). Vitamin D3 (cholecalciferol) is expressed in IU. The IU is 0.025 ug (1 ug = 40IU). Calcitriol is much more potent than the prehormone VitD3 in vitamin-D deficient animal models. Dietary sources of Vitamin D include egg yolk and fish oil (VitD3), and a number of plants (VitD2). Each form of VitD is hydrophobic, and is transported in blood bound to carrier proteins. Physiological effects of Vitamin D are facilitation of intestinal Ca absorption, effects on bone cells to provide optimal Ca and P balance to support mineralization, and effects on growth and differentiation of several cell types. Vitamin D receptors are present in most or all cells of the body. Calcium homeostasis is tightly controlled and regulated by hormones, parathyroid hormone, calcitriol and possibly calcitonin. Daily allowance currently recommended by most European countries and the USA is 200 -400 IU (5 -10 ug/day), but the level is recommended to be increased to 2000 IU/day.

MK-0217A is a combination product of alendronate-Na (70 mg free acid) and VitaminD3 (2800 IU). The tablet contains a single weekly dose of ALN/VitD3 of 70 mg/2800IU. This is an NDA application without clinical data.

CMC

The Vitamin D3 [redacted] is manufactured by [redacted]. It contains some impurities, [redacted]. They are not associated with unexpected toxicity and need no qualification.

Table P-1

Alendronate Sodium 70 mg/Vitamin D_3 2800 I.U.
Combination Tablets — Market Composition

Component	Reference	Function	mg/tablet
Alendronate Sodium	Ph. Eur.	Active	91.37[†]
Vitamin D_3	Ph. Eur..	Active	
Lactose Anhydrous	NF/Ph. Eur.		
Microcrystalline Cellulose	NF/Ph. Eur.		
Collodial 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

CLINICAL STUDIES

A bioequivalence study (Study P226) was carried out to determine alendronate and Vitamin D3 pharmacokinetics, each in a separate part of the study.
The conclusions of the biopharmaceutics program were:

1. The alendronate in the 70-mg alendronate/2800-IU vitamin D3 combination tablet is bioequivalent to the marketed 70-mg alendronate tablet.
2. The bioavailability of the 2800-IU vitamin D3 in the 70-mg alendronate/2800-IU vitamin D3 combination tablet is similar to that of the 2800-IU vitamin D3 administered alone.
3. Following administration of the 70-mg alendronate/2800-IU vitamin D3 combination tablet after an overnight fast and 2 hours before a standard meal, the mean vitamin D3 serum AUC0-120 hr is 296.4 ng.hr/mL and the mean Cmax is 5.9 ng/mL.

PHARMACOLOGY/TOXICOLOGY PROGRAM

The sponsor was not required to conduct preclinical pharmacology, toxicology or carcinogenicity studies for the combination product, and no pharmacology or toxicology studies with the combination (ALN + VitD3) were performed in animals. However, a review of preclinical toxicity data for Vitamin D obtained through the Freedom of Information Act and published literature was provided. Alendronate has been well characterized preclinically. Data in support of alendronate are provided by reference to NDA 20-560.

I. PHARMACOLOGY
No studies with the combination

II. PHARMACOKINETICS/TOXICOKINETICS
No studies with the combination

III. SAFETY PHARMACOLOGY
No studies with the combination

IV. GENERAL TOXICOLOGY

Data for alendronate are provided by reference to NDA #20-560.

The potential toxicity of 1,25-OH2VitD3 (RocaltrolTM) has been studied in vitro and in vivo. Studies with VitD3 also include an evaluation of potential tumor growth inhibition. All required toxicity studies with alendronate have been performed and are provided by reference to NDA #20-560 (Fosamax). Preclinical toxicity data are from FOIA or published literature.

Single dose
In a single oral dose study with calcitriol in mice (1,2,4 mg/kg), all doses (≥250,000 times the oral calcitriol dose recommended for humans of 0.25ug, or 0.004ug/kg) (on mg/kg basis) caused respiratory depression, decreased motor activity, tremors, ptosis, abnormal gait.

Repeat dose
In a 13-week IV study in rats, with doses of 0.05, 0.15, 0.45 ug/kg/day, there was dose-related hypercalcemia in all treated, hypercholesterolemia and hypoproteinemia in MD and HD, tissue deposition of calcium in MD, HD, and parathyroid atrophy in all groups. Decreased body weight and decreased weight of reproductive organs was seen in MD and HD. Effects were partially reversible. NOAEL was 0.05 ug/kg excluding calcemic effects (<0.05 ug/kg/day including calcemic effects).

In a 26-week IV study in rats with doses 0.05, 0.15, 0.45, 0.9 ug/kg/day, there were dose-related decreases in body weight, hypercalcemia, increase in kidney weight in females, tissue calcium deposition and parathyroid atrophy at all doses. Chemistry changes (cholesterol, protein) and adrenal histology changes were seen at the higher doses. NOAEL was <0.05 ug/kg/day excluding calcemic effects.

In a 13-week IV study in dogs, with 0.025, 0.05, 0.1 ug/kg/day calcitriol there was excessive toxicity and mortality at 0.1 ukd and dosing was stopped on Day 56. At 0.05 and 0.1 ukd, there was a decrease in BW, increase in BUN, hypercholesterolemia, hypo-chloremia and hypermagnesemia, and changes in organ weights. Dose-related hypercalcemia was seen in all treated, and there was calcium deposition in numerous tissues. Also seen were treatment-related C-cell hyperplasia, thymus atrophy, Kupffer cell pigment accumulation, salivary gland atrophy. NOAEL was 0.025 ug/kg/day excluding the calcemic effect.

In a 52-week study, dogs were given IV doses of calcitriol of 0.01, 0.02, 0.04/0.06 ug/kg, 3 times a week. There similar changes including hypercalcemia, tissue calcification, sclerosis/ fibrosis of bone marrow, as in 13-week study in the HD group. NOAEL was 0.02 ug (3x/wk) including or excluding the calcemic effect.

Rats were given oral doses of 5000 - 10,000 - 20,000 IU/kg/day of Vitamin D3, and sacrificed after 4, 8, 12, 26 weeks. Reduced BW gain in MD, HD. Dose-dependent increase in serum Ca and P, and increased urinary Ca/creatinine ratios in all treated. Mineralization of renal tubules in LD, MD, and nephrocalcinosis at HD at 4 weeks. Nephrocalcinosis in MD, HD at 26 weeks. Focal proliferative changes in adrenal medulla, including pheochromocytoma in LD, MD, HD, in majority

of animals in MD, HD. NOAEL was <5000 IU/kg/day (<125ug/kg/day). In humans dosed with 2800 IU weekly, dose is 70 ug/kg/week, or 10 ug/kg/day. Thus, doses of 5000, 10,000, 20,000 IU/kg/day in rats are equivalent to 2x, 4x, 8x the human dose proposed.

The results obtained in the toxicity studies reflect the well known calcemic effect of calcitriol, the active hormone metabolite of vitamin D3.

It is unclear how exposure in animals given IV doses of calcitriol relate to the expected calcitriol plasma levels in humans given a weekly dose of Fosamax plus (70 mg ALN + 2800IU VitD3).

IV. GENETIC TOXICOLOGY

Data for alendronate are provided by reference to NDA #20-560.

Information was from studies performed with calcitriol (available through FOIA). These studies are also described in the calcitriol label. Data for alendronate are provided by reference to NDA 20-560.

An Ames test in strains S.typhimurium TA 1535, TA 100, TA 1537, TA 98 with 2.5, 25, 250 ug/plate with or without S-9 activation was negative.

A mouse micronucleus test was performed in Fullinsdorf Moro Albino mice, with single oral doses of 1, 2, 4 mg/kg. Evaluation at 24h showed no significant increase in micronucleated PCE's compared to vehicle control, and no significant change in PCE/NCE ratios. The high dose was acceptable.

V. CARCINOGENICITY

Data for alendronate are provided by reference to NDA #20-560

There are no rodent carcinogenicity studies with Vitamin D3 reported in the literature. Vitamin D3 may be involved in the control of cell processes not directly related to calcium metabolism. Data from some published studies with cell lines and animals support the hypothesis that Vitamin D may inhibit tumor development. However, promoter-like effects have also been reported.

VI. REPRODUCTIVE TOXICITY

There are no studies with VitaminD3 in the published literature. However, there are studies with Vitamin D2.

New Zealand White rabbits were given Vitamin D2, 1000-10,000-100,000 IU every 2 days, for 14 doses, during gestation. BW gain decreased in all treated. In all treated (pooled) serum Ca was 15.2 mg/dL vs. 12.3 mg/dL in controls. HD does had higher number of abortions (6/26 pregnancies) vs. control (0/27).In mothers, 2/4 HD does had aortic calcifications. Supravalvar lesion (focal mural thickening of aorta) observed in 2/11MD, 6/20 HD fetuses. No lesions in control or LD fetuses (Chan et al, Pediatr.Res.13,121-126, 1979) (NDA Ref. 4.3.11).

Adult New Zealand rabbits were treated with i.m. Vitamin D2 every other day during pregnancy (total of 1.5 million units). Supravalvular aortic stenosis was observed in 4/18 neonates and 6/34 of the total offspring of treated animals. Blood levels of Vitamin D2 were 7 and 9 times (2190, 1290 units/100 mL) greater in treated does (and neonates as compared to controls (310, 150 units/mL). (Friedman and Roberts, 1966; NDA Ref 4.3:12)

Female albino rats were treated with high daily doses of Vit D2 (20,000IU, or 150,000-200,000 IU/kg/day) from various days before mating until sacrifice at end of pregnancy. Dosed from Day-6

before mating, caused persistent diestrus and inhibited pregnancy. Given 0-5 days before mating, Vit D2 caused resorptions. Uterine morphology was changed. Dosing 5-7 or 10-11 days after mating had no clear effect. (Nebel and Ornstein, Israel J.Med.Sci 1966, NDA Ref. 4.3.13).

Female albino rats were treated from Gestation Day 9 until GD 17, 19, or 21 with 40,000 IU Vit D2. There was decrease in fetal weight (30-50%) on all days. Femur weight and percent ash weight were decreased in parallel with dosing duration. On GD17, there was lack of calcifying cartilage and penetrating blood vessels. On GD19, 21 there were degenerative changes in fetal femora (chondrocyte necrosis in zone of reserve cartilage). Also, loss of columnar arrangement of femur epiphysis at GD19. Short and thin diaphysises with metaphyseal curvature were seen at GD21 (Ornoy et al, Arch Path 87, 1969; NDA Ref. 4.3.14).

Female albino rats were dosed with 40,000IU Vit D2 from GD10-GD21. Neonatal mortality (50%) after parturition. In survivors, there was impaired osteogenesis of long bones (retarded epiphyseal ossification, thinning of physeal hypertrophic cell layer, retention of metaphyseal endochondral bone, thickening of periosteum around diaphysis). These are considered exaggerated pharmacological effects of Vitamin D. (Ornoy et al, Israel J. Med Sci 1972; NDA Ref. 4.3.15).

VIII. SPECIAL TOXICOLOGY

N/A

IX. SUMMARY AND EVALUATION

See Executive Summary

X. APPENDIX

LABEL (with minor changes)

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Gemma Kuijpers
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PHARMACOLOGIST
concur with recommendations