No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Writ of Certiorari
To The United States Court of Appeals
For The Third Circuit

JOINT APPENDIX (VOLUME II OF II)
(Pages 400–771)

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[Exhibit 47 to Ecklund Declaration]

Subtrochanteric insufficiency fractures in patients on alendronate therapy

A CAUTION

We carried out a retrospective review over ten months of patients who had presented with a low-energy subtrochanteric fracture. We identified 13 women of whom nine were on long-term alendronate therapy and four were not. The patients treated with alendronate were younger, with a mean age of 66.9 years (55 to 82) *vs* 80.3 years (64 to 92) and were more socially active. The fractures sustained by the patients in the alendronate group were mainly at the femoral metaphyseal-diaphyseal junction and many had occurred after minimal trauma. Five of these patients had prodromal pain in the affected hip in the months preceding the fall, and three demonstrated a stress reaction in the cortex in the contralateral femur.

Our study suggests that prolonged suppression of bone remodelling with alendronate may be associated with a new form of insufficiency fracture of the femur. We believe that this finding is important and indicates the need for caution in the long-term use of alendronate in the treatment of osteoporosis.

Alendronate is a potent inhibitor of bone resorption and was the first drug of its class to be approved for

use in the prevention of osteoporotic fractures by the USA Food and Drug Administration in 1995.[1] In two randomised controlled studies, treatment with alendronate has been shown to decrease the incidence of vertebral and femoral-neck fractures in post menopausal osteoporotic patients.[2,3] We also prescribe it as a first-line treatment for patients with osteoporosis. There are now a considerable number of patients who have been taking alendronate for at least five years. The medication is excluded from health-service subsidy and the full cost has to be borne by the patient. It is thus only really available to the upper socioeconomic classes

We have observed an apparent rise in the number of subtrochanteric fractures of the femur in women aged between 50 and 70 years after minimal or no trauma. Many of these patients had been receiving alendronate for at least three years.

We considered that it was unusual for patients receiving alendronate to sustain such fractures so easily. In an attempt to establish if there is a link between the two we reviewed all low-energy subtrochanteric fractures presenting to our department over a period of ten months, and compared the patients who were taking alendronate or had been taking it within one year of a fracture, with those who were not.

Patients and Methods

Between 1 May 2005 and 28 February 2006 we carried out a retrospective review of the operating records of all orthopaedic surgeons from two hospitals (Singapore General Hospital and Changi General Hospital, Republic of Singapore) to identify patients

who had been treated surgically for subtrochanteric fracture of the femur. A subtrochanteric fracture was defined as one in the region of the femur which extended from the lesser trochanter to the junction of the proximal and middle third of the femoral shaft. We included only fractures sustained in low energy trauma and excluded those due to a car accident, a fall from a height or underlying malignancy. Ethical approval was obtained from the Institutional Review Board before the study was commenced.

We identified 13 women with a subtrochanteric fracture which had been sustained by low-energy trauma. Details of the patients are given in Table I. There were nine women who had been taking alendronate, and four who had not. The patients in the alendronate group were younger, with a mean age of 66.9 years (55 to 82) *vs* 80.3 years (64 to 92).

Case records of the patients were reviewed to determine the mechanism of injury, the presence or absence of prodromal pain before the fracture, the bone mineral density (BMD) if available, the past medical history, the histological findings of bone from the site of the fracture when available, and the administration of alendronate within a year of the fracture. Radiographs were reviewed by three authors (S-KG, JSBK, TSH) to classify the patterns of the fracture according to the AO classification (Table II)[4], and to look for abnormality in the contralateral limb. There was complete agreement on all classifications. When necessary, the patients were also interviewed by telephone to ascertain the details of their symptoms and pharmacological history.

Table I. Details of the 13 patients

	Alendronate	No alendronate
Number	9	4
Mean age in yrs (range)	66.9 (55 to 82)	80.3 (64 to 92)
AO classification of subtrochanteric fracture		
A	8	0
B	1	3
C	0	1
Mean duration of alendronate therapy in yrs (range)	4.2 (2.5 to 5)	-

Table II. Comprehensive AO classification of subtrochanteric fractures[4]

Type	Description
A	Simple transverse or short oblique fracture
B	Comminution in the form of a medial or lateral wedge fragment
C	Severe comminution representing a segmental loss of continuity

Measurements of bone density. Bone density data were only available for some of the patients within a year either prior to, or after the fracture. The measurements were made by dual-energy x-ray absorptiometry (DEXA). Measurements were performed on the femoral neck and L1 to L4 vertebral bodies. The World Health Organisation defines osteoporosis as a BMD value more than 2.5 SDs below that of the young adult peak BMD known as the *T* score.[5] Osteopenia is defined as a BMD between 1.0 SD and 2.5 SDs below the young adult peak BMD.[5]

Results

The mean follow-up from the time of admission for the fracture was 223 days (99 to 341).

Mechanisms of injury. The mechanisms of injury are given in Table III. Four patients in the alendronate group reported that the fracture had occurred in the absence of a fall. Each of them recalled experiencing a sharp pain or hearing a snapping sound at the moment of fracture.

Prodromal symptoms. In the alendronate group five patients reported experiencing pain or discomfort in the fractured limb, between two and six months before the injury, one of whom had prodromal pain in the groin on the fractured side, whereas the remainder localised the pain at the lateral aspect of the thigh. By contrast, none of the patients in the nonalendronate group had prodromal symptoms.

History of treatment with alendronate. Nine patients were taking alendronate and oral calcium for treatment of osteoporosis either at the time, or within the year before the injury. Of the four patients who were not currently taking alendronate, two were taking oral calcium supplements. The data concerning the administration of alendronate, and the BMD of the patients (when available) are given in Table IV.

Fracture configurations. In the alendronate group eight of the patients had AO type-A fractures occurring at the metaphyseal-diaphyseal junction while the ninth had a type-B fracture. In six, cortical hypertrophy was identified on the lateral, tension side of the subtrochanteric region of the femur (Figs 1 and 2). In three, a similar hypertrophied cortex could be seen in the contralateral subtrochanteric region (Fig. 3).

Three patients in the non-alendronate group had an AO type-B fracture and one a type-C fracture (Fig. 4).

As judged on the plain radiographs, the bones appeared to be extremely osteoporotic with the loss of the trabecular pattern.

Histological findings. In five patients in the alendronate group, bone biopsies were sent intra-operatively for histological analysis to exclude neoplasia. All were found to be benign.

No histological specimens were sent from the four patients who were not taking alendronate because there was radiological evidence of severe osteoporosis in each.

Discussion

Pauwels[6] was the first to identify that the subtrochanteric region of the femur is subjected to maximal bending movement. As such, this area is one of the strongest parts of the femur and it is unlikely to fail in low-energy trauma, unless extreme osteoporosis is present. It has been estimated that only 10% to 34% of all fractures of the hip are in the subtrochanteric region.[7]

The patients in the alendronate group were striking for several reasons. All had received alendronate and oral calcium therapy for a mean of 4.2 years (2.5 to 5), the trauma which these nine patients had sustained was minimal, a few had experienced prodromal pain in the months preceding the fracture and lastly, most were in the early stages of the menopause and had led relatively active lifestyles at the time of injury.

Table III. Biomedical data and mechanism of injury in all 13 patients

Case	Age (yrs)	Mechanism	Co-morbidities	Presence and duration of prodromal pain
Alendronate				
1	65	Tripped and fell	Alpha thalassaemia minor, hysterectomy and ovarectomy	Yes, 2 months
2	60	Heard a crack in the thigh while retrieving a shot during badminton	Nil	Yes, 6 months
3	67	Fell down three stairs and landed on buttocks	Nil	No
4	55	Right-anterior thigh pain after tripping awkwardly while crossing road	Eczema, on long-term oral steroids	No
5	69	Heard a crack while shopping	Diabetes mellitus. Cervical and lumbar spondylosis	Yes, 2 months
6	82	Right hip pain after fall	Supraventricular tachycardia Mycoplasma pneumonia	Yes, 6 months
7	69	Slipped and fell on to buttocks	Hysterectomy and ovarectomy. Cervical and lumbar spondylosis	Yes, 3 months
8	64	Fractured femur while walking down stairs	Nasopharyngeal carcinoma 10 years previously Panhypopituitarism	No
9	71	Tripped and fell while shopping	Ischaemic heart disease Osteoarthritis knees	No
No alendronate				
1	92	Fell after vertiginous episode	Hypertension. Hypothyroidism	No
2	64	Tripped and fell while walking	Hypotension, renal failure and osteodystrophy Diabetes mellitus	No
3	86	Fell after being pushed by grandson	Peptic ulcer disease. Patellofemoral arthritis	No
4	79	Slipped and fell in kitchen	Nil	No

Table IV. The bone mineral density (BMD) status of the alendronate patients and the duration of treatment at the time of the injury

	BMD				
Case	**Year of DEXA scan**	**Left femoral neck T-score**	**Lumbar spine T-score**	**Diagnosis**	**Alendronate duration (yrs)**
1	2003	-1.1	-0.8	Osteopenia	4
2	-	-	-	Osteoporosis	2.5
3	2003	-1.6	-1.2	Osteopenia	3
4	2005	-2.1	-1.1	Osteopenia	5
5	2005	-1.3	-1.2	Osteopenia	5
6	-	-	-	-	at least 5
7	-	-	-	Osteoporosis	at least 5
8	2005	-2.1	-2.5	Osteoporosis	5
9*	-	-	-	-	3

* unable to give details of BMD status

Alendronate belongs to the family of bisphosphonate drugs which are stable synthetic analogues of pyrophosphate characterised by a phosphorous-carbon-phosphorus bond.[8] The administration of bisphosphonates, as a group, is one of the first-line treatments for the prevention of osteoporotic fractures in menopausal patients.[9] The Fracture Intervention Trial[2] study showed that patients who were taking alendronate had a reduced risk of sustaining an osteoporotic fracture at a follow-up of three years. It has also been proven that alendronate therapy is associated with an increase in BMD in osteoporotic patients.[10] This effect was sustained throughout the duration of alendronate therapy when administered for up to ten years.[10]

Alendronate inhibits bone resorption by suppressing the activity of osteoclasts, and inducing them to undergo apoptosis.[8] While this leads to an increase in the BMD of patients with osteoporosis,[11] treatment with alendronate has also been shown to reduce the amount of bone turnover.[12,13] In animal experiments concern has been expressed that alendronate therapy can lead to the accumulation of skeletal microdamage.[14] In humans, prolonged administration of intravenous pamidronate can lead to the development of osteopetrosis or marble bone disease.[15] This microdamage may increase the risk of insufficiency fractures.

The fractures in the alendronate group were all simple, mostly AO type-A subtrochanteric fractures in patients who had radiologically good cortical bone stock. This contrasts with the radiological findings seen in patients who were not taking alendronate. It is interesting that thickening in the lateral femoral

cortex was present in six of the alendronate patients, and in three of these the cortical thickening was bilateral. This, and the history of prodromal pain, lend support to the possibility that these were insufficiency fractures which possibly resulted from altered bone metabolism.

This is the first report to document a series of fractures in the subtrochanteric region of the femur in patients who were receiving alendronate for a long period. However, our study certainly does not establish cause and effect. Indeed, many of these patients were originally on alendronate and calcium therapy because they were at a higher risk for osteoporotic fractures. Nevertheless, our findings identify a potential, originally unrecognised, side-effect of prolonged pharmacological suppression of bone turnover.

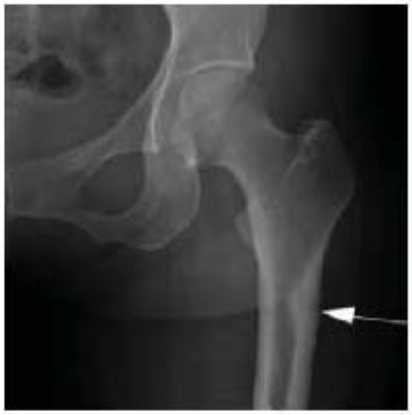

Fig. 1a

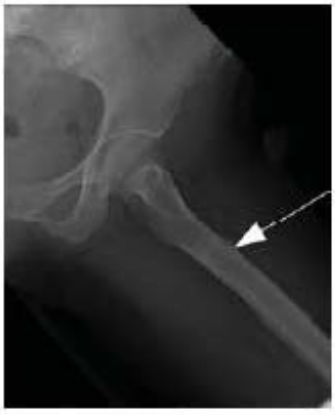

Fig. 1b

Radiographs of a 65-year-old woman who had tripped and fallen while walking on flat ground and had been

on alendronate for the past five years, showing a) a type-A left subtrochanteric fracture with b) a cortical reaction in the lateral (tension) side of the femur.

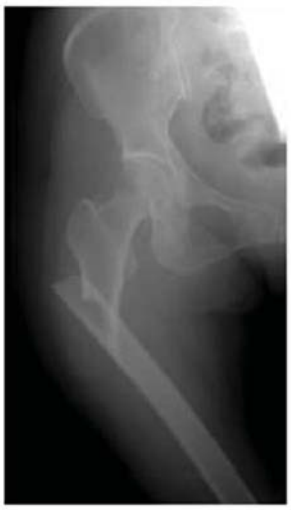

Fig. 2a

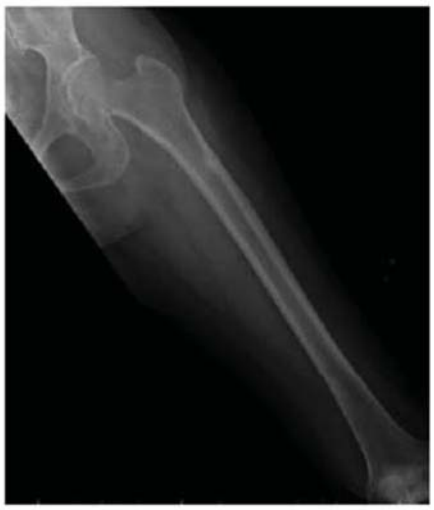

Fig. 2b

Radiographs of a 69-year-old woman with a history of cervical and lumbar spondylosis and who had bilateral thigh pain for two months before the fracture. She had been on alendronate for five years. She heard a snapping sound in a) her right thigh while shopping. b) The left lateral subtrochanteric region shows evidence of a stress injury.

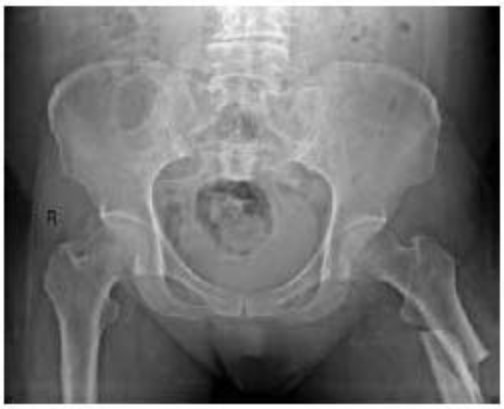

Fig. 3a

Fig. 3b

Radiographs of a 67-year-old woman who had fallen down three steps and landed on her buttocks, showing a) anteroposterior view of a subtrochanteric fracture with a transverse configuration and a medial sharp spike, and b) the right subtrochanteric region showing cortical hypertrophy on the lateral side. She had been on alendronate for three years.

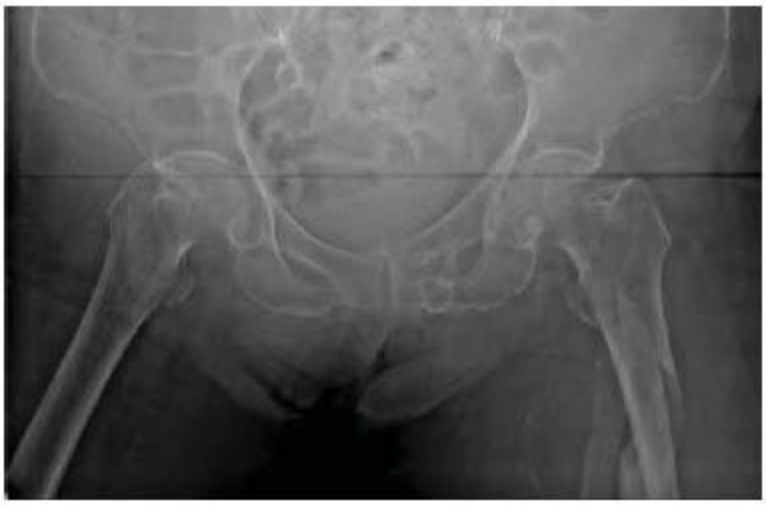

Fig. 4

A 92-year-old woman with chronic vertigo, hypothyroidism and hypotension who had a vertiginous fall and was found to be hyponatraemic and septic on admission. Radiograph showing a type-C subtrochanteric fracture. She was not taking alendronate.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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[Exhibit 48 to Ecklund Declaration]

Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy

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Alendronate, an inhibitor of bone resorption, is widely used in osteoporosis treatment. However, concerns have been raised about potential oversuppression of bone turnover during long-term use. We report on nine patients who sustained spontaneous nonspinal fractures while on alendronate therapy, six of whom displayed either delayed or absent fracture healing for 3 months to 2 yr during therapy.

First Published Online December 14, 2004

Abbreviations: BFR, Bone formation rate; BMD, bone mineral density; BsAP, bone-specific alkaline phosphatase; GIO, glucocorticoid-induced osteoporosis; NTx, N-telopeptide; SSBT, severe suppression of bone turnover.

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Histomorphometric analysis of the cancellous bone showed markedly suppressed bone formation, with reduced or absent osteoblastic surface in most patients. Osteoclastic surface was low or low-normal in eight patients, and eroded surface was decreased in four. Matrix synthesis was markedly diminished, with absence of double-tetracycline label and absent or reduced single-tetracycline label in all patients. The same trend was seen in the intracortical and endocortical surfaces.

Our findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures. Although coadministration of estrogen or glucocorticoids appears to be a predisposing factor, this apparent complication can also occur with mono therapy. Our observations emphasize the need for increased awareness and monitoring for the potential development of excessive suppression of bone turnover during long-term alendronate therapy. (*J Clin Endocrinol Metab* 90: 1294–1301, 2005)

ALENDRONATE, A POTENT inhibitor of bone resorption, is now widely used in the treatment of osteoporosis. A number of randomized clinical trials have shown that it significantly increases bone density of spine and hip and reduces the incidence of fractures in osteoporotic patients (1–4).

Although alendronate is generally safe and effective, it carries the potential risk of

oversuppressing bone turnover that can potentially impair some of the biomechanical properties of bone. In experimental animals, alendronate has been shown to inhibit normal repair of microdamage arising from marked suppression of bone turnover, which, in turn, results in accumulation of microdamage (5–7). A 2- to 7-fold increase in microdamage accumulation after pharmaceutical suppression of bone remodeling was associated with a 20% reduction in bone toughness (the ability to sustain deformation without breaking), without reduction in bone strength (6–8). However, the clinical significance of these changes in biomechanical measurements has not yet been well defined.

In addition to microdamage accumulation, chronic oversuppression of bone turnover by alendronate may allow secondary mineralization to continue (9), producing hypermineralized bone that may be more brittle (10, 11). The degree of mineralization has been shown to affect the material properties of bone, with low mineralization levels (as seen in osteomalacia) causing reduced stiffness and strength, and hypermineralization likely contributing to reduced fracture toughness (10, 11).

Ott (12) speculated that chronic alendronate therapy in humans might impair mechanical strength of bone. This suggestion was based on the apparent increase in fracture rate with prolonged therapy (2), though challenged by the authors of that report (13). Recently, Whyte *et al.* (14) described a 12-yr-old boy who, after 3 yr of treatment with iv bisphosphonate (pamidronate), presented with findings consistent with osteopetrosis, *i.e.* increased bone density and impaired remodeling. The authors, however,

acknowledged that the dose of pamidronate given to the patient was more than four times the amount typically given to children with osteogenesis imperfecta.

In this report, we describe bone biopsy data from nine patients with osteoporosis or osteopenia treated with alendronate for 3–8 yr alone or in combination with estrogen. All patients had spontaneous nonspinal fractures that developed after 1–8 yr of alendronate treatment. Histomorphometric analysis of bone biopsy samples revealed a marked suppression of bone turnover.

Subjects and Methods

Patients

Nine patients (eight postmenopausal women and one man) on longterm alendronate treatment were included in this report. Four patients (patients 1–4) were from the Henry Ford Hospital in Detroit, and five (patients 5–9) were from the University of Texas Southwestern Medical Center in Dallas. Alendronate was given at a dose of 10 mg/d or 70 mg/wk for 3–8 yr along with supplemental calcium. Eight patients were also given vitamin D, 400–800 IU/d, whereas one patient was maintained on a pharmacological dose of vitamin D. Relevant clinical data are summarized in Table 1.

In patients 1–4, alendronate was given alone, without estrogen or glucocorticoid (group A, Table 1). Patients 1–3 were postmenopausal women without prevalent fractures, in whom alendronate treatment was started elsewhere because of either osteoporosis or osteopenia by bone density. Patient 4 was started on alendronate when he presented with metatarsal

stress fractures and was found to have osteopenia by bone density.

In patients 5–7 (group B, Table 1), alendronate was administered with estrogen. Patients 5 and 7 took estrogen continuously for 12 and 15 yr, respectively, whereas patient 6 received it intermittently for 3 yr. Although none had prevalent fractures, alendronate was started elsewhere for postmenopausal osteoporosis (patients 5 and 6) or osteopenia (patient 7) of spine or hip by bone density.

Patients 8 and 9 were given alendronate for glucocorticoid-induced osteoporosis (GIO; group C, Table 1). Patient 8 has been taking glucocorticoid for asthma for 20 yr, and patient 9 for fibromyalgia for 8 yr, before alendronate was begun. Glucocorticoid was continued during and after alendronate was stopped in patient 9 and was tapered and eventually discontinued in patient 8. Patient 9 was on vitamin D, 50,000 IU thrice a week, for postsurgical hypoparathyroidism. Both women had fractures of the femoral shaft and metatarsal bones after minimal trauma before alendronate treatment.

Nonspinal fractures during alendronate therapy

All nine patients developed atraumatic nonspinal fractures while on alendronate treatment (Table 1) and while performing normal daily activities such as walking, standing, or turning around. Among the seven patients who were not on glucocorticoid (patients 1–7), atraumatic nonspinal fractures (sacrum, rib, ischium, pubic rami, femoral shaft) developed after 3–8 yr of alendronate treatment. One patient (patient 2) also had a lumbar vertebral fracture. Among those with GIO, patient 8 developed

a separation of previously formed callus of the fractured femoral shaft 1 yr after starting alendronate. Patient 9 fractured the right femoral shaft, at the site of a previous fracture, while walking, after 2 yr of alendronate treatment.

Because the patients continued taking alendronate after the fracture(s), we had the opportunity to radiographically assess fracture healing while still on treatment (Table 1). In six patients (patients 3 and 5–7 without glucocorticoid, and patients 8 and 9 on glucocorticoid), evidence of delayed fracture healing (lack of adequate callus formation and filling in of fracture gap) was observed 3 months to 2 yr after fracture occurrence in the ischium, pubic rami, and femoral shaft. In one (patient 8), delayed healing of the femoral fracture persisted for 2 yr despite internal fixation and bone graft. In the remaining patients (patients 1, 2, and 4), fracture healing could not be assessed because bone biopsy was obtained shortly after the incident fractures.

Bone biopsy

The decision to perform bone biopsy was based on the unusual clinical presentation of these patients. First, the fracture sites (*e.g.* bilateral femoral shaft, pubic bone, ischium) were not the typical sites for osteoporotic fractures. Second, a majority of these patients (patients 1–7) were fracture-free in the intervening years before the presentation. Last, six of nine patients (patients 3 and 5–9) presented with delayed fracture healing. After obtaining an informed consent, bone biopsies were performed while patients were still on alendronate therapy (3–8 yr) and about 1 month to 2 yr after incident fractures (Table 1).

A transiliac bone biopsy was obtained using a 7.5-mm diameter trocar under local anesthesia, following *in vivo* double-tetracycline labeling as previously described (15). A 2-10-4-4 labeling regimen with declomycin was used in Dallas, and a 3-11-3-4 regimen with oxytetracycline was used for the patients at the Henry Ford Hospital. Specimens were prestained for 72 h in Villanueva, Osteochrome (Polysciences, Inc., Warrington, PA). After dehydration in increasing concentrations of alcohol, the specimens were embedded in methylmethacrylate and kept at 37 C until fully polymerized. The embedded biopsy samples were then sectioned on a Reichert-Jung model E microtome (Cambridge Instruments, Heidelberg, Germany) at a thickness of 10 μm. A total of six sequential sections were cut from each specimen. Sections 1, 3, and 5 were mounted directly to slides and were examined under UV light for tetracycline uptake. Sections 2, 4, and 6 were mounted to slides, deplasticized in xylene, stained with toluidine blue, and examined for static measurements. Histomorphometric measurements were made with an Aus Lena microscope video camera, and an image capture program (Bioquant Bone Morphometry Program; R & M Biometrics, Nashville, TN). Histomorphometric measurements and calculations were based on modifications of previously published methods (16–18). The bone formation rate (BFR) was calculated as half of the single-labeled surfaces plus all the double-labeled surfaces multiplied by mineral apposition rate in $\mu m^3/\mu m^2/d$ (19). When no double-labeled surfaces were observed, BFR was calculated as half of the single-labeled surfaces multiplied by 0.3 μm / d as previously described (19). The nomenclature

of the measured and calculated variables is according to the criteria established by the Committee on Bone Histomorphometry of the American Society for Bone and Mineral Research (20). Slides, both for fluorochrome assessment and toluidine blue stained for static measurements, were analyzed by a single investigator (J.E.Z.) at the University of Texas Southwestern Medical Center, who was blinded to the patients' identity. For patients in whom no tetracycline double labels were observed, all three cut sections were examined for the presence of any tetracycline labeling.

Biochemical measurements and bone densitometry

Laboratory studies were done either on the day of, or shortly before, bone biopsy. In some patients, not all tests could be obtained. Serum samples were assayed for calcium, phosphorous, creatinine, PTH (ELISA kit; Alpco Diagnostics, Windham, NH), 25-hydroxyvitamin D (ELISA, Alpco Diagnostics), bone-specific alkaline phosphatase (BsAP=Alkphase-B; Quidel, Mountain View, CA), and osteocalcin (Oc, ELISA; Diagnostic Systems Laboratories, Webster, TX). Urine was collected in 24-h pools for calcium, creatinine, N-telopeptide (NTx, Osteomark; Ostex International, Seattle, WA), and hydroxyproline (OH-pro, Hypro nosticon; Organon Teknika Corp., Durham, NC). Spot fasting urine samples were used for the analysis of NTx and creatinine in patients 1–4. Except for serum calcium, phosphorous, and creatinine, the remaining serum and urine analyses from all patients were performed at the Mineral Metabolism laboratory in Dallas.

TABLE 1. Clinical data

Patient	Age (yr)/ sex	Diagnosis	Duration of alendronate treatment (yr)	Other medications	Incident fractures (yr on alendronate)	Delayed/absent healing on alendronate (fracture site)	Fracture healing yes/no (months off alendronate)
Group A							
1	55/F	PO	6	Ca, D	Sacrum (6)	NA	No (12)
2	76/F	PO	7	Ca, D	Vertebra, rib (7)	NA	Yes (6)
3	52/F	POpen	8	Ca, D	Femoral shaft (8)	4 months (femoral shaft)	No (9)
4	68/M	IO	8	Ca, D	Bilateral femoral shaft (8)	NA	No (8)
Group B							
5	68/F	PO	3	E2, Ca, D	Sacrum, ischium (3)	3 months (ischium)	Yes (8)
6	70/F	PO	5	E2, Ca, D	Pubic rami (3)	2 yr (pubic rami)	Yes (4)
7	67/F	POpen	5	E2, Ca, D	Bilateral femoral shaft (5)	9 months (left femoral shaft)	Yes (5)
Group C							
8	49/F	GIO (asthma)	3	Prednisone, Ca, D	Proximal femur (1)	2 yr (femur)	No (8)
9	64/F	GIO (fibromyalgia)	4	Prednisone, Ca, D	Metatarsal, proximal femur (3)	8 months (proximal femur)	Yes (3)

PO, Postmenopausal osteoporosis; POpen, postmenopausal osteopenia; IO, idiopathic osteoporosis; E2, estrogen; Ca, calcium; D, vitamin D; NA, not available or not applicable; F, female; M, male.

TABLE 2. Histomorphometric findings in cancellous bone

	Patient									Control (mean ± SD)
	1	2	3	4	5	6	7	8	9	
BV/TV (%)	14.3	15.2	14.7	9.7	9.4	12.2	17.2	10.9	8.9	21.2 ± 4.9
OV/BV (%)	0.42	0.66	0.17	0.07	0	0	2.5	0.89	0.05	1.85 ± 1.07
O.Th (μm)	4.3	8.0	4.6	4.5	0	0	10.2	4.0	3.9	9.3 ± 2.1
Ob.S/BS (%)	1.7	0	0.14	0	0	0	0.7	3.6	0.2	4.4 ± 2.0
ES/BS (%)	3.5	9.3	9.2	5.6	0.9	2.1	4.3	1.3	1.7	4.0 ± 2.0
Oc.S/BS (%)	1.0	0.3	0.35	0.12	0	0.2	0.35	0.3	0.1	0.7 ± 0.7
dLS/BS (%)	0	0	0	0	0	0	0	0	0	4.3 ± 2.9
sLS/BS (%)	0.6	0	0.42	0.44	0	0	0.5	0	0.3	6.0 ± 4.1
BFR ($\mu m^3/\mu m^2/yr$)	1.0	0	0.7	0.2	0	0	0.6	0	0.4	15 ± 0.8

BV, Bone volume; TV, total volume; OV, osteoid volume; Ob.S, osteoblastic surface; ES, eroded surface; Oc.S/BS, osteoclastic surface/bone surface; dLS, double-label tetracycline label; sLS, single tetracycline label. BFR, Bone formation rate calculated as ½ × sLS/BS × MAR (micrometers per day) obtained from cortical doubled-labeled surfaces as previously described (19). BFR for four patients was calculated as ½ × sLS/BS × 0.3 μm/d as previously described (19).

Bone mineral density (BMD) of L2–L4 vertebrae, femoral neck, and distal third of the radius was measured by dual-energy x-ray absorptiometry (Hologic QDR, Waltham, MA). Selected x-rays and bone scans were obtained to confirm the presence of fractures and to determine the status of fracture healing (callus formation and filling in of fracture gap).

Results

Bone histomorphometry

Quantitative bone histomorphometric findings of the cancellous bone are summarized in Table 2. Bone volume was reduced in all patients, but the most striking finding was severe depression of bone formation with absence of double-tetracycline labeling in all nine patients (Fig. 1, A and B). Five of the nine biopsy specimens revealed occasional single tetracycline labels (patients 1, 3, 4, 7, and 9). The mean calculated BFR was almost 100-fold lower than in healthy postmenopausal women (Ref. 16; see Table 4). In seven patients (patients 2–7 and 9), cancellous bone surfaces were quiescent with minimal, or no, identifiable osteoblasts (Fig. 2, A and B). Osteoid thickness and volume were either normal or reduced, excluding the possibility of osteomalacia. In addition, there was a trend toward low bone resorption; osteoclastic surface was low or low-normal, except in patient 1, who received alendronate without estrogen, and eroded surface was also reduced in four patients (patients 5, 6, 8, and 9).

All patients had decreased intracortical osteoid surface (Table 3A). Osteoblast surface was also reduced except in patient 1. Five patients (patients 2,

3, 5, 6, and 8) displayed low osteoclast and eroded surfaces. The same trend was observed for endocortical surface, with reduced osteoid and osteoblast surfaces in all patients. Osteoclast surface was low, except in three (patients 2, 4, and 7), and eroded surface was reduced except in four (patients 1–4). Dynamic parameters were also markedly reduced for both intracortical and endocortical bone surfaces, although a greater reduction was seen at the endocortical bone surfaces (Table 3B).

Table 4 summarizes the mean values for the different histomorphometric measurement at the three bone compartments (cancellous, endocortical, and intracortical bone surfaces) compared with control subjects. Except for the intracortical osteoclast surface, all the surface and dynamic parameters were significantly lower in the patients with severe suppression of bone turnover (SSBT) compared with the published controls. The mean BFR at the three bone surfaces was 30- to 100-fold lower than the corresponding values in healthy controls (15).

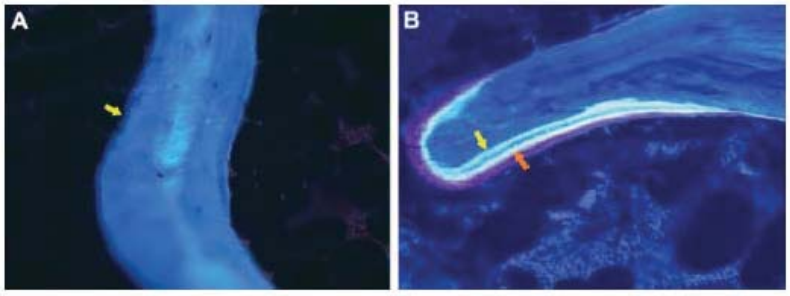

FIG. 1. A, Photomicrograph under UV light from patient 5, showing absence of double label (*yellow arrow*). B, Photomicrograph under UV light from a normal subject, showing two distinct areas of double

label with tetracycline. The faint inner label is from the first course of tetracycline (*yellow arrow*), and the more prominent outer label is from the course of tetracycline given 10 d later (*orange arrow*).

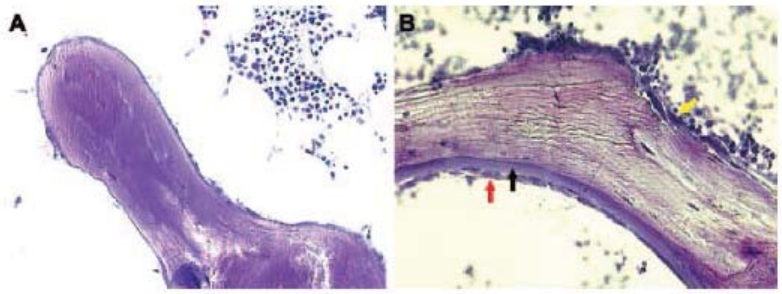

FIG. 2. A, Trabecular bone from patient 5, showing absence of surface osteoid, osteoclasts, and osteoblasts (×160). B, Trabecular bone from a normal subject, showing abundant osteoid (*black arrow*), surface osteoclasts (*yellow arrow*), and osteoblasts (*red arrow*) (×160).

Laboratory findings at the time of bone biopsy

Serum calcium, phosphorus, creatinine, 25-hydroxyvitamin D, and PTH were within the reference range (Table 5). Although serum BsAP ranged widely, serum Oc was either low or at the lower limit of the reference range. Urinary NTx was low to midnormal in seven and high-normal in two. Urinary OH-pro was low or low-normal in all five patients in whom it was measured.

BMD before and after alendronate therapy

BMD results before the initiation of alendronate therapy, obtained from outside institutional records, were limited. Among the six postmenopausal women

not on glucocorticoids, four had osteoporosis and two had osteopenia when alendronate treatment was begun. Among four patients with osteoporosis, the T-score of at least one site was still in the osteoporotic range (below –2.5 SD) in two patients (patients 2 and 6) but was in the osteopenic range (–1.0 to more than –2.5 SD) in two patients (patients 1 and 5) after alendronate treatment (Table 5). Among two with osteopenia, patient 7 was no longer osteopenic, whereas data for patient 3 were unavailable. In patient 4, T-scores were reported to be in the osteopenic range before alendronate treatment and remained in the osteopenic range after treatment. Baseline BMD data were reportedly in the osteopenic range in the two patients on glucocorticoids, and both had normal BMD after 3–4 yr of alendronate treatment.

Fracture healing after stopping alendronate

Therapy was stopped after obtaining a bone biopsy in all patients. Assessment of fracture healing after discontinuation of treatment was available in all patients (Table 1). Four patients had delayed healing. Patients 1, 3, and 4, who were on alendronate alone, continued to have evidence of nonhealing fractures 12, 8, and 9 months off treatment, respectively, and patient 8 (GIO) continued to have poor fracture healing 8 months after discontinuation of alendronate. The remaining four patients had satisfactory fracture healing. In patient 2, fracture healing was noted at 6 months. In patient 5, callus formation was noted at 3 months, and a significant reduction in pain and improvement in mobility occurred after being off of treatment for 8 months. Patient 6 showed robust callus formation in the nonhealing pelvic fracture 4

months after stopping alendronate, with associated improvement in pain. Patient 7 had evidence of fracture healing at 5 months associated with resolution of pain. In patient 9 (GIO), femoral shaft fracture showed complete healing at 3 months. None of the patients developed new fractures after alendronate was discontinued.

Discussion

We describe our clinical observations in nine unselected patients maintained on long-term alendronate therapy for osteoporosis/osteopenia who developed biopsy-proven SSBT. The universal presentation of these patients was spontaneous or atraumatic nonvertebral fracture(s), with delayed or nonhealing of fractures exhibited by six patients while still on alendronate, and by four patients after discontinuation of therapy.

All nine patients displayed histomorphometric evidence of SSBT, similar to the so-called adynamic bone or low turnover described in patients on chronic maintenance hemodialysis (21). The bone surfaces were virtually devoid of cellular elements, BFR was reduced, and matrix formation was severely impaired. In addition, bone resorption was reduced in most patients. Reduced rates of bone formation and resorption were also found on both intracortical and endocortical bone surfaces, indicative of a generalized involvement. To distinguish from adynamic bone, we refer to the condition described in this report as SSBT, defined histologically by reduced osteoblastic and osteoclastic surfaces with decreased or absent tetracycline labeling.

TABLE 3. Resorption and formation parameters on the intracortical and endocortical surfaces

	Patient									Control (mean ± SD)[a]
	1	2	3	4	5	6	7	8	9	
A. Intracortical surface										
OS/BS (%)	5.3	0.3	1.6	1.4	0	3.2	5.9	3.8	0.27	18.7 ± 7.9
Ob.S/BS (%)	11.8	0	0	0	0	2.2	0	1.4	0	5.86 ± 3.36
ES/BS (%)	4	0.22	2.8	7.5	0	0	7.5	0.9	2.9	6.30 ± 4.83
Oc.S/BS (%)	1.04	0.03	0.6	1.2	0	0	0.9	0.15	1	1.01 ± 0.79
dLS/BS (%)	3.2	0.2	0.6	0	0	1.1	0.14	1.4	0.2	
sLS/BS (%)	7.1	0.8	1.1	0	0	0	0.7	1.1	0.3	9.2 ± 4.9
MAR (μm/d)	1.0	0.5	1.0	0	0	0.8	0.6	0.7	0.8	0.65 ± 0.18
BFR/BS ($\mu m^3/\mu m^2/yr$)	24.0	1.0	4.0	0	0	3.0	1.0	6.0	0.5	23.0 ± 15
B. Endocortical surface										
OS/BS (%)	12.1	0.86	1.5	1.4	0	0	3.9	2.2	0.74	24.4 ± 14.4
Ob.S/BS (%)	0.94	0	0	0	0	0	0	0	0	6.86 ± 7.05
ES/BS (%)	10.5	10.9	4.2	7.3	0.63	3.8	4	3.1	2.7	9.56 ± 5.21
Oc.S/BS (%)	0	1.7	0.5	1.0	0	0.33	1.27	0.58	0	1.41 ± 1.68
dLS/BS (%)	0	0	0	0	0	0	0	0	0	
sLS/BS (%)	0.6	0	0	0.2	0	0	0.5	0	0	12.5 ± 9.8
MAR (μm/d)	0	0	0	0	0	0	0	0	0	0.53 ± 0.14
BFR/BS ($\mu m^3/\mu m^2/yr$)	0.3	0	0	0.1	0	0	0.3	0	0	25 ± 23

OS, Osteoid surface; BS, bone surface; Ob.S, osteoblastic surface; ES, eroded surface; Oc.S, osteoclastic surface; dLS/BS, double-labeled surface; sLS/BS, single-labeled surface; MAR, mineral apposition rate. Intracortical BFR was calculated as (dLS/BS + ½ sLS/BS) × MAR; endocortical BFR was calculated as ½ × sLS/BS × 0.3 μm/d (19).

[a] Refs. 15 and 16.

TABLE 4. Comparison of the mean values for selected histomorphometric measurements between patients and controls

	Cancellous bone		Endocortical surface		Intracortical surface	
	Patients	Control	Patients	Control	Patients	Control
OS/BS (%)	3.70 ± 5.09^c	14.30 ± 6.30	2.52 ± 3.79^c	24.40 ± 14.40	2.42 ± 2.22^c	18.70 ± 7.90
Ob.S/BS (%)	0.70 ± 1.22^c	4.40 ± 2.00	0.10 ± 0.31^c	6.86 ± 7.05	1.71 ± 3.87^c	5.86 ± 3.36
Oc.S/BS (%)	0.30 ± 0.29^a	0.70 ± 0.70	0.60 ± 0.61^b	1.41 ± 1.68	0.55 ± 0.50	1.01 ± 0.79
BFR ($\mu m^3/\mu m^2/yr$)	0.32 ± 0.37^c	15.0 ± 0.80	0.08 ± 0.13^c	25.0 ± 23.0	4.39 ± 7.63^c	23.0 ± 15.0

Data are presented as mean ± SD. OS, Osteoid surface; BS, bone surface; Ob.S, osteoblastic surface; Oc.S, osteoclastic surface. Statistical significance *vs.* control group depicted as $^a P < 0.05$; $^b P < 0.01$; and $^c P < 0.001$.

Clinically, SSBT was characterized by incident nontraumatic fractures involving the skeletal areas that are rich in cortical bone, with fractures usually occurring at atypical sites such as femoral shafts, pubic bone, and ischium. In addition, fracture healing appeared to be impaired in most patients with SSBT. Fracture healing was absent or incomplete in six patients, who continued alendronate therapy for 3 months to 2 yr after the onset of incident nonspinal fractures. When alendronate was stopped, fracture healing was still incomplete at 8–12 months in four patients.

There is some evidence that alendronate may have contributed to the histological and clinical picture of SSBT described above. Suppression of bone turnover, to the degree we encountered here, by bone histomorphometry is uncommon in untreated postmenopausal osteoporosis. Coadministration of estrogen has been shown to exaggerate suppression of bone turnover (22, 23), as was seen in three of our patients. However, fractures occurred at sites not typically seen in osteoporosis. Moreover, in some patients, the nonspinal fractures healed poorly while on alendronate, but healed satisfactorily after stopping treatment in most patients. Glucocorticoids alone could suppress osteoblastic bone formation, but sometimes increase osteoclastic resorption, a feature not seen in our two patients with GIO. Chronic steroid treatment in a patient with hypoparathyroidism (as in patient 9) may suppress both bone formation and resorption, but we are unaware of any report showing histomorphometric abnormality with nonspinal fractures.

Prior reports support the view that SSBT may be pathogenetically related to chronic bisphosphonate treatment. In experimental animals, alendronate can impair microdamage repair and compromise some of the biomechanical properties of bone (5–8). In humans, a clinical picture resembling socalled marble bone disease was described after intermittent iv pamidronate treatment (14). Based on an apparent increase in fracture rate after long-term alendronate treatment, a concern has previously been raised that alendronate might impair bone strength (12). More recently, osteonecrosis of the jaw requiring surgical removal of affected tissue was reported in 59 patients who had received iv bisphosphonate for malignancy and in seven patients who took oral bisphosphonate for osteoporosis (24). Although the mechanism was not clearly defined, low bone remodeling was cited as a possible cause of this condition. A recent article reported that alendronate given over a period of 10 yr was safe and effective (25). However, the nonvertebral fracture rate appeared to be numerically the same or higher (three and four women with nonvertebral facture/100 subject-year for the 10- and 5-mg groups, respectively) during the late period of alendronate treatment, compared with the early period (three women with fracture/100 subject-year), despite a higher bone density. Although this trial was not designed to test fracture efficacy, apparently no attempt was made to ascertain whether patients who sustained nonspinal fractures displayed evidence of impaired fracture healing. Overall, the above reports suggest that excessive suppression of bone turnover by bisphosphonate may affect biomechanical competence of bone (26).

Several factors may have contributed to the development of SSBT. One factor is concurrent diseases: GIO in two patients and postsurgical hypoparathyroidism in one patient. Both chronic glucocorticoid treatment (27) and parathyroid insufficiency (28) are known to reduce bone turnover and could have exaggerated the effect of alendronate. Thus, the nonspinal fractures appeared to develop sooner compared with the patients on alendronate alone (1–3 yr *vs*. 6–8 yr, respectively).

Another factor may have been concurrent estrogen therapy. Among six postmenopausal women with osteoporosis osteopenia, three were on both estrogen and alendronate, whereas three received alendronate alone. The onset of spontaneous fractures was earlier among patients on combination therapy, compared with those on monotherapy (3–5 yr *vs*. 6–8 yr), and the indices of bone resorption on bone biopsy tended to be lower in those taking estrogen. Thus, combination therapy with another antiresorptive agent, such as estrogen, might cause a more severe suppression of bone turnover (21, 22) and might have increased the potential for developing SSBT.

The third factor may be the duration of alendronate therapy. The skeletal half-life of alendronate is long (29), which could explain the residual effect on bone density 3 yr after withdrawal of the drug (30). It is therefore possible that the suppressive effect of this drug on bone resorption might be cumulative over time. Four patients in this report were treated with alendronate without estrogen or glucocorticoid; they developed spontaneous nonspinal fractures 6–8 yr after alendronate therapy, compared with 3–5 yr for

those taking alendronate with estrogen and 1–3 yr for patients who also received glucocorticoids.

We acknowledge that this report has some limitations and unanswered questions. First, the biochemical markers did not reveal as prominent a suppression of bone turnover as the histomorphometric indices. Most patients displayed low or low-normal urinary NTx, OH-proline, and serum Oc, but serum BsAP was inconsistent. The results are compatible with previous reports showing that alendronate may exert a more marked suppression (90–95%) of bone turnover at the tissue level (31) compared with only a 50% reduction from baseline in biochemical markers (32, 33). The discordance between the histomorphometric and biochemical markers of bone turnover could be related to the variable degree of suppression at different skeletal sites. Although bone histomorphometry reflects local bone turnover, the changes in biochemical markers are more reflective of changes in the whole skeleton. Another possible explanation is the effect of fractures on bone turnover. Development of fractures has been shown to significantly increase bone turnover markers (34). Last, the less impressive or inconsistent changes in biochemical markers of bone turnover may have been due to inherent analytical and biological variability of the assays. The key issue to consider is that the quantitative histomorphometric analysis, upon which we based the bone turnover state in the diagnosis of SSBT, is generally regarded as the gold standard for the assessment of bone turnover.

Second, the presentation of patient 1 appears to be somewhat different than in others. Serum BsAP and

urinary NTx were higher than in others, and osteoclastic and osteoblastic surfaces did not differ from the control group on the cancellous and intracortical bone surfaces. However, the patient shared many of the features of the other eight patients, both clinically and objectively, with BFR being markedly decreased on the cancellous and endocortical bone surfaces. It is possible that this case represents one end of the spectrum of varying degrees of bone turnover suppression manifested by SSBT.

Third, three of seven patients without GIO had the unusual occurrence of femoral shaft fractures. We offer no explanation for this finding except to note that the reduction in elastic modulus reported to occur during bisphosphonate treatment was more marked in cortical than in trabecular bone (35).

An important limitation of this report is the lack of a control group. Published randomized trials with alendronate showed that some patients developed nontraumatic appendicular fractures while receiving either alendronate or placebo (1–3). Thus, although arguments were presented earlier linking SSBT to bisphosphonate therapy, a definitive causal relationship cannot be made. It is also possible that the development of SSBT in the cases described in this report represents an atypical response to alendronate therapy. However, most of our patients demonstrated the expected treatment outcomes, at least in the first few years of therapy, such as a satisfactory rise in BMD. The absence of SSBT despite a substantial suppression of bone turnover in a previous bone histomorphometric study (31) might be a reflection of a relatively short duration of alendronate therapy of 2–3 yr. In our patients, nonspinal fractures did not

develop during the first 3–6 yr of treatment among those maintained on alendronate alone or with estrogen. Except for the two patients with GIO, we do not believe that there was an underlying condition that predisposed to the development of SSBT. Seven patients on alendronate alone or with estrogen did not have prevalent fractures. Vitamin D deficiency and osteomalacia were excluded as potential reasons for poor fracture healing.

Finally, we cannot infer from our observations whether SSBT is unique to alendronate or can also develop with other bisphosphonates. That all nine patients with SSBT described here took alendronate may simply reflect the longer availability and wider usage of this bisphosphonate.

In conclusion, our clinical experience suggests that alendronate can potentially cause SSBT, resulting in increased susceptibility to nonspinal fractures that heal poorly. This complication appears to occur earlier when alendronate is coadministered with either glucocorticoids or estrogen. However, it can also develop after treatment with alendronate alone if the treatment is prolonged. Our observation does not diminish the important role of alendronate in the management of osteoporosis. Rather, it emphasizes the need for awareness of this potential complication during therapy. Although biochemical markers of bone turnover appear to be of limited value, the onset of spontaneous nonspinal fractures, particularly of femoral shaft on alendronate treatment, should raise the level of suspicion for this complication. Additional studies are needed to determine how long bisphosphonates can safely be given.

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[Exhibit 70 to Ecklund Declaration]

To: Olivero, Kerin A. <kerin_olivero@merck.com>

From: Goldberg, Michael R. </O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=GOLDBERM>

Cc:

Bcc:

Received Date: 2005-08-03 13:06:22

Subject: FW: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

Can you do a quick search to see if the doc mentioned below has ever submitted reorts inthe past?

Mike

Michael R. Goldberg MD, PhD
Clinical Risk Management and Safety Surveillance
484-344-2860
FAX 484-344-7920
michael_goldberg@merck.com

A Where patients come first

CRMSS - Monitoring the safety of our products

Our mission is to proactively assess and describe the safety profile of our products.

-----Original Message-----

From: Santora, Arthur C.

Sent: Tuesday, August 02, 2005 5:41 PM

To: Goldberg, Michael R.

Subject: RE: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

Has the reported any Fx AEs in the past?

My NTx is 17 and I don't take anything. I'll talk to you tomorrow and try to be careful in the interim.

Art

-----Original Message-----

From: Goldberg, Michael R.

Sent: Tuesday, August 02, 2005 5:26 PM

To: Santora, Arthur C.

Subject: FW: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

FYI. Let's discuss. Tomorrow between 1 and 4 should be good.

Mike

Michael R. Goldberg MD, PhD
Clinical Risk Management and Safety Surveillance

484-344-2860
FAX 484-344-7920
michael_goldberg@merck.com

A Where patients come first

CRMSS - Monitoring the safety of our products

Our mission is to proactively assess and describe the safety profile of our products.

-----Original Message-----

From: Gundermann, Stephanie M.

Sent: Tuesday, August 02, 2005 3:03 PM

To: AER Mailbox

Cc: Goldberg, Michael R.

Subject: WAES0506USA01525 and WAES 0507USA01043 INCOMING SCANNING

Adverse Experience Reporting Telephone memo

WAES No.

0506USA01525

0507USA01043

Product Name

Fosamax* (alendronate sodium)

Adverse Experience(s): fractured thigh bone

Summary of Call:

On 02-AUG-2005, I phoned the office of **REDACTED** who returned my call.

WAES 0507USA01043 –

REDAC reported that he has 25 patients with long bone fractures who have taken Fosamax* (alendronate sodium) for a long time. He also reported that 100% of patients in his practice that have experienced femoral fractures (without being hit by a taxicab), were taking Fosamax* (alendronate sodium) for over 5 years. At New York Hospital they call it the "Fosamax Fracture". He stated that if a patient's Ntx marker goes down below 20, he switches them to risedronate (ACTONEL) and that attention should be paid to the Ntx and not the DEXA scan. He reported that biopsies of the bone show that the bone is asleep and there is a subset of people who are over-suppressed which is a small number in comparison to the number of hip fractures. **REDAC** is planning a study (with Cornell University) for 1 year to look at long bone fractures in patients who were treated with Fosamax* (alendronate sodium) versus a control group who was not. He referred to a publication by Dr. Charlie Pak, which describes similar experiences.

WAES 0506USA01525 –**REDAC** also reported that he had a patient in her 70's that was experiencing thigh pain and later twisted in a swimming pool with her grandchildren and broke her femur after taking Fosamax* (alendronate sodium) for 7 years. **REDAC** discontinued therapy with Fosamax* (alendronate

sodium), and switched the patient to (FORTEO). Subsequently, the patient slowly healed.

This was all the information provided by **REDAC**, so I thanked him and concluded my call.

AER Associate/Coordinator follow-up (check one):

Send all scheduled correspondence.

Cancel all scheduled correspondence.

v

Send Thank You only.

Other (describe):

Stephanie Gundermann
02-AUG-2005

AER Associate/Coordinator Name
Date

02-AUG-2005

Date(s) of Telephone Call

[Exhibit 71 to Ecklund Declaration]

To: Santora, Arthur C. <art_santora@merck.com>; Seebach, Frank <frank_seebach@merck.com>; Walters, Margaret <margaret_walters@merck.com>
From: Miteva, Yanna R </O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=MITEVAYA>
Cc: Bold, Thomas M. <thomas_bold@ merck.com>; Budzynski, Christina M. <christina_budzynski @merck.com>
Bcc:
Received Date: 2006-11-06 18:48:23
Subject: FW: AE reports of Brittle bones with Alendronate therapy

---

FYI, below is the query from Singapore regarding a local registry of cases of non-traumatic and/or non-healing fractures.

You will receive shortly an invitation for a teleconference with MSD Singapore where this issue will be further discussed.

Thank you.

Yanna

-----Original Message-----

From: Jen, Lai Hung
Sent: Tuesday, October 31, 2006 11:03 PM
To: Kilker, Diane M; Hostelley, Linda S; Bold, Thomas M.; Vilardo, Laura E
Cc: Lo, Thean Soo; Soon, Linda; Goh, Karen; Chin, Annie; Seah, Joleen

Subject: RE: AE reports of Brittle bones with Alendronate therapy
Importance: High

Hi All,

Please advise whether there is any criteria or SOP from a global perspective to set up a local registry.

If not, we will work internally and with local regulatory agency to discuss the need of a registry.

Regards
Lai

Lai Hung Jen, MD
Medical Director
Merck Sharp & Dahme (I.A.) Corp. Singapore
Tel. (65) 6296-7772
Fax. (65) 6296-0005
E-mail: laijen@merck.com

-----Original Message-----
From: Goh, Karen
Sent: Wednesday, October 18, 2006 6:48 PM
To: Kilker, Diane M; Hostelley, Linda S; Bold, Thomas M.; Vilardo, Laura E
Cc: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Subject: RE: AE reports of Brittle bones with Alendronate therapy

[Business Confidential - Merck & Co., Inc. Whitehouse Station, NJ USA]

Dear Diane,

Hi. Thanks for your guidance and sharing. Based on this, we have sent the following WAES reports to HQ:

1) 0610SGP00001
2) 0610SGP00002
3) 0610SGP00003
4) 0610SGP00006
5) 0610SGP00007

and will send any others which may later appear in publication later.

With regards to our earlier question, we are interested to know if WPS has been seeing a significant number of fracture non-healing type of reports similar to ours and as described by Odvina, that might be a signal for a label update. This would be for our internal information and will not be shared with external parties. Thanks.

In our attempt to obtain follow up information, one of the doctors had suggested the creation of a local registry to track such cases. Would HQ be able to advise on the criteria for setting up a local registry as initiated by Merck? Is there an SOP for this? Would this be warranted in this case?

Would appreciate your input once again. Many thanks!

Best regards,
Karen Goh
Regulatory Affairs Associate
Merck Sharp & Dahme I.A. Corp, Singapore
Tel: +65-6393 7637
Fax:+65-6296 0005

-----Original Message-----

From: Kilker, Diane M
Sent: Saturday, October 14, 2006 4:10 AM
To: Hostelley, Linda S; Goh, Karen; Bold, Thomas M.; Vilardo, Laura E
Cc: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Subject: RE: AE reports of Brittle bones with Alendronate therapy
Importance: Low

Hello Karen,

Your plan for data entry of these reports sounds reasonable. Unfortunately, until we are able to link the existing cases (and it sounds like this is unlikely), we leave them as separate reports without relating them. This also happens in the US where we suspect a duplicate but really cannot be certain. We leave the reports separate and attempt follow-up to ascertain specific identifiers. I don't see much else you could do at this time.

As for your question below, I will defer to our CRMSS group (Thomas Bold and Laura Vilardo) who are responsible for looking at the AE data in aggregate. Is there something specific you are looking for? I can confirm we have other cases in the WAES database as fracture non-healing has been noted in the literature (author Odvina). Please let Laura and Thomas know the specifics of your request unless a confirmation is all you needed.

Thomas and Laura, please see question below.

Kind regards,

Diane

-----Original Message-----

From: Hostelley, Linda S
Sent: Friday, October 13, 2006 7:01 AM
To: Goh, Karen; Kilker, Diane M; Bold, Thomas M.
Cc: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Subject: Re: AE reports of Brittle bones with Alendronate therapy

---

Karen

Thanks for the information

Your plan for waes sounds good

Diane will send you detailed language and can also address your question re other reports

Best regards

Linda

-----Original Message-----

From: Goh, Karen
To: Hostelley, Linda S
CC: Jen, Lai Hung; Lo, Thean Soo; Soon, Linda
Sent: Fri Oct 13 05:46:15 2006
Subject: AE reports of Brittle bones with Alendronate therapy

---

Dear Linda,

Hi. We've recently come to know of a number of local cases of adverse experiences of brittle bones in patients who have been on Fosamax therapy and we thought to alert you on this in view of the number of cases and as some of these will be published in a journal.

Our medical services colleagues have spoken to 1 doctor (an orthopedic surgeon) who said that he knows of 8 of such cases (some from other colleagues). He reported the following for these 8 cases:

- all sub-trochanteric transverse fractures of the shaft
- slow healing observed
- all have been on alendronate therapy (estimated average 2–3 years of use)

- these patients have no other medical conditions of note
- some of the patients' BMDs did not show that they were osteoporotic
- hence, he expressed concern about the overuse of alendronate in the local environment
- elaborated on 1 specific case where there was no trauma involved. Prior to the fracture, the patient had complained of pain in both thighs. He saw a GP who did an X-ray of the femur which showed that it was ok. However, the next day, the patient sustained a fracture in both femurs just from getting up from sitting in a chair.
- he knew of these reports from various sources (2 are his own)
- 6 of these patients are relatives of doctors

We have tried to find out further information on each of these cases from this orthopedic surgeon, explaining our obligation to report these as AEs and to monitor the safety profile of our product. However, the surgeon is unwilling to report these AEs or provide further information pertaining to this. He is working with several other doctors to collect more cases before considering if they would publish their findings. This orthopedic surgeon also informed us that another of his colleagues will be publishing an article in the British Bone & Joint Surgery journal on another 10 similar cases. The article has apparently been accepted for publication and would be expected to be in print in a few months' time.

We will be able to enter the AE report for the 10 cases that will be in the British Bone & Joint Surgery publication when the article has been published. We will also be creating a WAES report for the 1 specific case described above. We can create another report for the other 7 generalized cases described above. However, we have recently also reported 3 similar cases in NWAEs (0610SGP00001-3) that was received by another orthopedic surgeon, and are unable to ascertain if these are amongst the 7 cases described above. In view of this, would WPS be able to advise how we should capture this in the WAES report, as we are concerned about duplicate reports and in view that the doctors are unwilling to report or provide further information and clarification?

Would we also be able to find out if WPS has received similar reports from other countries worldwide?

Please do let us know if you require further information and clarification on this! Many thanks!

Best regards,
Karen Goh
Regulatory Affairs Associate
Merck Sharp & Dahme I.A. Corp, Singapore
Tel: +65-6393 7637
Fax:+65-6296 0005

[Exhibit 102 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: FOSAMAX PRODUCTS :No.1:06-Md-01789
LIABILITY LITIGATION :JFK-JCF

- - -

CROSS NOTICED IN VARIOUS OTHER ACTIONS

- - -

CONFIDENTIAL INFORMATION —
SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

- - -

May 7, 2008

- - -

Videotaped deposition of ARTHUR C. SANTORA, II, M.D., Ph.D., held in the offices of Hughes Hubbard & Reed, One Battery Park Plaza, New York, New York 10014, commencing at 10:08 a.m., on the above date, before Linda L. Golkow, a Federally-Approved Registered Diplomate Reporter and Certified Shorthand Reporter.

- - -

GOLKOW TECHNOLOGIES, INC.
deps@golkow.com
877.370.3377

* * *

Page 794

implied that Fosamax reduces the risk of fracture in women who don't have osteoporosis.

BY MR. O'BRIEN:

Q. I agree with you there. So, the FDA in this analysis, particularly in that sentence that Merck's counsel just read to you, the FDA just simply got it wrong; is that right?

A. No. The FDA did not get it wrong. I believe it's your interpretation that's wrong. If we had done what the reviewer considers disingenuous in pooling a treatment for a population in which the drug works with an effect of the drug in a population where it doesn't work, that would have been disingenuous. That's not what we did. We reported the data in this study looked at for a variety of different ways, noted that the drug did not reduce the risk of fracture in women who had not had either a fracture or low bone mineral density. That was included in both the

Page 795

clinical study report, and that's described in the labeling.

Q. So, based on —

It's my understanding, based on the clinical trial evidence that Merck had and presented to the FDA, Merck cannot say that for those patients without osteoporosis that the use of Fosamax prevents fractures, right?

MR. MARSHALL: Objection to the form, and now you've exceeded the scope of the redirect.

MR. O'BRIEN: This is my last question.

BY MR. O'BRIEN:

Q. Is that right?

A. Merck has stated that the drug works to reduce the risk of fracture in people who have osteoporosis defined as either vertebral fracture or defined as a low bone mineral density. Your question, I think, is related to whether we have promoted or stated the drug works in other populations to reduce the risk

of fracture. The answer is no, we have not indicated that Fosamax reduces the risk of fracture in women who don't have osteoporosis.

Q. Because there's no evidence that it does, right?

A. Right. There's no evidence that any drug reduces the risk of fracture in people who don't have osteoporosis.

MR. O'BRIEN: Thank you.

THE VIDEOTAPE TECHNICIAN:

We're going off the record. The time is 3:10 p.m. This is the end of tape 5.

- - -

(Whereupon, the deposition concluded at 3:10 p.m.)

- - -

C E R T I F I C A T E

I, LINDA L. GOLKOW, a Notary Public and Certified Court Reporter of the State of New Jersey, do hereby certify that prior to the commencement of the examination, ARTHUR C. SANTORA, II, M.D., Ph.D. was duly sworn by me to testify to the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.

_____

LINDA L. GOLKOW, CCR
Notary Number: 1060147
Notary Expiration: 1-2-11
CSR Number: 30X1176200

[Exhibit 113 to Ecklund Declaration]

To: Ross, Philip D. <rossph@NorthAmerica.msx.merck.com>

From: Stern, Lawrence S. <O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=STERNLAW>

Cc:

Bcc:

Received Date: 2001-10-25 20:45:01

Subject: FW: osteoporosis website - Susan Ott's opinions

Larry

-----Original Message----

From: Stern, Lawrence S.

Sent: Thursday, October 25, 2001 1:17 PM

To: Teutsch, Carol B; Yates, John; Kimmel, Donald B.; Krempasky, Marlene Y.; Lawler, Barbara J.

Subject: osteoporosis website - Susan Ott's opinions

Check it out

Susan Ott's Web site (Updated 4/16/01)

http://courses.washington.edu/bonephys/opbis.html#side

Alendronate deposits in the bone for over ten years, and will accumulate with use. Studies in beagles have shown that high doses result in accumulation of small

cracks in the bone and decreased mechanical strength. (Mashiba (2000). Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Mineral Res 15:613–620.)

Thus, I do not think it is wise to give alendronate for longer than 4.5 years. I would have to see definite proof of safety and benefit to the bones (in terms of fractures) before I would give it longer than that.

Estrogen is still my first choice for prevention of osteoporosis, because it has other benefits and a known safety record. In women already taking estrogen, alendronate causes only a slight increase in the bone density, so I do not recommend it unless the patient has demonstrated fractures or bone loss while on the estrogen, and has an elevated marker for bone resorption ...

Larry

[Exhibit 118 to Ecklund Declaration]

FINAL MEETING MINUTES July 15, 2008
June 27, 2008 MRL Osteoporosis Scientific Input Meeting

This document contains notes from the above-referenced June 27, 2008 consultants' meeting. It is not an attempt to create a transcript of the meeting or to include every thought or comment made at the meeting. Even if not indicated below, the external consultants did not agree with every comment made by others during the meeting.

Executive Summary

External Attendees: Felicia Cosman, David Dempster, Harry Genant, Joseph Lane, Michael McClung, Jeri Nieves, Regis O'Keefe, Robert Recker, Charles Turner[1]

Merck Attendees: Jim Adams, Julie Chandler, Anne de Papp, Donald Kimmel, Scott Korn, Graham Lumsden, Yanna Miteva, Fernando Osorio (MSD Spain), Arthur Santora, Sharon Scurato, Ted Reiss

Key Summary Points:

1) Overall incidence of low energy subtrochanteric/femoral shaft fractures in the

[1] Dr. Mark Bolander from the Mayo Clinic was also invited to attend and present at this meeting, but cancelled due to illness. Several consultants were aware of Dr. Bolander's preliminary data, discussed at a separate meeting in May 2008, suggesting that bisphosphonate users are not at an increased risk of developing subtrochanteric fractures. The consultants agreed that Dr. Bolander's data on this issue is important and should be fully analyzed, published and considered by the medical community.

osteoporotic population is very low (a recent estimate was 6% of all femur fractures).

2) The recently available data do not alter the well established benefit of bisphosphonates to reduce fracture risk in osteoporotic patients.

3) There is no good evidence to suggest an increased incidence of low energy subtrochanteric/femoral shaft fractures in patients treated with bisphosphonates over background rates.

4) Causality has NOT been demonstrated.

5) In Dr. Lane's observational study, the proportion of patients with "simple transverse fractures" and "thick cortices" appears greater and the proportion with "complex spiral fractures" and "thin cortices" appears smaller in patients treated with bisphosphonates.

6) The morbidity and mortality associated with the "simple transverse" fractures of the proximal femur is usually *less* than that with spiral fractures of the femur.

7) There was general agreement that bisphosphonates do not lead to cortical thickening, only prevention of cortical bone loss.

8) The consultants cautioned about hypothesizing on mechanism prior to establishing if there is an increased risk.

9) Many of the consultants thought that suggesting that low energy subtrochanteric/femoral shaft fractures occur in bisphosphonate users because of "oversuppression" of bone turnover was not appropriate as there has been no demonstration that reduction of bone remodeling in patients with these

atypical fractures was any greater than that seen in bisphosphonate treated patients in general.

10) There are no published case series with controls that would allow assessment of risk of subtrochanteric / femoral shaft fractures associated with bisphosphonate treatment. The only case study (Lenart, Lane et al, unpublished, abstract presented as a poster at the 2007 ASBMR scientific meeting) has significant limitations including potential referral bias, and inability to match cases with controls with similar osteoporosis severity, and other risk factors for fractures (e.g., glucocorticoid use). The fractures reported were low trauma fractures and the frequency of stress fractures (typically about 10% of all low-trauma fractures in the elderly) was not studied.

11) Studies to delineate the epidemiology of subtrochanteric / proximal femoral shaft fractures are required prior to a study of treatment-related risk of these rare fractures.

Scientific Questions Posed to Consultants and Consultant Comments:

What is a low energy fracture of the femur?

A low energy fracture of the femur is defined as one that occurs from a fall from standing height or less. Stress fractures are included in the larger group of low energy fractures.

What is the definition of a stress fracture?

Stress fractures are defined as fractures occurring with either normal or increased activity, but without an identifiable traumatic event. Characteristic clinical features of incomplete (unicortical) stress fractures of long bones include point tenderness or

pain on weight bearing at the site of fracture. Incomplete stress fractures may be diagnosed acutely with MRI, within several days with Tc-99m MBP bone scan, or as characteristic asymmetrical cortical hypertrophy of the periosteal and endosteal surface. A low energy traumatic event (i.e. fall from standing height or less) may result in completion of a pre-existing incomplete fracture.

Do stress fracture and insufficiency fractures differ?

The distinctions between stress fracture and insufficiency fracture are not rigorous. There was general agreement that insufficiency fractures occur **with normal activity in abnormal bone**. However, there was a minority opinion that some low trauma fractures (i.e., more force than that found with normal activity) of abnormal bone could be called insufficiency fractures. There was agreement that stress fractures may be caused by **increased activity in normal quality bone** in the absence of external trauma. Moreover, it was recognized that "increased activity" is a relative term. Stress fractures may occur when very sedentary people increase their level of activity to that of the average young or middle-aged adult. **Stress fractures** may occur in normal bone when there is an increase from normal to extremely high levels of activity, for example in the training of military recruits. There was some disagreement about the methods for separating insufficiency fractures from other stress fractures, particularly in older adults. Some consultants suggested that bone must be "fragile" to describe it as an insufficiency fracture (bone fracture without thickening of cortex). Others countered by stating that stress fractures may occur

in relative strong bone if the intensity of activity is sufficiently great. Thus, the pathology is similar.

One consultant commented that the fractures presented by Dr. Lane (and referred to as 'stress' fractures) should be characterized as pathologic fractures because they were complete fractures. By the description of generalized bone thickening, these would not be classified as stress fractures based on radiographic criteria alone.

What are the radiological features of a stress fracture?

Hot spots on bone scan, periosteal apposition, areas of osteolysis, focal thickening and usually only on one cortex, usually on the lateral side. Radiological changes due to stress fractures develop over a period of time. One point made by several consultants was that usually chronic incomplete stress fractures are asymmetric (by cortex) with bone formation only on one cortex, usually on the lateral cortex. The characteristic presentation in the Lane study (ie: subtrochanteric fracture with generalized symmetrical cortical thickening) is not typical of change due to a stress fracture.

What are the typical sites of stress fracture in the lower extremities?

Metatarsals, tibia, pelvis. In older women, sacral and pelvic fractures. In glucocorticoid-induced osteoporosis (GIOP), vertebral and femoral neck stress fractures may occur following aseptic osteonecrosis. Other stress fracture sites in GIOP include ribs.

Is there a difference in the site distribution according to age and gender?

Males - Metatarsal, tibia

Females - Tibia, metatarsals, pelvis.

Sacral and pelvic fractures are more common in the elderly.

What are the risk factors for stress fracture of the femur and other lower extremity bones?

Osteoporosis; radiotherapy; marathon training; dancing at a wedding; small bone diameter; amenorrhea, smoking, Depo-provera, previous inactivity; increased loading on bone. One consultant observed that many femoral shaft stress fracture patients have bowing of the legs; they are usually short in stature and have "big" bones.

What is the case finding definition of the fractures in question?

The radiographic pattern of fractures that appeared to be more frequently observed with bisphosphonate users in the reports from the Hospital for Special Surgery group required that fractures be in the subtrochanteric area (5 cm from the lesser trochanter) or more distal femoral shaft, with a simple transverse fracture path (not oblique or spiral), and cortical "hypertrophy" (the presence of cortical thickening on radiographs was a prominent feature of the fractures described by Lane et al.). The consultants agreed that "thick cortices" was the correct term and "hypertrophy" was incorrect, as there was no evidence that cortices had either enlarged or had a different cortical thickness from that found in younger adults. The HSS group did not find an association between

these fractures and prodromal pain or radiographic evidence of chronic incomplete stress fracture (e.g., focal asymmetrical cortical thickening).

Subtrochanteric fractures include those that are entirely below the level of the lesser trochanter. Some suggested that fractures with as much as 20% of their length above the level of the lesser trochanter could be labeled subtrochanteric, but there was not consensus on this point.

What are the clinical features?

While the majority of patients in the HSS series have not had reported prodromal pain, other case reports reported prodromal pain weeks or months before complete fracture. Consultants cautioned that hip pain is present from time to time in the great majority of elderly people, so care must be taken to investigate whether pain is characteristic of that of a stress fracture in that region and not the much more common pain of rheumatologic disease.

What are the radiographic features?

Dr. Lane reported that approximately 2/3 of patients on alendronate in his observational study had an easily identified X-ray pattern that he described as "simple with thick cortices" pattern. The proportion of patients in his study with "simple transverse fractures" and "thick cortices" appears greater and the proportion with "complex spiral fractures" and "thin cortices" appears smaller in patients treated with bisphosphonates. Several consultants commented that the "simple with thick" fractures seemed to be occurring in what appeared to be non-osteoporotic bone.

Generalized concentric cortical thickening or generalized cortical thickening with an area of reactive periosteum, sometimes bilaterally, was observed in Dr. Lane's series. When the fracture was complete, the fracture line was transverse oblique with a cortical beak on one side. This pattern was different from the spiral fractures, extending up above the lesser trochanter with thin cortices as observed in the majority of the non-bisphosphonate treated patients in Dr. Lane's series.

What type of epidemiology study might be used to better understand whether there is an association of bisphosphonates with low-energy subtrochanteric/femoral shaft fractures and/or altered distribution of femoral fractures?

There are currently no data on the epidemiology of the pattern of subtrochanteric fractures (e.g., simple transverse, oblique or spiral) or the thickness of proximal femoral cortices (thicker or thinner than average) in patients with subtrochanteric fractures. Studies to delineate the epidemiology of subtrochanteric / proximal femoral shaft fractures are required prior to a study of treatment-related risk of these rare fractures. A prospective controlled clinical trial to determine whether there is treatment-related risk would be unlikely to be acceptable to Ethical Committees (due to the need for placebo controlled design), and even without that barrier, would need to be much longer and larger than previous fracture end point studies as fractures in this region of the femur are rare.

The consultants suggested reviewing any large epidemiologic study with long-term follow up that has

evaluated fractures, such as the Study of Osteoporotic Fractures (SOF) that has also gathered data on femoral cortical bone thickness using pelvic radiographs. SOF also has HSA (Hip Structural Analysis of DXA data) and has data on hip and spine BMD to look for concordance (or discordance).

Another study that might yield useful data is an epidemiology study of low energy femoral shaft fractures in skeletally mature patients over a 10 year period (January 1985 to December 1994) in and around Helsinki, Finland. A publication [Salminen et al., Clin Orthop Rel Res 2000; 372: 241–249] from the group of investigators (predating bisphosphonate use) found an incidence of subtrochanteric fracture of 7.8 per 100,000 person-years for people over age 60. The most common fracture pattern was spiral (although there were some transverse and transverse/oblique fractures) and the average age at fracture was 79 years for women and 60 years for men.

It was acknowledged that review of large medical claim databases was not going to address the questions as precise information on the site of fracture is generally absent, and cortical thickness is not usually recorded. Access to actual radiographs was considered essential.

Prospective epidemiological surveys represent a potential way of assessing treatment-associated risk. However, it was noted that such a survey must be population based, control for selection bias based on fracture history and severity of osteoporosis, and medication use (e.g., glucocorticoid use) associated with both stress fractures and bisphosphonate use. Such a survey would also need to include an objective

review of radiographs by a person unaware of the patient's treatment. If these requirements were met, such a survey would need to be very large.

Pathophysiology:

What is the pathophysiology of low energy subtrochanteric/femoral shaft fractures in untreated patients?

Deficient bone quantity (low BMD and osteoporosis) and low bone strength (e.g., Paget's disease of bone, osteogenesis imperfecta, osteopetrosis, glucocorticoid osteoporosis, regional radiotherapy) all increase the risk of subtrochanteric fractures.

Does the pathophysiology differ with regard to bisphosphonate treatment?

It is not known whether treatment with bisphosphonates increases the risk of subtrochanteric fractures. No pathological mechanism has been demonstrated. After reviewing a series of radiographs presented by Dr. Lane, the consultants agreed with Dr. Lane that the distribution of the radiographic appearance of bone and the fracture pattern appeared to be different in bisphosphonate users as compared to non-users. It was pointed out by several consultants that the fracture pattern (simple transverse) was expected in people with thick cortices.

Consultants did not think that bisphosphonates could thicken cortices, rather they could only prevent cortical thinning. The hip structural analysis (HSA) data from FIT/FLEX only reflected an increase in cortical thickness of 3–4% over placebo after 3–4 years of treatment. Moreover, this very small change may be due to the either the effects of increased cortical BMD on the edge detection software used for HSA or

to a decrease in cortical thickness in the placebo group. Also, in a case report by Kwek [Kwek, Goh et al, Injury, Int J. Care Injured 2008, *in press*], serial X-rays of a patient before bisphosphonate therapy, during and then after the fracture appear to show that the patient's cortices were as thick before therapy began.

It was hypothesized that this group may be a subgroup of low turnover osteoporotic women that had been put on therapy, or perhaps patients with low BMD at the spine but normal BMD at the hip. Some proposed the thick cortices could be phenotypic of a low turnover state or some type of heterozygous unidentified bone disease state existing prior to the initiation of BPs. However, no one was aware of a study that investigated the relationship between bone turnover and cortical thickness in the femur of osteoporotic patients.

The importance of collagen to bone strength was also discussed. Collagen ages by accumulation of advanced glycation endproducts and is most responsible for conferring "toughness" to bone. It was opined that if collagen did not get adequately renewed through bone turnover that it would contribute to increased brittleness of bone and decreased strength.

"Oversuppression" of bone turnover was discussed as a potential mechanism of increased bone fragility. There are no data to indicate whether "oversuppression" exists and the consultants recommended against describing the potential mechanism of subtrochanteric/femoral shaft fractures as "oversuppression". Bone remodeling in patients treated with bisphosphonates decreases very early in

treatment and does not progress thereafter. The magnitude of bone turnover reduction correlated with lower non-vertebral fracture risk in FIT and in studies of several other bisphosphonates. It was pointed out that normal, healthy bone turnover on bone biopsies is skewed toward the left (toward low normal turnover). Even if tetracycline double-label is not observed in trabecular bone, it is usually always present in cortical bone and this fracture type is described as a cortical bone fracture. There are no data to indicate that patients with subtrochanteric fracture have a bone turnover rate lower than that seen in the typical bisphosphonate treated patients (without fracture). When biochemical markers of bone turnover were available in case reports, they tended to be within the normal range in these patients. Stress fractures in the patients with subtrochanteric fractures and prodromal symptoms suggestive of incomplete fracture show evidence of increased local bone formation (hot spots), in both bisphosphonate-treated and untreated patients.

There was consensus that "if" decreased bone turnover were associated with stress fracture risk it would be similar for all bisphosphonates (at doses used to treat osteoporosis), as well as other drugs (e.g., estrogen in the menopause, or RANK-L inhibitors) that inhibit osteoclast activity, although at this time evidence for an increase in subtrochanteric fractures and use of inhibitors of bone resorption has not been demonstrated.

The consultants wanted to develop some standard of care based on what we know now, i.e. if the patient has symptoms of prodromal pain suggestive of incomplete stress fracture, a femoral shaft X-ray should be taken

to rule out stress fracture. If there is evidence of a stress fracture on one side, an X-ray should also be taken on the opposite side. If the X-ray is not definitive, a bone scan should be done and the current standard of care for identified stress fractures should be followed.

Many of the consultants thought that they would consider stopping bisphosphonates in the setting of a stress fracture of the subtrochanteric / shaft regions of the femur. All acknowledged that there are no data to indicate that the fracture would heal more quickly and that fractures at more common sites of osteoporotic fracture may be more likely if treatment were discontinued. It was also acknowledged that although remodeling is delayed, there is no data to suggest impaired fracture healing in bisphosphonate treated patients. Most agreed that they would consider interruption of treatment in the setting of an incomplete stress fracture (documented by a positive bone scan or radiograph) as well, albeit no data supporting this practice is available either. There was consensus that the current state of knowledge regarding clinical management was extremely limited.

At the close of the meeting, Dr. Lane acknowledged that his data did not establish that bisphosphonates increase the risk for these types of fractures over their background rate of occurrence, and that he understood that his data was only hypothesis generating.

[Exhibit 122 to Ecklund Declaration]

James Adams
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September 15, 2008

Mary Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Annendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

Prior Approval Supplement

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, a supplement to NDA 20-560.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling Section of the approved New Drug Application for FOSAMAX.

Merck is proposing to add language to both the Precaution and Adverse Reaction/ Post-Marketing Experience section of the label to describe low-energy fractures that have been reported, of which some have been stress/ insufficiency, at the subtrochanteric region of the femoral shaft. While these fractures are less common than other osteoporotic low-energy fractures, they occur in a familiar population of elderly individuals and have been reported prior to the availability of bisphosphonates. It is not possible with the present data to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures. Nevertheless, considering the clinical importance of these fractures in patients with osteoporosis and their temporal association with bisphosphonate use, the Company believes that it is important to include an appropriate statement about them in the product label. This may further increase physicians' awareness of possible fractures in some osteoporotic patients at risk and all ow early intervention, thereby possibly preventing the progression to complete fracture and/or other complications.

As per FDA Guidance to Industry: *Providing Regulatory Submissions in Electronic Format – Content of Labeling*, the proposed labeling is provided in SPL format. Content of labeling [(201.100(d)(3)] has been included in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within Section 1.14.1.3 Draft labeling text.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. This submission is being transmitted through the FDA's electronic submission gateway.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Amendments of 2002 (PDUFA III), as indicated in the attached Form 3397, no user fee is required for this supplemental application.

We consider the filing of this supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any further communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely
s/ James Adams
James Adams

Associate Director
Worldwide Regulatory Affairs

* * *

CURRENT CIRCULAR SHOWING REVISIONS

FOSAMAX®
(alendronate sodium) Tablets and Oral Solution

women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Low-Energy Femoral Shaft Fracture

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma.**[1]** Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates.**[2]** Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care.**[3]** Interruption of bisphosphonate therapy in patients with stress fractures **[4]** should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.**[3]**

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <34 mL/min). (See DOSAGE AND ADMINISTRATION.)

COMMENTS/SUPPORT

1. [Sec. 2.5: p. 5]
2. [Sec. 2.5: p. 7]
3. [Sec. 2.5: p. 5]
4. [Sec. 2.5: p. 8]

* * *

CURRENT CIRCULAR SHOWING REVISIONS

FOSAMAX®
(alendronate sodium) Tablets and Oral Solution

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

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3%

of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 nM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

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

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*); joint swelling; low-energy femoral shaft fracture (see PRECAUTIONS. *Low-Energy Femoral Shaft Fracture).*

Nervous system: dizziness and vertigo.

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

Special Senses: rarely uveltis, scleritis or episcleritis.

COMMENTS/SUPPORT

Addition of Post-Marketing Adverse Reaction, "low-energy femoral shaft fracture," based on the WAES reports listed on pages 37, 38.

* * *

[Exhibit 124 to Ecklund Declaration]

FDA Media Call
Possible increased risk of thigh bone fracture with bisphosphonates
Moderator: Karen Riley
October 13, 2010

Coordinator: Welcome and thank you for standing by. All participants are in a listen-only mode. During the question and answer portion of today's call, please press star 1 if you would like to ask a question. Today's call is being recorded. If you have any objections, please disconnect at this time. I'll now turn the meeting over to Ms. Karen Riley. Thank you. You may begin.

Karen Riley: Thank you operator. Thank you very much. Welcome ladies and gentlemen. My name is Karen Riley from the FDA's Office of Public Affairs. This is an FDA Teleconference for credential media to discuss safety warnings about bisphosphonates.

By now you should have received an email copy of the FDA press release on this subject or reviewed the press release on the FDA Web site. I also suggest that you take a look at the drug safety communication. You'll

find a link to that document at the bottom of the press release.

Before we take your questions, Rear Admiral Sandra Kweder will make some opening remarks. Dr. Kweder is Deputy Director of the Office of New Drugs in FDA's Center for Drug Evaluation and Research better known by its acronym, CDER. Dr. Kweder.

Sandra Kweder: Thank you Karen and thank you all for joining us this afternoon. I want to reiterate Karen's urging to take a look at our drug safety communication on our Web site where you'll probably find more detailed information.

Today FDA is warning patients and their healthcare providers again about the possible risk of an uncommon form of fracture in patients who take a class of drug known as bisphosphonates to treat or prevent osteoporosis. As you probably know, osteoporosis is a progressive thinning of bone tissue and a loss of bone density. It is most common in women who have gone through menopause.

Over time osteoporosis can put people at risk of fractures that result in pain, hospitalization and surgery. The fractures are usually in the hip

or the spine or the wrist. Patients take bisphosphonates and other medicines to inhibit or slow this loss of bone mass and prevent fractures.

Studies of these drugs which typically last from three to five years have shown that these drugs do reduce the rate of osteoporotic fractures but no treatment has ever been shown to eliminate the risk completely.

What FDA is warning about today is the risk of an uncommon or atypical type of fracture in the thigh bone. Subtrochanteric femur, or thigh bone, fractures are known to occur in patients with osteoporosis. Always have been. However in recent years there has been an increasing number of reports of femur fractures with some unusual features in patients taking bisphosphonates. And one of the things that's unusual about them is they are often associated with very little or no trauma at all.

In 2008 FDA — because of reports of these types of fractures, FDA asked the bisphosphonate manufacturers to provide us with all of the information they had on cases of these types of unusual or atypical fractures from their clinical trials of the drugs.

In March of this year we issued a safety communication about our ongoing review of those data. We found that these fractures were very rare in clinical trials. Patients taking bisphosphonates in the clinical trials were not more likely to have such fractures than patients taking placebo. And epidemiology studies that we had reviewed also did not suggest that the atypical fractures were clearly caused by bisphosphonates.

Recently FDA reviewed a new report by the American Society of Bone and Mineral Research which helped to clarify the features of atypical femur fractures in patients with osteoporosis both with relation to X-ray findings and some clinical characteristics of the patients.

Based on this report we've been able to better assess some of the cases reported to us through our post-marketing adverse event reporting system and hopefully we'll be able to do that also for medical literature reports.

The American Society for Bone and Mineral Research report also provides more information that more closely associates these atypical fractures with long-term

bisphosphonate use. What's important to know about these atypical fractures is that the patients who experience them have fractures — can have a fracture occurring anywhere in the femur shaft which is the long bone of the thigh.

In addition to being less likely to be associated with trauma, patients taking bisphosphonates who experience an atypical fracture are generally younger than patients with typical osteoporotic fractures. In some cases the patients have bilateral fractures of both femurs. And importantly many of these patients describe a dull aching thigh or groin pain that begins weeks to months before a complete fracture occurs.

Now we don't know what the optimal length of time is for patients, particularly post-menopausal women, for taking a bisphosphonate. But in looking at the data the atypical fractures of concern have occurred predominantly in patients who have taken bisphosphonates for five years or more.

In response to these reports, FDA today requested a labeling change in the warnings and precautions section of all bisphosphonate products that

are used to prevent and treat osteoporosis. FDA is also requiring that these products come with a medication guide to better inform patients of the possible risk. This is important because having informed patients may be able to prevent the occurrence of these rare but debilitating fractures. And I want to emphasize that they are quite rare.

I also want to make it clear that our announcement today is an update and should not cause patients taking bisphosphonates to be fearful of their medicine. Bisphosphonates are an important mainstay of osteoporosis management and they have prevented innumerable fractures in their years of use but patients should be informed.

We at FDA will continue to evaluate data about the safety and effectiveness of bisphosphonates when used over a long period of time to prevent and treat osteoporosis.

In the interim, FDA recommends that healthcare professionals be aware of the possible risk of fracture in patients taking bisphosphonates and consider periodic reevaluation of the need for continued therapy once patients have been taking the drug for five or more years.

Certainly any patient on these medicines who develop unexplained thigh or groin pain should be evaluated for the risk of these unusual fractures. For patients who take bisphosphonates for osteoporosis management, we urge them that they should not stop using their medication unless advised to do so by their healthcare professional. They should also report any new thigh or groin pain and be evaluated for a possible risk of femur fracture.

To put this in context, in the United States in 2009 there were over 5 million patients who filled prescriptions for bisphosphonates, most of them women and most of them over the age of 55. And these — the drugs that we are describing in relation to — have an association with these possible fractures are drugs such as Fosamax, Actonel, Boniva and Reclast.

And I'll stop there and we'll take your questions.

Karen Riley: Thank you Dr. Kweder. Again, this is Karen Riley in the press office. And before we take questions, I want to point out that we've also posted on our Web site the letters on bisphosphonates that we sent to the manufacturers. And those can be

accessed by looking — by scrolling down the page where we have posted the drug safety communication and you can find the links to those in that spot.

And I want to remind reporters that when asking a question, please state your name and affiliation and it goes without saying that the questions are to be asked by report credential media only. Please limit yourself to one question and one follow-up so we can get to as many questions as possible.

Operator, we'll take the first question. Thank you.

Coordinator: If you would like to ask a question, please press star 1. Again, that is star 1 to ask a question. The first question comes from Donna Young. Your line is open.

Donna Young: Hello. Thanks for taking my call. I appreciate it. I just had a question as far as like you had said Dr. Kweder that taking bisphosphonates has prevented innumerous or innumerable fractures. Where — kind of what do you base that on? And then also last March when this came up, the agency sort of downplayed the studies that were showing this. So what new data

between March and now have you reviewed?

Sandra Kweder: Okay. Well that's two questions. And I can say that we know that from clinical trials of thousands of patients and these drugs, placebo controlled trials, that they prevent the common osteoporosis-related fractures. The fractures that we're talking about today are really unusual and rare.

I would say from the data from the National Hospital Discharge Survey showed that per 100,000 patients in 1996, this is the year after Alendronate was first approved, there were — in 2006 there were 598 fracture per 100,000 patients hip — I can't even say this — why don't I stop with the numbers. Let's just suffice it to say — because there are lots of sources of data and if we need to get more specific we can come back to that.

Donna Young: Okay.

Sandra Kweder: But the studies that have been done, epidemiology studies showing the benefits of these drugs have over and over and over again demonstrated that they do prevent fractures.

With regard to what has changed since March, several things. And I would say the most — the data that

we were able to review up until March was from the clinical trials as well as from some case reports in the literature. There were also some epidemiology studies that really didn't show very much in the way — that really helped us tease out the association between these drugs and these rare atypical fractures.

However, the report by — that recently was put out by the American Society for Bone and Mineral Research using some Kaiser data have really helped us understand these fractures a little bit better and make us confident that this is something that is potentially more closely related to these drugs, particularly long-term use than we previously had evidence for.

There were certainly — when you read the individual reports or as we have met with patients who have experienced these rare fractures, their cases are quite striking but trying to sort that out from clinical trial data and other things in the literature was hard. The report by the American Society of Bone and Mineral Research has really been helpful to us in better understanding this. Does that answer your question?

Donna Young: Yes. Thank you.

Karen Riley: Thank you. And before we go on I was remiss in not also introducing Dr. Theresa Kehoe who's the team leader in the Division of Reproductive and Urologic Products in CDER's Office of Drug Evaluation 3 who will also be able to chime in and answer any questions if need be.

So let's go on to the next — oh, and I'll spell her name. It's Theresa with a T-H, T-H-E-R-E-S-A and then Kehoe is K-E-H-O-E. So okay, let's go to the next question please.

Coordinator: And we have a question from Jennifer Corbett. You're line is open.

Jennifer Corbett: Yeah. Hi. Thanks for taking my question. The question I had again was just trying to put this in context. Dr. Kweder mentioned that there is — you said there were about 5 million prescriptions filled last year and the American Society for Bone and Mineral Research, their task force looked at 310 fractures. Do you guys — I mean is that about the universe that you think we're looking at, the 310 figure? Or do you have different information or additional reports of these atypical fractures?

Theresa Kehoe: This is Theresa Kehoe. I think our numbers are similar to what the ASBMR has looked at. But obviously

notorious with the AERS reporting system is the underreporting rate. So we suspect that there is a lack of awareness among both patients and physicians that these type of fractures may be associated with the actual drugs that they're taking to prevent fractures.

Jennifer Corbett: Right.

Theresa Kehoe: But so we are aware of that and that's one of the reasons to go ahead and get this message out.

Jennifer Corbett: Okay. Thank you.

Karen Riley: Thank you. Next question please. The next question is from Cheryl Thompson from the American Journal of Health-System Pharmacy. Your line is open.

Cheryl Thompson: Hi. Thank you. Does the addition of a medication guide mean that these drugs have a Risk Evaluation and Mitigation Strategy formally?

Sandra Kweder: Yes, actually it does. It does mean that. The existence of a medication guide does formally fall under the rubric of a REMS. And for those that aren't aware, a medication guide is an information pamphlet or an information sheet that must be given to the patient every time a prescription is dispensed.

Cheryl Thompson: Okay. Thank you. And a follow-up. Are there any other components of this REMS?

Sandra Kweder: No, there are not.

Cheryl Thompson: Thank you.

Karen Riley: And that was Dr. Kweder answering that question. Next question please.

Coordinator: Comes from Lisa Richwine from Reuters. Your line is open.

Lisa Richwine: Hi. Thanks for taking my question. In the earlier FDA communications I seem to recall there is — it singled out oral drugs as having this risk but the warning is going to apply to the injectable drugs as well. Have you seen cases with both the oral and the injectable drugs?

Sandra Kweder: Yes, we have. We certainly have more reports associated with the oral drugs but they are also much more commonly prescribed. But we do have — we have had reports from all of them.

Lisa Richwine: Okay. And if I could get a follow-up question. Can you give us an exact number? You said the cases you had were similar to the 310 or so reported by the Bone and Mineral Research Group and can you give us your exact number?

Sandra Kweder: Yeah. Actually we probably — we can't give you an exact number. One

of the things that — one of the main reasons is that the reports are often quite incomplete. And based on the definition of, you know, what constitutes absolutely an atypical fracture that the American Society of Bone and Mineral Research has put forward, a lot of that information is missing in the reports that we have so we need to go back and reevaluate those to see how many we actually have.

I think that going forward now that that standard case definition is out in the public domain, the information that we get in these reports will be much better and we'll be able to have a more accurate accounting of how often these occur and learn even more about their characteristics.

Lisa Richwine: Okay. Thanks.

Karen Riley: And that was Dr. Kweder. Thank you. Next question please.

Coordinator: Your next question comes from Martin Gorvine from Pink Sheet. Your line is open.

Martin Gorvine: Yes. Hello. Thanks for taking my question. Do the labeling changes — it was mentioned those are going into warnings and precautions, are they going to also be in a boxed warning section for these drugs?

Theresa Kehoe: This is Theresa Kehoe. No, it will not be a boxed warning. This will be in the warnings and precautions section.

Martin Gorvine: All right. Thank you.

Karen Riley: Thank you. Next question please.

Coordinator: Your next question comes from Deborah Kotz from U.S. News and World Report. Your line is open.

Deborah Kotz: Hi there. Thanks for taking my question. I'm wondering about one of the lines in the press release that says that — recommending that health professionals be aware of the risks and evaluating patients who are on bisphosphonates for longer than five years and in terms of the larger topic of whether bisphosphonates are safe to take beyond five years. What exactly should patients ask their physicians to do? What should they — how should they be evaluating them to determine whether they should stay on these drugs?

Theresa Kehoe: I think in many cases when we look at the case reports, what we are seeing is that patients are on bisphosphonates and they actually normalize or close to normalize their bone density and they remain on the bisphosphonates. So this may be a case where if because

bisphosphonates are retained in the bone for such a long period of time where if the bone mineral density is significantly improved that a patient may be able to come off the bisphosphonate for it could be years, it could be a shorter time.

But what I can tell you is that we are very actively evaluating this issue and we are not necessarily ready to make recommendations as far as the duration of treatment, whether drug holidays versus stopping the drug. We are still looking at all of those issues.

Sandra Kweder: That was Theresa Kehoe and this is Sandy Kweder. I'm going to add to that. I think that any — you know, when patients and physicians should be having conversations about just like any medicine. Do I still need this medicine? Is this still the best medicine for me? And the answer to that will depend on what else is happening.

Maybe other medications that they started taking that maybe may be substitutes or just as good as a bisphosphonate. Or in particular related to as we're warning today, if the patient has been experiencing any kind of unexplained pain of the groin or thigh. Making sure that

they have a conversation with their physician about any symptom like that is extremely important to govern what kind of management is appropriate.

I hope that answer — those help you.

Deborah Kotz: Yes. Thanks. And just one follow-up. Do you have a percentage of how many patients had this unexplained pain in their groin or thigh before they had the fracture?

Theresa Kehoe: In the case reports that we have it's over 50%. So it is the majority of patients.

Sandra Kweder: And again, that often occurs weeks to months — begins weeks to months before the actual fracture.

Karen Riley: Thank you. Next question please.

Coordinator: Your next question comes from Robert Lowes from Medscape Medical News. Your line is open.

Robert Lowes: Hi. Thank you for taking my call. I wanted to ask for some clarification about this dull aching thigh or groin pain that precedes the complete fracture. Looking at your data summary, you're summarizing what the American Society for Bone and Mineral Research says, what its task force reported. They — it says here, "Many patients report this pain

weeks to months before a complete fracture occurs."

So I'm wondering what does that pain actually signify? Does it signify the beginnings of a fracture or does it signify something else that's related to the fracture? And if a person recognizes this pain, what can possibly be done for that patient in terms of dealing with an impending total fracture? Is there anything a patient can do or any treatment they can receive that might avert this complete snap so to speak?

Theresa Kehoe: Well I think that the American Society for Bone and Mineral Research does bring out the thigh pain in their report. But we have also gone back to the reports that we have received and again have found that over 50% of patients are having — are also in the reports we have had the thigh and groin pain.

As far as treatments, what we have right now is we do not have any clinical studies to say that one treatment is better than the other. Certainly as outlined in the American Society for Bone and Mineral Research they recommend stopping the drug. Sometimes patients can be treated conservatively with non-weight

bearing and be able to avert a complete fracture. And sometimes if the pain continues, they may need orthopedic care.

So I think a lot of this will depend on the patient and the physician and what exactly the history is and what the patient's symptoms are.

Robert Lowes: But is the — to follow up, is the pain the result of a partial fracture or is it related to something else?

Theresa Kehoe: It appears that it might be related to an actual partial fracture such as a stress fracture.

Sandra Kweder: The problem is that we don't know because the descriptions of pain having been there usually come, you know, are something that's reported in retrospect. There aren't studies or really much in the literature that follows these patients prospectively to understand the evolution of the pain and what the pathology is that is paralleling it.

Robert Lowes: Okay. Thank you very much.

Karen Riley: And by non-weight bearing, you mean don't stand on your leg or something?

Sandra Kweder: Yeah.

Karen Riley: Okay. Very good. Operator, do we have any more people on the line?

Maybe we have time for two more questions.

Coordinator: Yes. We have one person. And again if you'd like to ask a question, please press star 1. Star 1 to ask a question please. And next is Matt Perrone. Your line is open.

Matt Perrone: Hi guys. Can you talk about the typical duration that people stay on these drugs? You said this was more common in people who have been taking bisphosphonates for five years. But is that rare or is that pretty typical?

Theresa Kehoe: We don't really have any data to tell us exactly how long patients remain on bisphosphonates. We — in the reports that we have seen there are some patients that have been on bisphosphonates for 10 to 15 years. Certainly I think there's probably a spectrum.

Matt Perrone: Okay. And can you talk at all about how these drugs typically are supposed to work, how they typically strengthen bones and how that could in rare cases lead to these type of fractures?

Theresa Kehoe: The drugs, the bisphosphonates work by inhibiting the osteoblast which is the cell that resorbs bone, that lessens bone. How — but exactly how the method for what the

association is, there are many postulates of what could possibly be the mechanisms that bisphosphonates cause these types of fractures. What I would recommend, I think the American Society for Bone and Mineral Research does a very nice job of looking at what all of the possible mechanisms are.

Matt Perrone: And how is the FDA going to determine which of those is the culprit here?

Sandra Kweder: I think this is an area of intense research. This is Sandy Kweder. This is in the area of intense research in the bone and mineral community. You know, the whole not only related to these fractures but related to what optimal therapies are in general to prevent or treat osteoporosis. So we will be following that very closely as we do — related not just to these drugs but in looking at all kinds of treatments for osteoporosis.

Karen Riley: Thank you Matt. We did have — I did get an email from one of the reporters on the call who did ask for a little bit more information on the numbers of fractures prevented and we do have some information on that. Dr. Kehoe will explain.

Theresa Kehoe: Sure. I think probably the best data out there is the study looking at the

National Hospital Discharge Survey which looks at discharge rates per 100,000 persons for hip fractures. And obviously hip fractures are one of the more problematic fractures in the osteoporotic population.

If you recall Alendronate was the first bisphosphonate approved for osteoporosis in 1995 and all of the other ones have been subsequent to that. In 1996 when we look at the National Hospital Discharge Survey, the rate of hip fracture discharges was 598 per 100,000 persons. In 2006, so after approximately ten years of bisphosphonates being on the market for treating osteoporosis, the hip fracture discharge rate had fallen to 428 per 100,000 persons. So that is a pretty substantial decrease in hip fracture rates over that ten-year period due to osteoporosis therapies, mostly the bisphosphonates.

Karen Riley: Thank you. Thank you. That was Dr. Theresa Kehoe. And again for those of you who didn't catch the spelling of her name, her last name is spelled K-E-H-O-E and her first name Theresa, T-H-E-R-E-S-A. And she is a team leader in the Division of Reproductive and Urologic Products in CDER's Office of Drug Evaluation 3.

Okay. This concludes today's media teleconference. Thank you for your participation. A replay will be available in about an hour. If you have any follow-up questions, please don't hesitate to call me, Karen Riley, at 301-796- 4674 or even better email me at karen.riley, that's R-I-L-E-Y, @fda.hhs, as in Sam, dot gov. Thank you.

Coordinator: Thank you. This concludes today's call. You may disconnect at this time.

END

[Exhibit 148 to Ecklund Declaration]

To:	Adams, James H (WRG) <james_adams@merck.com>
From:	Stiller, Karl <Karl.Stiller@fda.hhs.gov>
Cc:	
Bcc:	
Received Date:	2009-04-15 19:51:43
Subject:	Tcon for Fosamax products

There seems to be some confusion regarding the discussion last week. What Dr. Monroe and Dr. Kehoe proposed to Charlotte Merrick was that the currently pending SLRs (20-560 s052; 21-575 s013; 21-762 s006) for atypical fracture could be approved at this time only for inclusion of the atypical fracture language proposed in the postmarketing adverse events section of the label. If Merck agrees to hold off on the W&P language at this time, then we can go ahead and close out these supplements.

We would then work with OSE and Merck to decide on language for a W&P atypical fracture language, if it is warranted. We also let Merck know that we are working with our dental colleagues on acceptable ONJ language and once we have that, we will work with Merck on the ONJ language.

What Dr. Kehoe proposed was that she was hopeful that an agreement could be reached with Merck regarding the language for ONJ and possibly atypical fracture in time to allow that language to be included in the PLR conversion supplement.

At this time, we are not able to commit to doing a "quick" review of a new SLR supplement. However, if Merck is accepting the language from the esophageal SRL, that may be able to be included - we would be able to approve that with the atypical fracture postmarketing language.

I have reserved 3:30 pm - 4:00 pm for a Tcon to discuss the matter, if necessary.

Call in number: 1-888-397-4120
Pass code: 8088980

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Urologic and Reproductive Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

[Exhibit 149 to Ecklund Declaration]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 20-560/S-054, NDA 21-575/S-015,
NDA 21-762/S-008

COMPLETE RESPONSE

James H. Adams
May 22, 2009

Merck & Co., Inc.
Attention: James Adams, M.S.
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065-0900

Dear Mr. Adams

Please refer to your supplemental new drug applications (sNDAs) dated September 15, 2008, received September 15, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

FOSAMAX (alendronate sodium) Tablets
(NDA 20-560/S-054)
FOSAMAX (alendronate sodium) Oral Solution
(NDA 21-575/S-015)

FOSAMAX Plus D
(alendronate sodium/cholecalciferol) Tablets
(NDA 21-762/S-008)

We acknowledge receipt of your amendments for FOSAMAX Tablets and FOSAMAX Oral Solution, both dated September 19, 2008.

These supplemental new drug applications propose adding language to the **PRECAUTIONS** section and the **ADVERSE REACTIONS, Post-Marketing Experience** subsection of the Package Inserts (PIs) to describe low-energy fractures at the subtrochanteric region of the femoral shaft. In addition these supplements propose adding language describing this type of fracture in the Patient Package Inserts (PPIs).

We have completed the review of your applications, as amended, and have determined we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.

1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the FOSAMAX Tablets and Oral Solution and FOSAMAX Plus D Tablets labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported

by the available literature and post-marketing adverse event reporting.

2. We recommend that you add "low energy femoral shaft and subtrochanteric fractures" in the **ADVERSE REACTIONS, Post-Marketing Experience** subsection of the respective package inserts.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/datacouncil_spl/html.

When responding to this letter, submit labeling that includes all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

Scott Monroe, M.D.
Director
Division of Reproductive and
Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation
and Research

/s/ Scott Monroe
5/22/2009 11:06:15 AM

[Exhibit 150 to Ecklund Declaration]

To: **Adams, James H (WRG) <james_adams@merck.com>; Santora, Arthur C. <art_santora@merck.com>; Miteva, Yanna R <yanna_miteva@merck.com>; Hampton, Tonja W <tonja_hampton@merck.com>; Holston, James <james_holston@merck.com>; Hutnyan, John J. <john_hutnyan@merck.com>; Frank, Lori J. <lori_frank@merck.com>; Birzin, Elizabeth T. <ellzabeth_birzin@merck.com>; Stebbins, Enid <enid_stebbins@merck.com>; Thornton, Rosemary A <rosemary _thornton@ merck.com>**

From: **Reiss, Theodore F. <./O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=REISST>**

Cc: **Bold, Thomas M. <thomas_bold@merck.com>; Merritt, Charlotte B. <charlotte_merritt@merck.com>; Kloss, Michelle W. <michelle_kloss@merck.com>; King, Vicki M <vicki_king2@ merck.com>**

Bcc:

Received Date: 2009-05-22 21:58:57

Subject: RE: FDA letter regarding low energy femoral shaft fractures

---

What are the next steps?

From: Adams, James H (WAG)
Sent: Friday, May 22, 2009 12:41 PM
To: Reiss, Theodore F.; Santora, Arthur C.; Miteva, Yanna R; Hampton, Tonja W; Holston, James; Hutnyan, John J.; Frank, Lori J.; Birzin, Elizabeth T.; Stebbins, Enid; Thornton, Rosemary A
Cc: Bold, Thomas M.; Merritt, Charlotte B.; Reiss, Theodore F.; Kloss, Michelle W.; King, Vicki M
Subject: FDA letter regarding low energy femoral shaft fractures

Dear all,

Please find attach a fax from the FDA not approving our PAS re. low-energy femoral shaft fractures << File: Document.pdf >>. The Division agrees that a description of these fractures should be added to the Adverse Reactions, Post-Marketing section of the label. However, it believed that our justification to support the proposed Precaution text was inadequate. It believes that "stress fractures" may not be clearly related to atypical subtrochanteric fractures. Furthermore, the Division to not agree with the inclusion of risk factors for stress fractures.

Please note that the Division has requested that the following text be added to the Post-marketing section- "low energy femoral shaft and subtrochanteric fractures"

Diane,

Please add fax to e-dossier. Thanks.

Jim

[Exhibit 151 to Ecklund Declaration]

To:	**Adams, James H (WRG) <james_adams@merck.com>**
From:	**Santora, Arthur C. </O=MERCK/OU=NORTHAMERICA/ CN=RECIPIENTS/CN=SANTORAA>**
Cc:	
Bcc:	
Received	**Date: 2009-05-22 21:18:16**
Subject:	**RE: FDA letter regarding low energy femoral shaft fractures**

Thanks, Jim. Timely FAX.

Kind of ironic that the TGA wouldn't let us mention low energy fractures in general and the FDA wouldn't let us mention stress fractures.

Art

From:	Adams, James H (WAG)
Sent:	Friday, May 22, 2009 12:41 PM
To:	Reiss, Theodore F.; Santora, Arthur C.; Miteva, Yanna R; Hampton, Tonja W; Holston, James; Hutnyan, John J.; Frank, Lori J.; Birzin, Elizabeth T.; Stebbins, Enid; Thornton, Rosemary A

Cc: Bold, Thomas M.; Merritt, Charlotte B.; Reiss, Theodore F.; Kloss, Michelle W.; King, Vicki M

Subject: FDA letter regarding low energy femoral shaft fractures

Dear all,

Please find attach a fax from the FDA not approving our PAS re. low-energy femoral shaft fractures << File: Document.pdf >> . The Division agrees that a description of these fractures should be added to the Adverse Reactions, Post-Marketing section of the label. However, it believed that our justification to support the proposed Precaution text was inadequate. It believes that "stress fractures" may not be clearly related to atypical subtrochanteric fractures. Furthermore, the Division to not agree with the inclusion of risk factors for stress fractures.

Please note that the Division has requested that the following text be added to the Post-marketing section- "low energy femoral shaft and subtrochanteric fractures"

Diane,

Please add fax to e-dossier. Thanks.

Jim

[Exhibit 156 to Ecklund Declaration]

FDA **U.S. Food and Drug Administration**

Protecting and Promoting Your Health

Drugs

FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures

The FDA has issued new information about this safety issue, see the FDA Drug Safety Communication issued 10-13-2010[1].

Safety Announcement

[03-10-2010] Patients and healthcare professionals may have questions about oral bisphosphonate medications and atypical subtrochanteric femur fractures – fractures in the bone just below the hip joint. Oral bisphosphonates are commonly prescribed to prevent or treat osteoporosis in postmenopausal women. Common brand names of medications in this class include Fosamax, Actonel, Boniva, and Reclast.

Recent news reports have raised the question about whether there is an increased risk of this type of fracture in patients with osteoporosis using these medications. At this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures. FDA is working closely with outside experts, including members of the

recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue.

Based on published case reports of atypical subtrochanteric femur fractures occurring in women with osteoporosis using bisphosphonates, FDA, in June 2008, requested information from all bisphosphonate drug manufacturers regarding this potential safety signal. All available case reports and clinical trial data were requested. FDA's review of these data did not show an increase in this risk in women using these medications.

In addition, FDA reviewed a December 2008 article in the Journal of Bone and Mineral Research by *Abrahamsen* et al[1], that analyzed data from two large observational studies in patients with osteoporosis. The authors concluded that atypical subtrochanteric femur fractures had many similar features in common with classical osteoporotic hip fractures, including patient age, gender, and trauma mechanism. The data showed that patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures relative to classical osteoporotic hip fractures.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs. The agency will continue to review new information as it becomes available and will update the public once the agency's review is complete.

Healthcare professionals should continue to follow the recommendations in the drug label when

prescribing oral bisphosphonates. **Patients** should not stop taking their medication unless told to do so by their healthcare professional. Patients should talk to their healthcare professional about any concerns they have with these medications.

Additional Information for Patients

If you currently take an oral bisphosphonate you should:

- Not stop taking your medication unless told to do so by your healthcare professional.
- Talk to your healthcare professional if you develop new hip or thigh pain or have any concerns with your medications.
- Report any side effects with your bisphosphonate medication to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking oral bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing oral bisphosphonates.
- Discuss with patients the known benefits and potential risks with using oral bisphosphonates.
- Report any adverse events with the use of oral bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

References:

1. Abrahamsen B., Eiken P., Eastell R. Subtrochanteric and Diaphyseal Femur Fractures in Patients Treated With Alendronate: A Register-Based National Cohort Study. *J Bone Miner Res*. 2009 Jun;24(6):1095–102.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[2]
- Podcast for Healthcare Professionals: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures[3] 3/17/2010
- FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures[4] 10/13/2010

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

MedWatch Online[5]

Regular Mail: Use postage-paid FDA Form 3500[6]

Mail to: MedWatch 5600 Fishers Lane Rockville, MD 20857

Page Last Updated: 07/18/2011

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

[Exhibit 159 to Ecklund Declaration]

FDA **U.S. Food and Drug Administration**

Protecting and Promoting Your Health

Drugs

FDA Statement on ASBMR report: Possible Increased Risk of Certain Types of Thigh Bone Fractures with Long-Term Bisphosphonates Use

[9/14/2010] FDA appreciates the report from the American Society of Bone and Mineral Research's (ASBMR's) expert Task Force, released today, providing important perspectives on the potential association between long term treatment with the class of osteoporosis drugs known as bisphosphonates and a rare but serious type of fracture of the thigh bone (femur). The report includes a case definition that describes the atypical features of these unusual femur fractures. FDA believes this case definition will help greatly in identifying cases and reporting on them, and should facilitate future studies comparing the frequency of these unusual fractures both in patients treated with bisphosphonates and those who have not received bisphosphonates.

Bisphosphonates have long been effective in reducing common bone fractures in individuals with osteoporosis. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been identified in patients taking these drugs. FDA recommends that healthcare

professionals be aware of the possible risk of unusual femur fractures in patients taking bisphosphonates. Patients should talk to their healthcare professional if they develop new thigh or groin pain so that they may be evaluated to rule out a femur fracture. Patients should not stop taking their medication unless told to do so by their healthcare professional. Patients and healthcare professionals should report any side effects with the use of bisphosphonates to FDA's MedWatch program.

The optimal duration of bisphosphonate treatment for osteoporosis is unknown. Clinical trial data for bisphosphonates approved for the prevention and/or treatment of osteoporosis support effectiveness for the reduction of common bone fractures for three to five years.

Since the initial report of unusual fractures with bisphosphonates was published, FDA has been diligently monitoring this issue. We have been reviewing all the scientific data available regarding their safety and effectiveness when used for more than three to five years for the treatment and prevention of osteoporosis. We have talked with patient groups and have requested clinical trial data from the manufacturers of bisphosphonate products as part of this ongoing safety review.

The ASBMR Task Force's recommendations include recommended changes to product labels alerting healthcare professionals and patients to the possibility of unusual femur fractures with long-term use of bisphosphonates. FDA has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports, and is

considering label revisions. FDA will keep the public informed of additional findings and actions on this issue.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[1]

Contact FDA

Toll Free
(855) 543-3784, or
(301) 796-3400
druginfo@fda.hhs.gov
Human Drug Information
Division of Drug Information (CDER)
Office of Communications
Feedback Form[2]
10001 New Hampshire Avenue
Hillandale Building, 4th Floor
Silver Spring, MD 20993

Page Last Updated: 09/15/2010

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-88-INFO-FDA (1-888-463-6332)
Email FDA

[Exhibit 160 to Ecklund Declaration]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 0993

NDA 021762

SAFETY LABELING CHANGE AND REMS NOTIFICATION

Merck Sharp & Dohme Corp
Attention: Elinor Chen, Ph.D.
Director, Worldwide Regulatory Affairs
PO Box 2000, RY33-212
Rahway, NJ 07065

Dear Dr. Chen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fosamax Plus D, (alendronate sodium/cholecalciferol) 70 mg/2800 IU and 70 mg/5600 IU tablets.

Sections 505(o)(4) and 505-1 of the FDCA authorize FDA to require holders of approved drug and biological product applications to make safety related labeling changes, and to develop and comply with risk evaluation and mitigation strategies (REMS) based upon new safety information that becomes available after approval of the drug or biological product.

Since Fosamax Plus D was approved on April 7, 2005, we have become aware of a possible increased risk of atypical subtrochanteric and diaphyseal femoral fractures in patients taking bisphosphonates, including Fosamax Plus D, for the treatment and/or prevention of osteoporosis. Recent publications, including the 2010 Report of a Task Force of the American Society for Bone and Mineral Research, suggest that the risk of atypical fractures and diaphyseal femoral fractures increases with increased duration of bisphosphonate exposure. We consider this information to be "new safety information" as defined in section 505-l(b)(3) of the FDCA.

SAFETY LABELING CHANGE

In accordance with section 505(o)(4) of the FDCA, we are notifying you that, based on the new safety information described above, we believe that the information regarding possible increased risk of atypical fractures and diaphyseal femoral fractures should be included in the labeling for bisphosphonates approved for the treatment and/or prevention of osteoporosis as follows:

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Recent Major Changes: add the following two bullets (underlined):

   Recent Major Changes:

   - Indications and Usage (insert date)
   - Warnings and Precautions (insert date)

2. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Indications and Usage: add the following (underlined):

The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

3. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under Warnings and Precautions: add the following bullet (underlined):

   • Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture

4. Add the following language to the **INDICATIONS AND USAGE** section of the package insert (underlined):

   1.3 Important Limitations of Use

   The safety and effectiveness of Fosamax Plus D for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

5. Revise the **WARNINGS AND PRECAUTIONS** section of the package insert to add the following paragraphs (underlined) as described below:

   5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures:

   Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse

or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

6. Medication Guide

In addition to the labeling changes described above, you should convert your patient package insert to a Medication Guide for Fosamax Plus D, as shown in the Medication Guide attached (See ENCLOSURES). Your Medication Guide must include information about the serious risk of atypical subtrochanteric and diaphyseal femoral

fractures and will be considered part of the proposed REMS described below.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT**" or "**SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED**."

If you do not submit electronically, please send 5 copies of the submission.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

In accordance with section 505-l of FDCA, we have determined that a REMS is necessary for Fosamax Plus D to ensure the benefits of the drug outweigh the risks of atypical subtrochanteric and diaphyseal femoral fractures in patients using bisphosphonates for the treatment and/or prevention of osteoporosis.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Fosamax Plus D poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Fosamax Plus D. FDA has determined that Fosamax Plus D is a product for which patient labeling could help prevent serious adverse effects and/or that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Fosamax Plus D.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Fosamax Plus D.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven

years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

In accordance with section 505-1, within 30 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to Fosamax Plus D (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package

includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS for NDA 021762/S-###**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 021762**." If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

[See appended electronic signature page]

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
REMS Appendix A
REMS Appendix B
Medication Guide

Initial REMS Approval: XX/XXXX
Most Recent Modification: XX/XXXX

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

To inform patients about the serious risks associated with the use of [drug name].

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18

months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B:

REMS SUPPORTING DOCUMENT TEMPLATE MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
   a. Medication Guide
   b. Describe in detail how you will comply with 21 CFR 208.24
   c. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

MEDICATION GUIDE

FOSAMAX PLUS D® (FOSS-ah-max PLUS D)

(*alendronate sodium/ cholecalciferol*)

Tablets

Read the Medication Guide that comes with FOSAMAX PLUS D before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about FOSAMAX PLUS D.

What is the most important information I should know about FOSAMAX PLUS D?

FOSAMAX PLUS D can cause serious side effects including:

1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Bone, joint, or muscle pain
4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

1. **Esophagus problems**.

   Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

   - It is import ant that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems.

(See the section "How should I take FOSAMAX PLUS D?")

- Stop taking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.

2. **Low calcium levels in your blood (hypocalcemia)**.

   FOSAMAX PLUS D may lower the calcium levels in your blood. If you have low blood calcium before you start taking FOSAMAX PLUS D, it may get worse during treatment. Your low blood calcium must be treated before you take FOSAMAX PLUS D. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

   - Spasms, twitches, or cramps in your muscles
   - Numbness or tingling in your fingers, toes, or around your mouth

   Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take FOSAMAX PLUS D. Take calcium and vitamin D as your doctor tells you to.

3. **Bone, joint, or muscle pain**.

   Some people who take FOSAMAX PLUS D develop severe bone, joint, or muscle pain.

4. **Severe jaw bone problems (osteonecrosis)**.

   Severe jaw bone problems may happen when you take FOSAMAX PLUS D. Your doctor should examine your mouth before you start FOSAMAX PLUS D. Your doctor may tell you to see your

dentist before you start FOSAMAX PLUS D. It is important for you to practice good mouth care during treatment with FOSAMAX PLUS D.

5. **Unusual thigh bone fractures**.

   Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is FOSAMAX PLUS D?

FOSAMAX PLUS D is a prescription medicine used to:

- Treat osteoporosis in women after menopause. FOSAMAX PLUS D increases bone mass and reduces the chance of having a hip or spinal fracture (break).
- Increases bone mass in men with osteoporosis.

FOSAMAX PLUS D should not be used to treat Vitamin D deficiency.

It is not known how long FOSAMAX PLUS D works for the treatment of osteoporosis. You should see your doctor regularly to determine if FOSAMAX PLUS D is still right for you.

FOSAMAX PLUS D is not for use in children.

Who should not take FOSAMAX PLUS D?

Do not take FOSAMAX PLUS D if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes

- Have low levels of calcium in your blood
- Are allergic to FOSAMAX PLUS D or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking FOSAMAX PLUS D?

Before you start FOSAMAX PLUS D, be sure to talk to your doctor if you:

- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant, or plan to become pregnant. It is not known if FOSAMAX PLUS D can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if FOSAMAX PLUS D passes into your milk and may harm your unborn baby.

Especially tell your doctor if you take:

- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how FOSAMAX PLUS D works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take FOSAMAX PLUS D tablet?

- Take FOSAMAX PLUS D exactly as your doctor tells you.
- **FOSAMAX PLUS D works only if taken on an empty stomach.**
- Take 1 dose of FOSAMAX PLUS D 1 time a week, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX PLUS D while you are sitting or standing.
- Take your FOSAMAX PLUS D with plain water only as follows:
- TABLET: Swallow one tablet with a full glass (6-8 oz) of plain water.
- **Do not chew or suck on a tablet of FOSAMAX PLUS D.**
- Do **not** take FOSAMAX PLUS D with mineral water, coffee, tea, soda, or juice.
- Do not take FOSAMAX PLUS D at bedtime.

After swallowing FOSAMAX PLUS D, wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take FOSAMAX PLUS D and after you eat your first food of the day.

If you miss a dose of FOSAMAX PLUS D, do not take it later in the day. Take your missed does the next morning and then return to your normal schedule. Do not take 2 doses at the same time.

You should take calcium and vitamin D as directed by your doctor.

If you take too much FOSAMAX PLUS D, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of FOSAMAX PLUS D?

FOSAMAX PLUS D may cause serious side effects.

- See "**What is the most important information I should know about FOSAMAX PLUS D**?"

The most common side effects of FOSAMAX PLUS D are:

- Stomach area (abdominal) pain
- Heartburn
- Constipation
- Diarrhea
- Upset stomach
- Pain in your muscles
- Nausea

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of FOSAMAX PLUS D. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store FOSAMAX PLUS D?

- Store FOSAMAX PLUS D at room temperature, 68°F to 77°F (20°C to 25°C).
- Keep FOSAMAX PLUS D away from light.
- Keep FOSAMAX PLUS D package and tablets dry.
- Store FOSAMAX PLUS D in the original package.

Keep FOSAMAX PLUS D and all medicines out of the reach of children.

General information about the safe and effective use of FOSAMAX PLUS D.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FOSAMAX PLUS D for a condition for which it was not prescribed. Do not give FOSAMAX PLUS D to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about FOSAMAX PLUS D. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOSAMAX PLUS D that is written for health professionals.

For more information, go to www.fosamaxplusd.com or call 1-877-408-4699.

What are the ingredients in FOSAMAX PLUS D?

Active ingredient: alendronate sodium and cholecalciferol (D3)

Inactive ingredients: cellulose, lactose, medium chain triglycerides, gelatin, croscarm ellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

Manufactured by:

MSD FROSST IBERICA, S.A.
Madrid, Spain

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued Month/Year

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN

10/13/2010

Reference ID: 2848812

[Exhibit 161 to Ecklund Declaration]

To: Chen, Elinor H. <elinor_chen@merck.com>
From: Stiller, Karl <Karl.Stiller@fda.hhs.gov>
CC:
Bcc:
Received Date: 2010-12-16 17:21:34
Subject: Merck bisphosphonate labeling

Dr. Chen: Here is the Fosamax labeling for Merck. The changes include: 1) edits to the W&P for atypical fracture 2) removal of several sentences from 14.1, per DDMAC/OMP discussion 3) significant edits to Highlights to conform to the half page requirement 4) edits to the indication statements in the MG (from increases BMD to helps increase BMD, and from reduces fracture to helps reduce fracture) 5) carton/container comments. Please review and respond by Monday, December 19, 2010. If you agree with the proposed changes, accept tracked changes and send the labeling back to me with a statement indicating your acceptance. Final labeling should be submitted to the applications by December 23, 2010.

LCDR Karl Stiller, R.Ph. Regulatory Health Project Manager Division of Reproductive and Urologic Products Office of Drug Evaluation Ill Center for Drug Evaluation and Research 301-796-1993

Attachments:

Fosamax Plus D DRISK clean MG 11.23.10.doc

Fosamax Plus D DRISK marked up MG 11.23.20.doc
Fosamax Tablets OS DRISK clean MG 11.23.10.doc
Fosamax Tablets OS DRISK marked up MG 11.23.10.doc
Fosamax_Labeling Comments.doc
Fosamax-pi-pas-_FDA_121310.doc
FosamaxPlusD-pi-pas-FDA_121310.doc

MEDICATION GUIDE

FOSAMAX PLUS D® (FOSS-ah-max PLUS D)

(*alendronate sodium/cholecalclferol) Tablets*

Read the Medication Guide that comes with FOSAMAX PLUS o® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about FOSAMAX PLUS D.

[DRISK Comment: We revised this MG to reflect the identical class labeling language sent to the Applicant by DRUP on 10/13/10. We deleted the extensive information at the end of the MG concerning Vitamin D and osteoporosis to be consistent with the patient information across the drug class. The Applicant added in this additional information that is not necessary in the Medication Guide. The purpose of the Medication Guide is to educate the patient on the necessary information needed to take the medication safely, not on the disease process the medication treats.]

What is the most important information I should know about FOSAMAX PLUS D?

FOSAMAX PLUS D can cause serious side effects including:

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1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Bone, joint, or muscle pain
4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

1. Esophagus problems.

Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- *** It is important that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX PLUS D?"**
- *** Stop talking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.** ***[DRISK Comment: We bolded this information for consistency across bisphosphonate patient labeling.]***

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2. Low calcium levels in your blood (hypocalcemia)

FOSAMAX PLUS D may lower the calcium levels in your blood. If you have low blood calcium before you start taking FOSAMAX PLUS D, it may get worse during treatment. Your low blood calcium must be treated before you take FOSAMAX PLUS D. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- **Spasms, twitches, or cramps in your muscles**
- **Numbness or tingling in your fingers, toes, or around your mouth**

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Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take FOSMAX PLUS D. Take calcium and vitamin D as your doctor tells you to.

3. Bone, joint, or muscle pain.

Some people who take FOSMAX PLUS D develop severe bone, joint, or muscle pain.

4. Severe jaw bone problems (osteonecrosis).

Severe jaw bone problems may happen when you take FOSAMAX PLUS D. Your doctor should examine your mouth before you start FOSAMAX PLUS D. It is important for you to practice good mouth care during treatment with FOSAMAX PLUS D.

5. Unusual thigh bone fractures.

Some people have developed unusual fracture in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is FOSAMAX PLUS D?

FOSAMAX PLUS D is a prescription medicine used to:

- Treat osteoporosis in women after menopause. FOSAMAX PLUS D helps increase bone mass and reduces the chance of having a hip or spinal fracture (break).
- Increase bone mass in men with osteoporosis.

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< # > Esophagus problems¶
< # > Severe jawbone problems (osteonecrosis) ¶
< # > Thigh bone fractures¶
< # > Esophagus problems. ¶
Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed. ¶
< # > It is important that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX PLUS D?") ¶
< # > Stop taking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow. ¶ ...[1]

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FOSAMAX PLUS D should not be used to treat vitamin D deficiency.

It is not known how long FOSAMAX PLUS D works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if FOSAMAX PLUS D is still right for you.

FOSAMAX PLUS D is not for use in children.

Who should not take FOSAMAX PLUS D?

Do not take FOSAMAX PLUS D if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to FOSAMAX PLUS D or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking FOSAMAX PLUS D?

Before you start FOSAMAX PLUS D, be sure to talk to your doctor if you:

- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium

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- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have sarcoidosis, leukemia, lymphoma. These conditions may cause changes in vitamin D.
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant or plan to become pregnant. It is not known if FOSAMAX PLUS D can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if FOSAMAX PLUS D passes into your milk and may harm your baby.

Especially tell your doctor if you take:

- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how FOSAMAX PLUS D works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

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How should I take FOSAMAX PLUS D tablet?

- Take FOSAMAX PLUS D exactly as your doctor tells you.
- **FOSAMAX PLUS D works only if taken on an empty stomach.**
- Take 1 dose of FOSAMAX PLUS D 1 time a week, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX PLUS D while you are sitting or standing.
- Take your FOSAMAX PLUS D tablet with a full glass (6–8 oz) of plain water.
- **Do not chew or suck on a tablet of FOSAMAX PLUS D.**

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Deleted: < # > Choose the day of the week that best fits your schedule. ¶
< # > Take 1 tablet of FOSAMAX PLUS D every week on your chosen day **after** you get up for the day and **before** taking your first food, drink, or other medicine. ¶

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- **Do not** take FOSAMAX PLUS D with mineral water, coffee, tea, soda, or juice.
- Do not take FOSAMAX PLUS D at bedtime

After swallowing FOSAMAX PLUS D, wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take FOSAMAX PLUS D and after you eat your first food of the day.

If you miss a dose of FOSAMAX PLUS D, do not take it later in the day. Take your missed dose on the next morning after you remember and then return to your normal schedule. Do not take 2 doses on the same day.

You should take calcium and vitamin D as directed by your doctor.

If you take too much FOSAMAX PLUS D, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of FOSAMAX PLUS D?

FOSAMAX PLUS D may cause serious side effects.

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- See **"What is the most important information I should know about FOSAMAX PLUS D?"**

The most common side effects of FOSAMAX PLUS D are:

- Stomach area (abdominal) pain
- Heartburn
- Constipation
- Diarrhea
- Upset stomach
- Pain in your bones, joints, or muscles
- Nausea

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of FOSAMAX PLUS D. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store FOSAMAX PLUS D?

- Store FOSAMAX PLUS D at room temperature, 68ºF to 77ºF (20ºC to 25ºC).
- Keep FOSAMAX PLUS D away from light.
- Keep FOSAMAX PLUS D package and tablets dry.

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- Store FOSAMAX PLUS D in the original package.

Keep FOSAMAX PLUS D and all medicines out of the reach of children.

General information about the safe and effective use of FOSAMAX PLUS D.

Medicines are sometimes prescribed for conditions other than those listed in a Medication Guide. Do not use FOSAMAX PLUS D for a condition for which it was not prescribed. Do not give FOSAMAX PLUS D to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about FOSAMAX PLUS D. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOSAMAX PLUS D that is written for health professionals.

For more information, go to: www.fosamaxplusd.com or call 1-877-408-4699.

What are the ingredients in FOSAMAX PLUS D?

Active ingredients: alendronate sodium and cholecalciferol (vitamin D_3).

Inactive ingredients: cellulose, lactose, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide,

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magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

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

By:
FROSST IBERICA, S.A.
28805 Alcalá de Henares
Madrid, Spain

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised Month Year

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Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. Winter sunlight in most of the United States is too weak to produce vitamin D. Even in the summer, clothing or sun block can prevent enough sunlight from getting through. In addition, as people age, their skin becomes less able to make vitamin D. Very few foods are natural sources of vitamin D. Some foods, such as milk, some brands of orange juice and breakfast cereals are fortified with vitamin D. ¶ ¶ Too little vitamin D leads to low calcium absorption and low phosphate. These are minerals that make bones strong. Even if you are eating a diet rich in calcium or taking a calcium supplement, your body cannot absorb calcium properly unless you have enough vitamin D. Too little … … [11]

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FOSAMAX PLUS D may cause side effects which can be serious including:

Esophagus problems

Severe jawbone problems (osteonecrosis)

Thigh bone fractures

Esophagus problems.

Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

It is important that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX PLUS D?")

Stop taking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.

Esophagus problems may get worse if you continue to take FOSAMAX PLUS D.

Severe jawbone problems (osteonecrosis).

Tell your doctor about all of your dental conditions. FOSAMAX PLUS D may cause jawbone problems in some people. Jawbone problems may include infection, and delayed healing after teeth are pulled. It is important for you to practice good oral hygiene and regular

dental care during treatment with FOSAMAX PLUS D.

Thigh bone fractures.

Rarely patients have developed fracture in a specific part of the thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

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drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

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Low calcium levels in your blood (hypocalcemia).

If you have been told you have low blood calcium tell your doctor. You

* * *

Numbness or tingling in your fingers, toes, or around mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels

in your blood, while you take FOSAMAX PLUS D. Take calcium and vitamin D as your doctor tells you.

Bone, joint, or muscle pain.

Some people who take FOSAMAX PLUS D develop bone, joint or muscle pain. Call your doctor if you develop severe bone, joint or muscle pain.

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Mouth sores (ulcers) may occur if the FOSAMAX PLUS D tablet is chewed or dissolved in the mouth.

You may get flu-like symptoms typically at the start of treatment with FOSAMAX PLUS D.

You may get allergic reactions, such as hives or, in rare cases, swelling of your faces, lips, tongue, or throat.

Other side effects are vomiting, a full or bloated feeling in the stomach, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, hair loss, headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs.

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What should I know about Vitamin D?

Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. Winter sunlight in most of the United States is too weak to

* * *

foods, such as milk, some brands of orange juice and breakfast cereals fortified with vitamin D.

Too little vitamin D leads to low calcium absorption and low phosphate. These are minerals that make bones strong. Even if you are eating a diet rich in calcium or taking a calcium supplement, your body cannot absorb calcium properly unless you have enough vitamin D. Too little vitamin D may lead to bone loss and osteoporosis.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar

amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, you spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher change of getting osteoporosis:

Women who:
Are going through or who are past menopause

Men who:
Are elderly

People who:
Are white (Caucasian) or oriental (Asian)
Do not exercise

Smoke
Drink alcohol often
Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help treat osteoporosis?

In addition to FOSAMAX PLUS D, your doctor may suggest one or more of the following lifestyle changes:

Stop smoking. Smoking may increase your chance of getting osteoporosis.

Reduce the use of alcohol. Too much alcohol may increase the chance of osteoporosis and injuries that can cause fractures.

Exercise regularly. Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.

Eat a balanced diet. Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or additional vitamin D.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Labeling Comments Regarding NDAs 020560, 021575, and 021762; See accompanying documents with FDA edits (full prescribing information, MG marked and MG clean copies. The clean MG copy contains all appropriate formatting).

Regarding the Full Prescribing Information:

After consideration of all labeling comments received from all sponsors, the Division has accepted two changes to the labeling requested. These changes are:

1) Changed the word "impact" to "trauma" in the first sentence of the second paragraph of the Atypical and Subtrochanteric Femoral Fractures Warning and Precaution.
2) Changed the word "subjects" to "patients" in the second sentence of the third paragraph of the Atypical and Subtrochanteric Femoral Fractures Warning and Precaution.

All other Sponsor proposed changes to this class labeling are not acceptable. This is reflected in the accompanying FDA edited labeling document.

Specifically, for the proposed changes to the Fosamax labels, the term "stress fracture" was considered and was not accepted. The Division believes that for most practitioners, the term "stress fracture" represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use. In addition, the risk factors listed in the proposed changes have not been sufficiently validated to include in labeling at this time.

For labeling in PLR format, edits to the Highlights have been made in order to conform to the half-page requirement.

In addition for the Fosamax Plus D FPI, in order to provide better consistency among the labeling for the bisphosphonate class of products, the following edits were made:

- Section 14.1 Treatment of Postmenopausal Osteoporosis, Effect on Bone Mineral Density: "*Thus, overall FOSAMAX reverses the loss of bone mineral density, a central factor in the progression of osteoporosis."* This sentence has been removed as it is represents an interpretation of the data which may not be true for a given patient. It is best to present the data and allow the prescriber to interpret the results in the context of the patient being treated, from both a safety and an efficacy standpoint. This approach is being consistently applied with all bisphosphonate labels.
- Section 14.1 Treatment of Postmenopausal Osteoporosis, Effect on Bone Mineral Density: *"These data indicate that continued treatment with FOSAMAX is required to maintain the effect of the drug."* This sentence has been removed in light of the ongoing concerns regarding long-term safety and duration of use.

Similar changes have also been made to the non-plr Fosamax FPI where appropriate.

Regarding the Medication Guide:

Both the Division of Reproductive and Urologic Products and the Division of Risk Management do not agree with the proposed dual Medication Guides. The

daily and weekly Medication Guides have again been combined into one document, similar to the others in the bisphosphonate class.

Regarding Carton and Container Labeling:

Fosamax Tablets (NDA 020560/S-060)

Carton labeling — 70 mg tablets (Four count):

The Medication Guide statement lacks prominence. Revise and increase the font size of the Medication Guide statement to at least that of the information on osteoporosis presented in the same panel.

35 mg and 70 mg Card Backs:

"For the treatment of osteoporosis in postmenopausal women. Osteoporosis is a disease that causes bones to become thin, weak and easy to break. That's why it is important you take *Once Weekly* FOSAMAX to help protect your bones.

These claims are considered promotional and require fair balance presentation. The claims should be deleted or presented with adequate risk information to provide fair balance.

Container labels — 10 mg tablets (30 count):

Relocate the Medication Guide statement to the principal display panel. To provide space for the Medication Guide statement, relocate the "Each tablet contains…" statement to the side panel. If additional side panel space is needed, delete the "For important instructions for use…" statement on the side panel.

Fosamax Plus D Tablets (NDA 021762)

General Comment

We note that some of the carton/container labels state "Fosamax Plus" as the proprietary name. Please consider revising the tradename to "Fosamax Plus D," where applicable, for accuracy.

Carton labeling — 70 mg/2800 international units and 70 mg/5600 international units tablets (Four count):

The Medication Guide statement lacks prominence. Revise and increase the font size of the Medication Guide statement to at least that of the "Usage Dosage" statement.

Carton/Container Label

U.S. Complimentary Carton 1 count 5600 IU:

"For treatment of osteoporosis in postmenopausal women"

This claim is considered promotional and requires adequate fair balance presentation. We note that statement, "Side effects in studies usually have been mild and generally have not caused patients to stop taking FOSAMAX PLUS [D]. The most commonly reported side effect was abdominal (stomach) pain." However, this statement is not only inadequate in terms of a balanced risk presentation, but also minimizes the risks associated with Fosamax Plus D, by failing to include (but not limited to) hypocalcemia, severed irritation of upper gastrointestinal mucosa, and osteonecrosis of the jaw. Delete this claim or present adequate risk information in conjunction with this claim.

The U.S. Complimentary Carton 1 count 5600 IU label presents an image of a woman on the carton label. This image is misleading because Fosamax Plus is also indicated for "treatment to increase bone mass in men with osteoporosis" and may cause confusion if this carton is distributed to a male patient. In addition, this image suggests that this drug is used for a particular patient population, which is also considered promotional in nature. Consider removing this image from this container label.

Container 10 — Physician sample (1 ct) (outside):

"For the treatment of osteoporosis in postmenopausal women and to help ensure adequate vitamin D nutrition."

This claim is considered promotional and requires fair balance. We note the statement, "side effects in studies usually have been mild and generally have not caused patients to stop taking FOSAMAX PLUS [D]. The most commonly reported side effect was abdominal (stomach) pain." However, this statement is not only inadequate in terms of a balanced risk presentation, but also minimizes the risks associated with Fosamax Plus, by failing to include (but not limited to) hypocalcemia, severe irritation of upper gastrointestinal mucosa, and osteonecrosis of the jaw. Delete this claim or present adequate risk information in conjunction with this claim.

The Physician sample (1 ct) (outside) label presents an image of a woman on the container label. This image is misleading because

Fosamax Plus D is also indicated for "treatment to increase bone mass in men with osteoporosis" and may cause confusion if this sample pack is distributed to a male patient. In addition, this image suggests that this drug is used for a particular patient population, which is also considered promotional in nature. Please consider removing this image from this container label.

Fosamax Oral Solution (NDA 021575/S-020)

Carton Labeling — 70 mg bottles (Four count):

The Medication Guide statement lacks prominence. Revise and increase the font size of the Medication Guide statement to at least that of the information on osteoporosis presented in the same panel.

To provide adequate space, delete the country of origin statement from the principal display panel as it is duplicative to information added to the side panel.

"For the treatment of osteoporosis in postmenopausal women. Osteoporosis is a disease that causes bones to become thin, weak and easy to break. That's why it is important you take *Once Weekly* FOSAMAX to help protect your bones."

These claims are considered promotional and require fair balance presentation. The claims should be deleted or presented with adequate risk information to provide fair balance.

Container label

The information on the label appears crowded which makes the Medication Guide statement

difficult to find. Therefore, delete the country of origin statement from the principal display panel to allow for the increase in prominence of the Medication Guide statement.

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

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FOSAMAX®

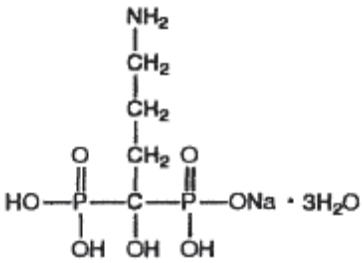
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

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

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

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_23H_20$ and its formula weight is 325.12. The structural formula is:



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

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

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 70 mg of free acid. Each bottle also contains the following inactive ingredients: raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled

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

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.65% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg table in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

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

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

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

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

Metabolism

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

Excretion

Following a single IN dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a

single 10 mg IV dose, the renal clearance of alendronate was 71 Ml/MIN (64, 78; 90% CONFIDENCE INTERVAL [CI], and systemic clearance did not exceed 200 Ml/MIN. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: The oral bioavailability in children was similar to that observed in adults; however, FOSAMAX is not indicated for use in children (see PRECAUTIONS, *Pediatric Use*).

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

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

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

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks

dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearances 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.**

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary. *Drug Interactions* (also see PRECAUTIONS, *Drug Interactions*)

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

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

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

Pharmacodynamics

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

Osteoporosis in postmenopausal women

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

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent

inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

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

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

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

Osteoporosis in men

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

Glucocorticoid-induced Osteoporosis

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

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

Paget's disease of bone

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

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical

index of disease activity, provides an objective measure of disease severity and response to therapy.

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

Clinical Studies

Treatment of osteoporosis

Postmenopausal women

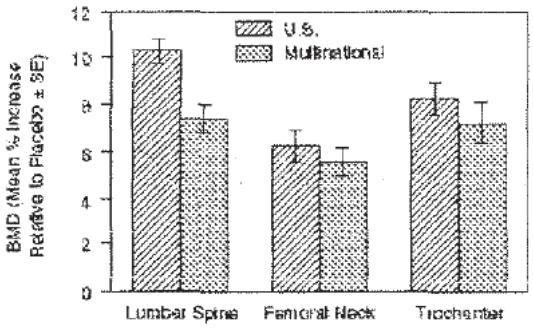
Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of a least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to

placebo-treated patients at three years for each of these studies.

Osteoporosis Treatment Studies in
Postmenopausal Women

Increase in BMD
FOSAMAX 10 mg/day at Three Years

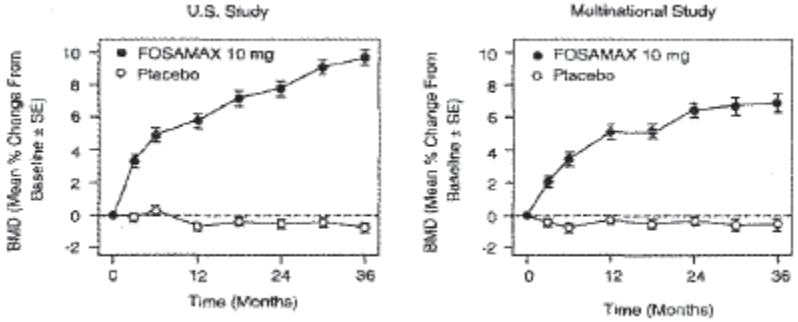


At three years significant increases in BMD, relative to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not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

body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean).

Deleted: Thus, overall FOSMAX reverses the loss of bone mineral density, a central factor in the progression of osteoporosis

Osteoporosis Treatment Studies in Postmenopausal Women
Time Course of Effect of FOSAMAX 10 mg/day Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



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

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

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the poled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients

treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 v. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

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

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

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

[see next page for table]

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

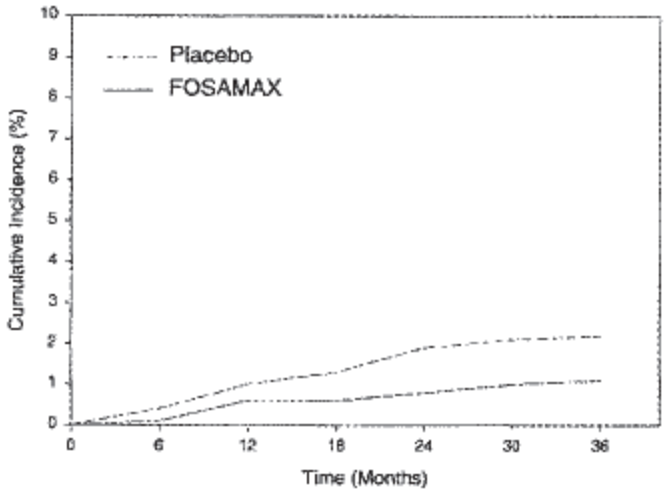
	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)[†]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical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

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

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

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

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



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

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

[see next page for table]

Effect of FOSAMAX on Fracture Incidence in Osteoporotic[†] Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

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

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

Fracture results across studies

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

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

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic

women whether or not they had a previous radiographic vertebral fracture.

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

Bone Histology

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

Men

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

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score $\leq$-2 at the femoral neck and $\leq$-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score $\leq$-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were

significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD –score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

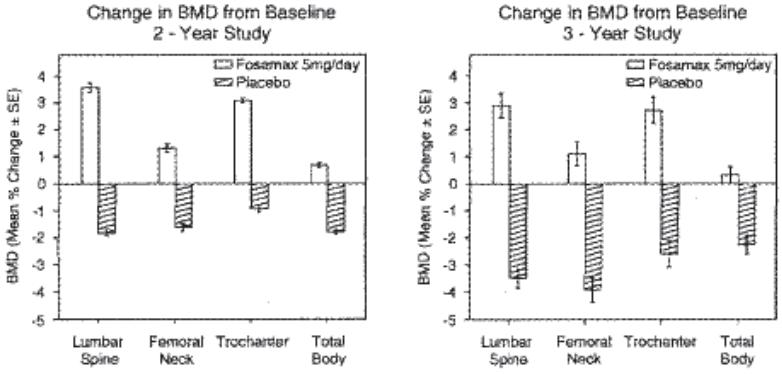
In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >2.5).

Prevention of osteoporosis in postmenopausal women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40-60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n=498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day; n=88), who

were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women



The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%;

95% CI) in the 5-mg daily group (n=298). The two treatments groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone histology

Bone histology was normal in the 28 patient biopsied at the end of three years who received FOSAMAX at doses of up to 01 mg/day.

Concomitant use with estrogen/hormone replacement therapy (HRT)

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

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

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

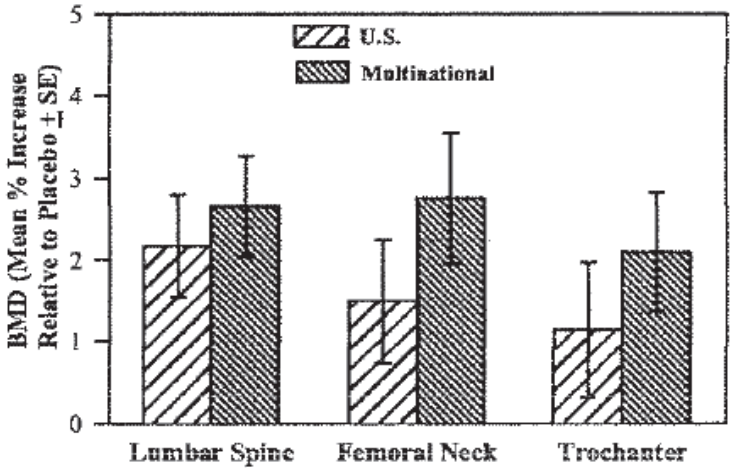
Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone.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

Glucocorticoid-induced osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.

[see graph on next page]

Studies in Gincocorticoid – Treated Patients
Increase in BMD
FOSAMAX 5 mg/day at One Year



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

gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

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

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

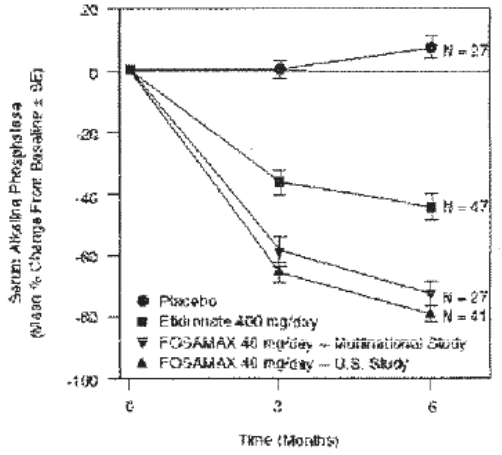
After one year, 2.3% of patients treated with FOSAMAX 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX (pooled dosage groups: 5 or 10 mg for two years or 2.5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

Paget's disease of bone

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

figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.

Studies in Paget's Disease of Bone
Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day Versus Placebo of Etidronate



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

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for

6 months. As in patients treated for osteoporosis (see *Clinical Studies, Treatment of osteoporosis in postmenopausal women, Bone histology*), FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality

ANIMAL PHARMACOLOGY

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

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the

premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients

treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

- Treatment of Paget's disease of bone in men and women

[continued on next page with edits]

- Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

The safety and effectiveness of FOSAMAX for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration for use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

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CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes (see WARNINGS)
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the

underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates including FOSAMAX and/or who fail to swallow oral bisphosphonates including FOSAMAX with the recommended full glass (6-8 oz) of water, and/or who continue to take oral bisphosphonates including FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking

bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs incudes FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrent of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including FOSAMAX. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide

the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma, fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from below the lesser trochanter to above the supracondular flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

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Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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Deleted: evaluated to rule out a stress fracture. Patients presenting with an atypical fracture should also be

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Deleted: Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocoticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

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

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

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is

taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6-8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

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

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

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

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

Nonsteroidal Anti-inflammatory Drugs (NSA/Ds)

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oralcarcinogenicity study at doses of 1 and 3. 75 mglkg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the in vitro microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo*

chromosomal aberration assay in mice. In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg!m2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths)

occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

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

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in

human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

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

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies, Osteogenesis lmperfecta*.)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%; respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention

Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

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

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

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

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and

gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 1 0 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

[see next page for table]

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

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

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 105% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in the following table.

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

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

Prevention of osteoporosis in postmenopausal women

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

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

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

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

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

Concomitant use with estrogen/hormone replacement therapy

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

Treatment of glucocorticoid-induced osteoporosis

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

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

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

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

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment

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

Osteogenesis lmperfecta

FOSAMAX is not indicated for use in children.

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

(29.4%} patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

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

Laboratory Test Findings

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

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

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

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*). *Musculoskeletal*: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*); joint swelling; low-energy femoral shaft and subtrochanteric fractures (see PRECAUTIONS, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures).*

Nervous system: dizziness and vertigo.

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

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

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

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

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, Drug Interactions). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6-8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal

adverse experiences (see WARNiNGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women notreceiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment

may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

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

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

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

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

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

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

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

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

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

NDC 0006-0031-44 unit-of-use blister package of4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 – Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

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

Storage

FOSAMAX Tablets:

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

FOSAMAX Oral Solution:

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

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[Exhibit 162 to Ecklund Declaration]

The rationales provided in blue were lifted from our previous submission. Obviously we will need to provide a stronger argument because they did not agree with our last proposal.

USPC: Warnings and Precautions

Merck proposes the following revisions to the FDA proposed labeling. We believe it is essential to inform physicians that the pain syndrome (perceived as thigh or groin pain) indicates the possibility of an incomplete fracture of the proximal femur that a physician needs to evaluate. While many physicians commonly equate the term "stress" fracture with an "incomplete" fracture, the description of a fracture as a stress fracture simply indicates that the fracture —complete or incomplete —was not due to external trauma but caused by one or more high loading episodes that produced a fracture that extended partially (i.e., incomplete) or completely through both cortices of a bone. The objective of the precaution stated in the last paragraph of this section of labeling is to identify incomplete stress fractures before they evolve into a completed femur fracture. Merck believes it is important to make it clear to physicians that there are a number of causes of stress fracture of the proximal femur that may be well known to orthopedic surgeons and metabolic bone disease experts, but not widely known by general

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physicians. Thus it is important to inform the group of physicians who prescribe bisphosphonates that the drugs are only one potential factor involved in the development a stress fracture of the femur. Thus, physician should evaluate a patient for concurrent conditions that may have caused or contributed to the stress fracture.

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Deleted: . There are a wide variety of reasons for a stress fracture.

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Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

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Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femoral stress

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fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of incomplete stress fracture in the contralateral limb. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors and receive appropriate orthopedic care. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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FOSAMAX PLUS MG

Ariene Comment: At the meeting I wrote this statement: This is contradictory to what is below? Almost never serious although you may get bone pain. Sometimes severe yes, serious no.

Merck agrees to the Medication Guide format inclusion of the serious side effects noted in Warnings and Precautions in the Physician's Information. Merck believes that it is more accurate to state "may cause serious side effects" as for example, the esophageal problems and bone, joint or muscle pain are common, but severe cases are rare.

FOSAMAX PLUS D may cause serious side effects including:

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1. Esophagus problems
2. Low calcium levels in your blood
3. Bone, joint, or muscle pain

4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

* * *

Merck proposes the following revisions to the FDA proposed labeling. Merck has added information to explain that patients with current hypocalcemia should not take FOSAMAX PLUS D.

1. Low calcium levels in your blood (hypocalcemia)

FOSAMAX PLUS D may lower the calcium levels in your blood. If you have low blood calcium should not take Fosamax Plus D FOSAMAX PLUS D. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take FOSAMAX PLUS D. Take calcium and vitamin D as your doctor tells you to.

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Deleted: , it may get worse during treatment
Deleted: your low blood calcium must be treated before you take FOSAMAX PLUS D
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Merck proposes the following revisions to the FDA proposed labeling. Merck believes it is important for a patient to tell their doctor about all their dental problems. It is an effective way for patients to provide a complete dental history to their physician, it is critical for physicians to recognize dental problems such as periodontal disease and other risk factors for osteonecrosis. Patients need information regarding the nature of jawbone problems, to give the patient some idea of what adverse experience we are referring to.

4. Severe jaw bone problems (osteonecrosis).

Tell your doctor about all of your dental conditions. FOSAMAX PLUS D may cause jawbone problems in some people. Jawbone problems may include infection, and delayed healing after teeth are pulled. Severe jaw bone problems may happen when you take FOSAMAX PLUS D. Your doctor should examine your mouth before you start FOSAMAX PLUS D. Your doctor may tell you to see your dentist before you start FOSAMAX PLUS D. It is important for you to practice good mouth care during treatment with FOSAMAX PLUS D.

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Merck proposes to retain the sentence stating "FOSAMAX PLUS D is not for use in premenopausal women." It is inappropriate to give FOSAMAX PLUS D to premenopausal women.

FOSAMAX PLUS D is not for use in premenopausal women.

Merck proposes to retain some of the overdose labeling Local toxicity is anticipated, not systemic toxicity from high oral doses of the drug. Also, it is important for the patient to know not to vomit or lie down as both situations would increase the potential for esophageal toxicity. Vomiting specifically would increase the risk of aspiration pneumonia. You want to prevent the occurrence of reflux.

> If you take too much FOSAMAX PLUS D, call your doctor or go to the nearest hospital emergency room right away. Do not try to vomit. Do not lie down.

Merck proposes to retain the other important potential side effects as shown below.

* * *

[Exhibit 167 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION	**MDL No. 2243** Civil Action No. 08-08(GEB)
THIS DOCUMENT RELATES TO: **DENMAN JONES,** **Plaintiff,** **v.** **MERCK SHARP & DOHME CORP. f/k/a MERCK & CO., INC.,** **Defendant.**	**Civil Action No.:** **COMPLAINT AND JURY DEMAND**

Plaintiff, DENMAN JONES ("Plaintiff"), by and through his attorneys, WEITZ & LUXENBERG, P.C., for Plaintiff's Complaint against Defendant, MERCK SHARP & DOHME CORP. f/k/a MERCK & CO., INC. ("Merck" or "Defendant"), alleges as follows:

NATURE OF THE CASE

1. This is a civil action for personal injury suffered by Plaintiff, DENMAN JONES against the Defendant, MERCK SHARP & DOHME CORP. f/k/a MERCK & CO., INC., who was responsible for the design, manufacture and sale of the prescription drug, Fosamax, a bone loss preventative medication which was a substantial contributing factor in causing Plaintiff's femur fracture.

* * *

Defendant's Failure to Warn of the Dangers of Fosamax

41. Despite its knowledge of these dangerous side-effects that can result from long-term Fosamax/alendronate use, Defendant refuses to warn patients, physicians and the medical community about the risk of severely suppressed bone turnover. Defendant continues to defend Fosamax, mislead physicians and the public, and minimize unfavorable findings.

42. Defendant knew of the significant risk of severely suppressed bone turnover, brittle bones, and multiple stress fractures that could result from long-term Fosamax use, but did not adequately and sufficiently warn consumers, including Plaintiff, Plaintiff's physician or the medical community of such risks.

43. Defendant, particularly with its heightened knowledge and experience, knew or should have known that long-term use of bisphosphonates, including Fosamax, could inhibit the production of new bone cells (osteoblasts) and therefore, would prevent repair of naturally occurring micro-fractures in the femur which could lead to serious femur fractures, and/or that prolonged suppression of bone remodeling with Fosamax could lead to serious femur fractures, and the femur fractures caused by long-term Fosamax use could occur despite the apparent absence of sufficient trauma.

44. Prior to Plaintiff's suffering from a fracture of his right femur, Defendant received adverse reaction reports regarding numerous Fosamax users throughout the country that these patients were

experiencing bone brittleness, susceptibility to fractures, femoral stress fractures and/or femoral shaft fractures after the long-term use of Fosamax.

45. Defendant has disregarded and has refused to follow-up on the reports of patients, who after using Fosamax, have experienced and reported bone brittleness, susceptibility to fractures, femoral stress fractures and/or femoral shaft fractures.

46. Defendant has failed to submit these reported adverse consequences to the FDA and have failed to advise physicians and the public.

47. Defendant failed to change any of its prescribing information, package inserts or drug manuals supplied to the medical and pharmaceutical professions and the general public in order to warn of the potential for femur fractures after long-term Fosamax use, until finally ordered to do so by the FDA on October 13, 2010.

48. Consumers, including Plaintiff, who have used Fosamax had several alternative safer products available to treat their condition.

49. Adverse Event data maintained by the FDA indicate serious Adverse Events reported in connection to Fosamax, including, femur fractures, severe esophageal adverse reactions requiring hospitalization, musculoskeletal pain, osteonecrosis of the jaw and renal insufficiency.

50. At all relevant times Defendant was responsible for or involved in designing, manufacturing, marketing, advertising, distributing and selling Fosamax.

51. Defendant has marketed their alendronate drugs as effective for the treatment and prevention of osteoporosis in post-menopausal women, to increase bone mass in men with osteoporosis, for the treatment of glucocorticoid induced osteoporosis in men and women and for the treatment of Paget's disease, and that it lacks certain side-effects of other bone loss treatments.

52. Defendant has been warned at least five times by the FDA; three times in 1997, once in 1999, and once in 2001, for misleading the public through use of brochures, Journal Ads, slide presentations, web sites and television advertisements which made false and misleading statements, and overstated the benefits and efficacy of Fosamax, while minimizing the serious risks associated with the drug.

53. Defendant ignored the correlation between the use of Fosamax and the increased risk of developing brittle bones, multiple stress fractures and femur fractures, despite the scientific and medical evidence available.

54. Defendant did not provide adequate warnings to doctors, the health care community and the general public about the increased risk of serious adverse events that are described herein and that have been reported by the medical community.

55. Defendant knowingly withheld or misrepresented information required to be submitted under the FDA's regulations, which information was material and relevant to the harm in question.

56. Defendant expressly warranted that Fosamax was safe and fit for use by consumers, that they were of merchantable quality, that they did not produce

dangerous side-effects, and that they were adequately tested and fit for their intended use, even though they are not safe and have numerous serious side-effects, many of which Defendant did not accurately warn about.

Plaintiff's Use of Fosamax

57. Plaintiff, Denman Jones is a citizen of the United States of America, and is a resident of the City of Grand Junction, in Mesa County in the State of Colorado.

58. Plaintiff, Denman Jones was born on May 6, 1960.

59. Upon information and belief, Plaintiff, Denman Jones was prescribed and began taking Fosamax as prescribed by Plaintiff's physicians, beginning in approximately 2005, and used it until approximately 2008. Fosamax was provided to Plaintiff in a condition that was substantially the same as the condition in which it was manufactured and sold.

60. Plaintiff, Denman Jones used Fosamax as prescribed and in a foreseeable manner.

61. Upon information and belief, on or about November 21, 2008, Plaintiff, Denman Jones suffered a fracture of his right femur.

62. Upon information and belief, as a result of using Defendant's Fosamax, Plaintiff, Denman Jones suffered from a fracture of his right femur, diagnosed on or about November 21, 2008.

63. Upon information and belief, on or about November 21, 2008, Plaintiff, Denman Jones underwent surgery for his right femur fracture at St.

Mary's Hospital & Regional Medical Center in Grand Junction, Colorado.

64. Plaintiff's femur fracture was due to the harmful long-term effects of Fosamax use, a consequence that was never made known to Plaintiff or Plaintiff's physicians by Defendant.

65. Defendant knew or should have known and failed to warn that long-term use of Fosamax was unsafe because it could cause femur fractures of the type that Plaintiff suffered.

66. Plaintiff would not have used Fosamax for so many years had Defendant properly disclosed the risks associated with its long-term use.

67. Defendant knew or should have known, at all times material hereto, that Fosamax was in a defective condition, and was and is inherently dangerous and unsafe when used in the manner instructed and provided by Defendant.

68. As a result of Defendant's actions, Plaintiff and Plaintiff's prescribing physicians were unaware and could not have reasonably known or have learned through reasonable diligence that Plaintiff had been exposed to the risks identified in this complaint, and that those risks were the direct and proximate result of Defendant's acts, omissions and misrepresentations.

69. As a result of taking Fosamax, Plaintiff, Denman Jones suffered compensable injuries, including but not limited to the following:

(a) severe and permanent physical and medical injuries and associated disabilities;

(b) severe past and future pain and suffering;

(c) severe past and future mental anguish;

(d) loss of enjoyment of life

(e) increased risk of health problems;

(f) past and future medical care and monitoring; and

(g) loss of past and future income.

FIRST CLAIM FOR RELIEF:
FAILURE TO WARN
New Jersey Product Liability Act
(N.J.S.A. 2A:58C-1, *et seq.*); and
In the Event
Colorado Failure to Warn Law
is to be Applied

70. Plaintiff realleges and incorporates by reference all other paragraphs of this Complaint as if each were set forth fully and completely herein.

71. Defendant researched, tested, developed, designed, licensed, manufactured, packaged, inspected, labeled, distributed, sold, marketed, promoted and/or introduced Fosamax into the stream of commerce and in the course of same, directly advertised or marketed Fosamax to consumers or persons responsible for consumers, and therefore, had a duty to warn Plaintiff and Plaintiff's physicians of the risk associated with the use of Fosamax, which they know or have reason to know and are inherent in the use of pharmaceutical products.

72. Defendant had a duty to warn of adverse drug reactions, which they know or have reason to know can be caused by the use of Fosamax and/or are associated with the use of Fosamax, including its propensity to cause and/or contribute to femur fractures.

73. Fosamax was under the exclusive control of Defendant and was not accompanied by appropriate warnings regarding all possible adverse side-effects and complications associated with the use of Fosamax, nor with adequate warnings regarding the risk of severely suppressed bone turnover, resulting stress fractures, femur fractures and other severe and permanent injuries associated with its use. The warnings given did not accurately reflect the risk, incidence, symptoms, scope or severity of such injuries to the consumer as compared with other older bone loss treatment medications, which possessed a lower risk of adverse events regarding the comparative severity, duration and extent of the risk of injuries with such use of Fosamax.

74. Defendant downplayed the serious and dangerous side-effects of Fosamax to encourage sales of the product. Consequently, Defendant placed their profits above its customers' safety.

75. Defendant failed to timely and reasonably warn Plaintiff and Plaintiff's prescribing physicians of material facts regarding the comparative safety and efficacy of Fosamax. Fosamax would not likely have been prescribed or used had those facts been made known to such providers and consumers, including Plaintiff.

76. Due to the inadequate warning regarding femur fractures, Fosamax was in a defective condition and unreasonably dangerous at the time that it left the control of the Defendant.

77. Defendant's warnings were overwhelmed, downplayed and otherwise suppressed by Defendant's advertisement campaign, which did not demonstrate

that Fosamax presented multiple and dangerous medical risks, including the risk of suppressed bone turnover resulting in stress fractures and femur fractures.

78. Defendant failed to perform or otherwise facilitate adequate testing. Such testing would have shown that Fosamax posed serious and potential life threatening side-effects and complications with respect to which full and proper warning accurately and fully reflecting the symptoms, scope and severity should have been made to medical care providers, the FDA, and the public, including Plaintiff.

79. Defendant, as a manufacturer of pharmaceutical drugs, is held to the level of knowledge of an expert in the field. Further, Defendant had knowledge of the dangerous risks and side-effects of Fosamax.

80. Plaintiff did not have the same knowledge as Defendant and no adequate warning was communicated to Plaintiff's physicians.

81. Had Plaintiff been adequately warned of the potential serious adverse effects of the Defendant's Fosamax, Plaintiff would not have purchased or taken Fosamax and could have chosen to request other treatments or prescription medications.

82. Upon information and belief, had Plaintiff's prescribing physicians been adequately warned of the potential adverse effects of the Defendant's Fosamax, Plaintiff's prescribing physicians would have discussed risks of femur fractures with Plaintiff and/or would not have prescribed Fosamax

83. Defendant had a continuing duty to warn consumers, including Plaintiff, Plaintiff's physicians

and the medical community of the dangers associated with Fosamax. By negligently and/or wantonly failing to adequately warn of the dangers associated with its use, Defendant breached their duty.

84. As a foreseeable, direct, and proximate result of the aforementioned wrongful acts and omissions of Defendant, Plaintiff was caused to suffer from a fracture of his right femur and endured surgery to repair said fracture, as well as other severe and personal injuries which are permanent and lasting in nature, physical pain, mental anguish and diminished enjoyment of life. Plaintiff has endured and continues to suffer the mental anguish and psychological trauma of living with the knowledge that Plaintiff has suffered these serious and dangerous side-effects.

WHEREFORE, Plaintiff demands judgment against the Defendant individually, jointly and/or severally and demands compensatory, statutory and punitive damages available under applicable law, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems just and proper.

* * *

[Exhibit 174 to Ecklund Declaration]

To:	Daifotis, Anastasia G. <anastasia_daifotis@merck.com>
From:	Santora, Arthur C. </O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=SANTORAA>
Cc:	
Bcc:	
Received Date:	2003-03-04 13:56:47
Subject:	FW: My Concerns

Anastasia,

I am happy to do this type of interaction with the thought leaders when they don't have their facts straight (probably been to one to many Lilly hired gun presentations) as I think they are critical to the success of FOSAMAX in Phase V. I think all the MDs in the Bone Group (AKA, CR. Endocrine) share this belief. However, I don't think that this approach is shared in all therapeutic areas. Perhaps that is why FOSAMAX does better than management expects and some other products that don't have full MRL MD support for this type of activity (for one reason or another) don't live up to their potential.

I think that Barry knows "in his heart" how important this type of activity is. But, he also knows that his management hasn't given him the funds to support staff to deal with Phase V issues and that his performance will be rated on the speed and quality of Phase I-III development. You have seen his 2003

objectives -- is there a Clinical Research Phase V support objective on it?

That said, do you think a polite memo to Barry and/or Peter Kim might 1) help get them thinking more about the importance of Clinical Research to a product's Phase V life; 2) not be at all useful ; or 3) get me fired or at least "in trouble"? Given that the memo that I wrote to Ed Scolnick several years ago pointing out that he had given out Divisional Awards to number of other Merck staff for things (FOSAMAX developmental activities) that I had actually done didn't get me fired, I doubt a respectful memo would do so now.

What do you think?

Art

-----Original Message----

From: Nebel, Mark W

Sent: Tuesday, March 04, 2003 6:29 AM

To: Yates, John; Santora, Arthur C.

Cc: Daifotis, Anastasia G.; Orloff, John J; Harris, Michael M. HSA; Neal, Greg J.

Subject: RE: My Concerns

Thank you for the support.

I have asked Mike Harris (HSA) to help coordinate a conference call.

Mark

-----Original Message----

From: Yates, John

Sent: Monday, March 03, 2003 8:39 PM

To: Santora, Arthur C.

Cc: Daifotis, Anastasia G.; Nebel, Mark W; Orloff, John J

Subject: RE: My Concerns

Thanks Art. I know you will be able to convince Gratton with reason. John

-----Original Message----

From: Santora, Arthur C.

Sent: Monday, March 03, 2003 12:22 PM

To: Yates, John

Cc: Daifotis, Anastasia G.; Nebel, Mark W; Orloff, John J

Subject: RE: My Concerns

John,

Anastasia and I will discuss and one of us will discuss this with Dr. Woodson. He has some basic misconceptions about dead bone, pharmacokinetics of bisphosphonates and the like. Why would he think that bone containing alendronate cannot undergo resorption?

Interesting that he is not concerned about raloxifene's (unknown) cardiovascular safety profile. As raloxifene has the same risk of thrombosis and PE as does estrogen, I am going to have to see a lot of safety data to convince me that it would not have the same effect as HRT did in HERS and the WHI.

Art

-----Original Message----

From: Yates, John

Sent: Monday, March 03, 2003 11:26 AM

To: Daifotis, Anastasia G.; Santora, Arthur C.; Nebel, Mark W

Subject: FW: My Concerns

Art and Anastasia

Grattan Woodson copied me on this. I think we should address his concerns directly. The rat medullary remodelling model provides proof that old bone impregnated with ALN can be resorbed. The dog fracture studies also help. Would one of you be willing to follow up?

Thanks

John

-----Original Message-----

From: Grattan Woodson
[mailto:gwoodson@mindspring.com]

Sent: Monday, March 03, 2003 12:07 AM

To: Nebel, Mark W

Cc: Harris, Michael M. (HSA); Kotzin, Robin; John_ Yates@merck.com

Subject: My Concerns

Hi Mark,

Yes, I am fine. No health or personal problems or anything. I do owe you an explanation though for my decision for suspending my speaking programs for Fosamax.

For a couple of years I have been looking into the bisphosphonate half-life issue. I have found that there is very little data on this area. What is known is that small bisphosphonates like alendronate are retained during bone formation, virtually life-long, in the skeleton in an unaltered state. The 10 year half-life figure in the PI is, in my opinion, an unwarranted estimate that depends on the ability of the bone containing the alendronate being susceptible to osteoclastic resorption. That human bone doped with alendronate can undergo osteoclastic bone resorption is as far as I can tell an unproven assumption. If retained alendronate prevents resorption, old dead bone would be expected to accumulate and become hyper-mineralized and fracture prone. Mircofractures developing in scattered islands of dead bone would

weaken the bone ultimately resulting in clinical fractures.

Under this scenario the fractures would be an iatrogenic complication of therapy. I have been looking for any signs that this scenario developing in my patients since I have been prescribing small bisphosphonates to patients since 1984. Last year, I had two patients who had been on Didronel for several years before beginning alendronate in 1995 suffered vertebral fractures. These are the first such patients I have cared for in years and came as a surprise to me. Of course I realize that fractures are common event in osteoporosis patients even treated ones. While I can not be sure whether of not these patient's fractures were related to my theoretical concern or not, this development has weighed heavily on me for several months. I have also been concerned by the upturn in fractures in the patient treated continuously for 10 years now with alendronate.* My attempts to learn more about the fracture rates in these patients have not proved fruitful. Until I can be convinced of the long-term safety of alendronate, I have decided that it would not be ethical for me to speak on behalf of Fosamax. Certainly this decision will also effect my clinical management of patients however I have not yet thought this through thoroughly.

I have no intention of discussing these speculations with others or spreading unfounded notions about Fosamax. Furthermore, I have no plans to speak for P&GP or Aventis nor will I discuss this communication to them or anyone else. I do plan to continue to speak for Lilly but do not plan to discuss my concerns about small bisphosphonates with them either. My long experience working with MRL and the

sales side of Merck has left no doubt in my mind about your commitment to patient safety and science. I suspect that MRL has been aware of this potential adverse drug side effect of small bisphosphonates and has already given these concerns careful thought. Hopefully then, this concern can be cleared up quickly.

Best regards,

Grattan Woodson, MD

* Lieberman (NEJM 1995), Favus (ASBMR 1997), Tonino (JCE 2000)

----- Original Message -----

From: Nebel, Mark W

To: Grattan Woodson

Sent: Sunday, March 02, 2003 9:27 PM

Subject: RE: 4-10-03, 4-23-03 & 6-6-03 Cancellations

Dr. Woodson,

Is everything ok?

Mark Nebel

Cell 678 427-6312

-----Original Message-----

From: Grattan Woodson
[mailto:gwoodson@mindspring.com]

Sent: Sunday, March 02, 2003 10:18 AM

To: Fortier, Melissa A

Cc: Kotzin, Robin; Nebel, Mark; Harris, Michael M. (HSA)

Subject: 4-10-03, 4-23-03 & 6-6-03 Cancellations

Dear Melissa,

With regret, I have decided to cancel these three Merck programs that were previously scheduled and do not plan to accept any new Merck speaking programs at this time. I am very sorry for the inconvenience these cancellations may cause you and the sales team at Merck who were depending on me to speak for the. Please forgive me and pass on my apologies. I have been a very happy and satisfying experience working with the Fosamax Sales and Scientific Team in the past and hope that my decision to suspend speaking for Merck at this time will not interfere too greatly with my relationship with Merck in the future. My door, ears, and eyes will always be open to my friends and colleagues at Merck.

GW

4-10-03: MESA#1622280 Atlanta

4-23-03 MESA#1618760, Decatur

6-6-03: MESA#1620228 Gainesville, GA

Grattan Woodson, MD, FACP

Osteoporosis Center of Atlanta and
The Atlanta Research Center
2801 North Decatur Road
Suite 375
Decatur, GA 30033
Phone: 404-298-9951
Fax: 404-298-5577

[Exhibit 12 to Confoy Declaration]

James Adams
Associate Director
Worldwide Regulatory
Affiars

Merck & Co., Inc.
P.O. Box 2000, RY 33-200
Rahway NJ 07065-0900
Tel: 732 594 2552
Fax: 732 594 5235
james_adams@merck.com

July 2, 2009

Scott Monroe, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901 -B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Monroe:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

WITHDRAWAL LETTER

Reference is made to the New Drug Application (NDA) cited above for FOSAMAX™ Tablets, submitted by Merck Research Laboratories (MRL), a division of Merck & Co., Inc. Reference is also made to a 22-May-2009 letter received from FDA regarding NDA 20-560/S-054, NDA 21-575/S-015, and NDA 21-

762/S-008 (originally submitted as prior approval supplements changes to the Precaution section of the Product Circular (PC). Further reference is made to a recent 15-Jun-2009 telephone conversation between Mr. Karl Stiller, FDA, and Mr. James Adams, MRL, in which it was confirmed that the quickest route to update the PC with the text recommended in FDA's 22-May-2009 letter was to (1) withdraw the prior approval supplement submitted on 15-Sep-2008, and (2) submit a Changes Being Effected (CBE) Submission.

With this letter, MRL is withdrawing the supplemental application for NDA 20-560/S-054, NDA 21-575/S-015, and NDA 21-762/S-008. Similar letters are being submitted simultaneously with regard to each of the three NDAs to withdraw their corresponding supplements. A CBE has been submitted that updates the FOSAMAX label with the language in the ADVERSE REACTIONS, Post-Marketing Experience as recommended in the Division's 22-May-09 letter. Merck will also be submitting a request for a Type C meeting to discuss with the Division language to describe low-energy fractures of the proximal femur for inclusion in the Precaution section of the FOSAMAX label.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document — Annex — Granularity Document, and the*

International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification. This submission is being transmitted through the FDA's electronic submission gateway.

A list of reviewers who should be provided access to this electronic submission on their desktops may be obtained from Karl Stiller, Senior Regulatory Project Manager, Division of Reproductive and Urologic Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely,

/s/ James Adams
James Adams
Associate Director
Worldwide Regulatory Affairs

James Adams
Associate Director
Worldwide Regulatory
Affiars

Merck & Co., Inc.
P.O. Box 2000, RY 33-200
Rahway NJ 07065-0900
Tel: 732 594 2552
Fax: 732 594 5235
james_adams@merck.com

July 2, 2009

Scott Monroe, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901 -B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Monroe:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

SUPPLEMENT – CHANGES BEING EFFECTED

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 506A(d)(3)(B)(*ii*) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, a supplement to NDA 20-560.

Reference is made to the New Drug Application (NDA) cited above for FOSAMAX™ Tablets, submitted by Merck Research Laboratories (MRL), a

division of Merck & Co., Inc. Reference is also made to a 22-May-2009 letter received from FDA regarding NDA 20-560/S-054, NDA 21-575/S-015, and NDA 21-762/S-008 (originally submitted on 15-Sep-2008), in which the Agency indicated that it did not approve the proposed changes in the Precaution section of the Product Circular (PC). Further reference is made to a recent 15-Jun-2009 telephone conversation between Mr. Karl Stiller, FDA, and Mr. James Adams, MRL, in which it was confirmed that the quickest route to update the PC with the text recommended in the 22-May-2009 letter was to withdraw the prior approval supplement submitted on 15-Sep-2008, followed by a Changes Being Effected Submission. Final reference is made to the withdrawal letter dated 02-Jul-2009.

Merck believes that further discussion in regard to text for the Precaution section of the label concerning low-energy femoral shaft and subtrochanteric fractures would be beneficial. A Type C meeting request will be submitted in order to discuss this issue in more detail.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling Section(s) of the approved New Drug Application for FOSAMAX™.

As per FDA Guidance to Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling*, the proposed labeling is provided in SPL format. Content of labeling [(201.100(d)(3))] has been included in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html. We understand that this version will be transmitted to the

National Library of Medicine for posting on the DailyMed website.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within Section 1.14.1.3 Draft labeling text.

The composed USPC [and USPPI] Final Printed Labeling will be submitted on approximately 30-Jul-2009.

The revised labeling will be used on or before 01-Mar-2010 in all packages sold or distributed from the Company's manufacturing facilities.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document — Annex — Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. This submission is being transmitted through the FDA's electronic submission gateway.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Amendments of 2002 (PDUFA III), as indicated in the attached Form 3397, no user fee is required for this supplemental application.

A list of reviewers who should be provided access to this electronic submission on their desktops may be

obtained from Karl Stiller, Senior Regulatory Project Manager, Division of Reproductive and Urologic Products.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely,

/s/ James Adams
James Adams
Associate Director
Worldwide Regulatory Affairs

[Exhibit 50 to Confoy Declaration]

Atypical Fractures of the Femoral Diaphysis in Postmenopausal Women Taking Alendronate

TO THE EDITOR: The long-term safety of bisphosphonates for the treatment of osteoporosis has been questioned. Two case series have suggested a link between prolonged bisphosphonate therapy and atypical fractures. In one series, a small number of patients sustained low-energy nonvertebral fractures while receiving long-term alendronate therapy; three were fractures of the femoral shaft.[1] Bone biopsies in these patients showed evidence of severely suppressed bone turnover and fracture healing that was delayed or absent. In the other series, low-energy subtrochanteric fractures were found in nine women who had been receiving long-term alendronate therapy.[2] Theoretically, bisphosphonates suppress bone turnover and thus might be associated with accumulated microdamage in bone. To our knowledge, no study has demonstrated microdamage accumulation in patients treated with bisphosphonates, and data from studies in animals remain difficult to interpret because supranormal doses of bisphosphonates are used. Nevertheless, the possibility that bisphosphonates alter bone strength with prolonged use appears to exist.

We identified 15 postmenopausal women who had been receiving alendronate for a mean (±SD) of 5.4±2.7 years and who presented with atypical low-energy fractures, defined as fractures occurring in a fall from a standing height or less. All patients sustained

subtrochanteric or proximal diaphyseal fractures. Bisphosphonate use was observed in 37% of all patients presenting with low-energy subtrochanteric or diaphyseal fractures. Fractures of the subtrochanteric or diaphyseal regions are relatively rare in postmenopausal women, representing 6% of all osteoporotic hip fractures in our patient population (unpublished data).

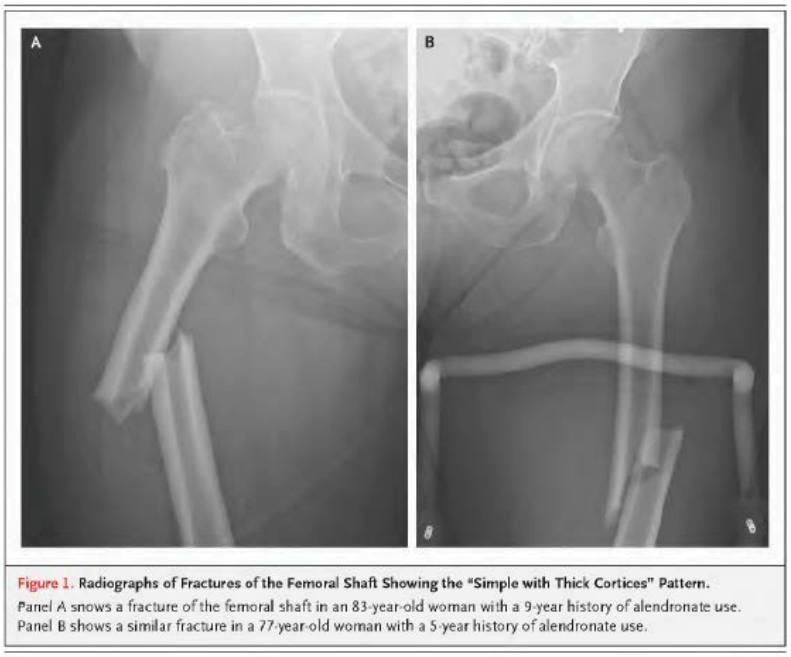

Figure 1. **Radiographs of Fractures of the Femoral Shaft Showing the "Simple with Thick Cortices" Pattern.**
Panel A shows a fracture of the femoral shaft in an 83-year-old woman with a 9-year history of alendronate use. Panel B shows a similar fracture in a 77-year-old woman with a 5-year history of alendronate use.

Ten of the 15 patients were found to share a unique radiographic pattern, defined as a simple transverse or oblique (≤30°) fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft. We call this pattern "simple with thick cortices" (Fig. 1). These patients had an average duration of alendronate use of 7.3±1.8 years, which was significantly longer than the duration of 2.8±1.3 years for the five patients without this pattern ($P<0.001$).

Cortical thickening was present in the contralateral femur in all the patients with this pattern. Three of the 15 patients had a history of femoral fractures, all in the contralateral femur, whereas no patients had a history of vertebral fractures. Vitamin D and parathyroid hormone measurements and bone densitometry were not performed during fracture care; therefore, we cannot determine the status of the patients with respect to metabolic bone disease.

Our results provide further evidence of a potential link between alendronate use and low-energy fractures of the femur. In light of the limitations of our study, a prospective study is indicated. Although many possible explanations exist, patients with the unique radiographic pattern shown here may represent a subgroup of the population that is more susceptible to the effects of prolonged suppression of bone turnover. Additional studies are needed to characterize this subgroup and to establish a clear association between atypical fractures of the femur and prolonged bisphosphonate treatment.

Brett A. Lenart, B.S.
Dean G. Lorich, M.D.
Joseph M. Lane, M.D.
Weill Cornell Medical College
New York, NY 10021
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Supported by the Cohn Foundation.

Dr. Lane reports receiving speaking fees from Aventis, GlaxoSmithKline, Eli Lilly, Merck, Novartis, Procter & Gamble, and Roche. No other potential conflict of interest relevant to this letter was reported.

[Exhibit 53 to Confoy Declaration]

To:	Adams, James H (WAG) <james_adams@merck.com>
From:	Marchick, Julie <Julie.Marchick@fda.hhs.gov>
Cc:	
Bcc:	
Received Date:	2008-06-24 18:09:41
Subject:	RE: Fosamax Information Request - Atypical Fractures

Hi Jim,

All case reports of hip and femur fractures should be submitted. We also ask that you further define the fracture site location, if possible. It would be helpful if you classify the fractures based on the location, as follows:

For hip fracture:
intracapsular (neck and head of femur, inside the capsule)
intertrochanteric
subtrochanteric

For femur fracture:
proximal femur (likely will fall into one of the above hip fracture categories)
femoral shaft
supracondylar

We ask that you submit all case reports, from clinical trials and from postmarketing experience.

Thanks,

Julie

———

From: Adams, James H (WAG)
[mailto:james_adams@merck.com]

Sent: Monday, June 16, 2008 2:36 PM

To: Marchick, Julie

Subject: RE: Fosamax Information Request - Atypical Fractures

Hi Julie,

Could you please clarify that the request includes hip fractures (i.e., hip neck and intertrochanteric) as well as other femoral fractures (sub-trochanteric and fractures lower in the femur) since the references are specific to femoral shaft and subtrochanteric fractures. Thank you.

Best regards,

Jim

———

From: Marchick, Julie
[mailto:Julie.Marchick@fda.hhs.gov]

Sent: Friday, June 13, 2008 12:24 PM

To: Adams, James H (WAG)

Subject: Fosamax Information Request - Atypical Fractures

Jim,

We are aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates (1–5). The subtrochanteric type of hip or femoral fracture is reportedly rare in patients with osteoporosis not on bisphosphonates. We are concerned about this developing safety signal. Please submit any investigations that you have conducted regarding the occurrence of atypical fractures with bisphosphonate use as well as any investigational plans. Please submit all hip and femoral fracture case reports you have received. Where possible, efforts should be made to clarify the fracture location and the duration of bisphosphonate exposure for all case reports.

We request a written response by Friday, July 11, 2008.

Please contact me if you have any questions.

Thanks,

Julie

Julie Marchick
Regulatory Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

References:

1) Neviaser AS, et. al. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma. 2008; 22:346–350.

2) Goh SK, et. al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: A caution. J Bone Joint Surg Br. 2007; 89:349–353.

3) Odvina CV, et. al. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005; 90: 1294–1301.

4) Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density: Multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. J Endocrinol Invest 2007; 30:590–597.

5) Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab. 2008 epublished ahead of print 6/3/2008.

[Exhibit 59 to Confoy Declaration]

James Adams
Associate Director
Worldwide
Regulatory Affairs

Merck & Co., Inc.
P. O. Box 2000, RY 33-200
Rahway NJ 07085-0900
Tel: 732 594 2552
Fax: 732 594 5235
james_adams@merck.com

September 15, 2008

Mary Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research Division of
Metabolism and Endocrinology Products
590 J -B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 20-560: FOSAMAX™ Tablets
(Alendronate Sodium)

Prior Approval Supplement

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, a supplement to NDA 20-560.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the

Labeling Section of the approved New Drug Application for FOSAMAX.

Merck is proposing to add language to both the Precaution and Adverse Reaction/ Post-Marketing Experience section of the label to describe low-energy fractures that have been reported, of which some have been stress/ insufficiency, at the subtrochanteric region of the femoral shaft. While these fractures arc less common than other osteoporotic low-energy fractures, they occur in a similar population of elderly individuals and have been reported prior to the availability of bisphosphonates. It is not possible with the present data to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures. Nevertheless, considering the clinical importance of these fractures in patients with osteoporosis and their temporal association with bisphosphonate use, the Company believes that it is important to include an appropriate statement about them in the product label. This may further increase physicians' awareness of possible fractures in some osteoporotic patients at risk and allow early intervention, thereby possibly preventing the progression to complete fracture and/or other complications.

As per FDA Guidance to Industry: *Providing Regulatory Submissions in Electronic – Format Content of Labeling*, the proposed labeling is provided in SPL format. Content of labeling [(201.100(d)(3)] has been included in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED DOC within Section 1.14.13 Draft labeling text.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy. Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Amendments of 2002 (PDUFA III), as indicated in the attached Form 3397, no user fee is required for this supplemental application.

We consider the filing of this supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to James Adams, (732-594-2552) or, in his absence, to Charlotte B. Merritt (732-594-4060).

Sincerely,

/s/ James Adams
James Adams
Associate Director
Worldwide Regulatory
Affairs

CURRENT CIRCULAR SHOWING REVISIONS

MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

FOSAMAX®

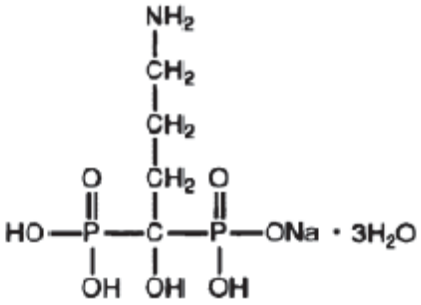
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

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

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

The empirical formula of alendronate sodium is $C_4H_{12}NNO_7P_2 \bullet 3H_2O$ and its formula weight is 325.12. The structural formula is:



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* * Registered trademark of MERCK & CO., Inc.

COMMENTS/SUPPORT

KEY TO ANNOTATIONS

Sec. 2.5 = Clinical Overview

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

Tablets FOSAMAX for oral administration contain 6. 53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption.

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

Pharmacokinetics

Absorption

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

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

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49

postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

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

Distribution

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

Metabolism

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

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a

single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min, Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: The oral bioavailability in children was similar to that observed in adults; however, FOSAMAX is not indicated for use in children (see PRECAUTIONS, Pediatric Use).

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

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

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

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is

available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.**

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

Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

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

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

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

Pharmacodynamics

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

Osteoporosis in postmenopausal women

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

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent

inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

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

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

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

Osteoporosis in men

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

Glucocorticoid-induced Osteoporosis

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

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

Paget's disease of bone

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

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical

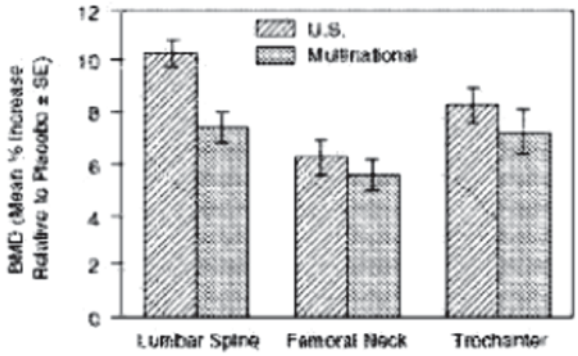
index of disease activity, provides an objective measure of disease severity and response to therapy.

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

Clinical Studies
Treatment of osteoporosis
Postmenopausal women
Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.

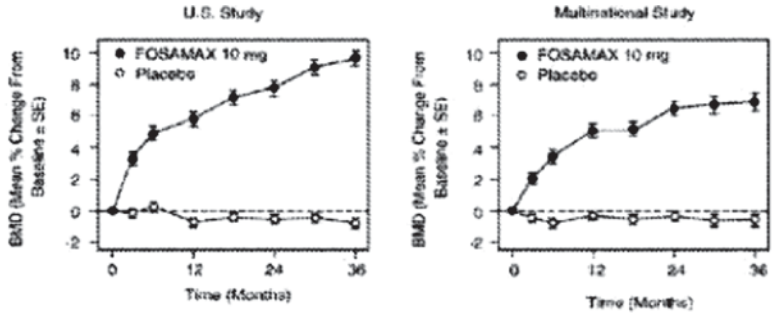
Osteoporosis Treatment Studies in
Postmenopausal Women
Increase in BMD
FOSAMAX 10 mg/day at Three Years



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

standard deviations below the premenopausal mean). Thus, overall FOSAMAX reverses the loss of bone mineral density, a central factor in the progression of osteoporosis.

Osteoporosis Treatment Studies in
Postmenopausal Women
Time Course of Effect of FOSAMAX 10 mg/day
Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



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

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the

70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

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

statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

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

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

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

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

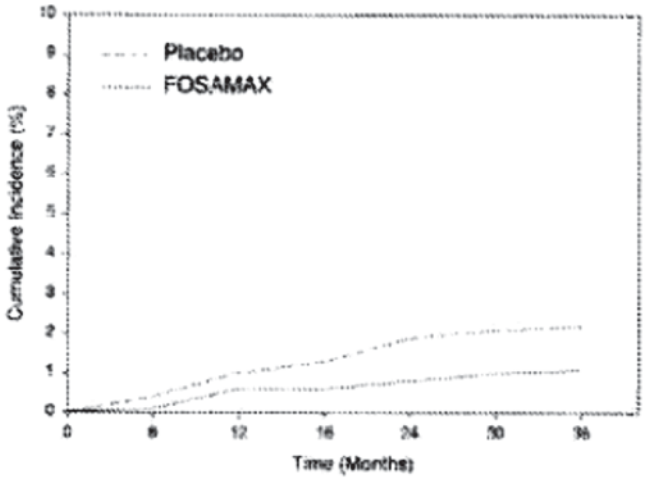
	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk □
Patients with:				
Vertebral fractures (diagnosed by X-ray)□				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47□□□
≥ 2 new vertebral fractures	0.5	4.9	4.4	90□□□
Clinical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

□Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
□p<0.05, □□p<0.01, □□□p<0.001, □p=0.007

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

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2 2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.

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



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

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study

was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of FOSAMAX on Fracture Incidence in Osteoporotic[1] Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

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

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

Fracture results across studies

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

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

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

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

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging

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

Men

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

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

A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the

femoral neck. Alone year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

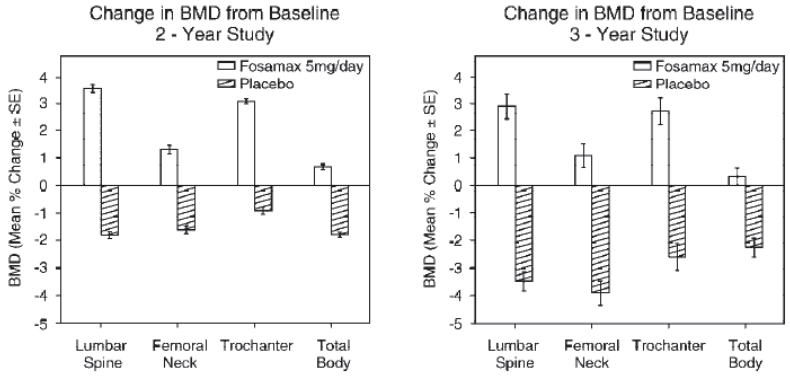
In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dl vs. 29 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2. 5 vs. >-2. 5).

Prevention of osteoporosis in postmenopausal women

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

since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women



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

Bone histology

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

Concomitant use with estrogen/hormone replacement therapy (HRT)

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

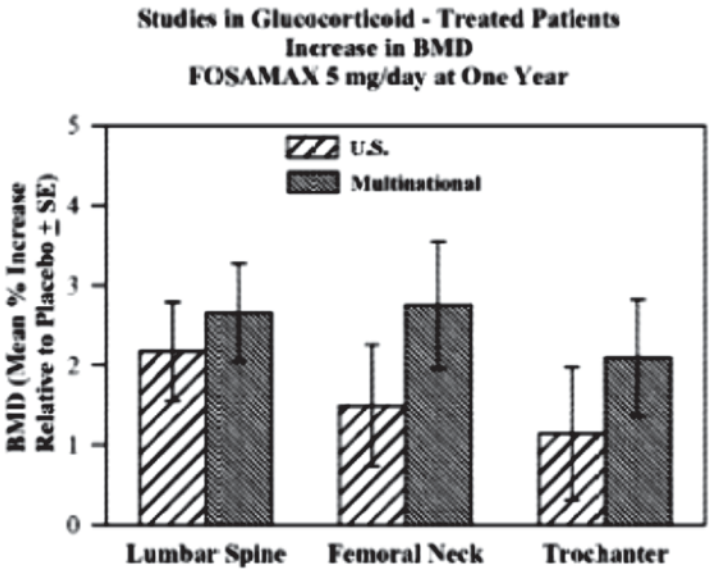
The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo- controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly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

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

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

Glucocorticoid-induced osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7. 5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, place controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.



After one year, significant increases relative to placebo in BMD were seen in the combined studies at

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

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

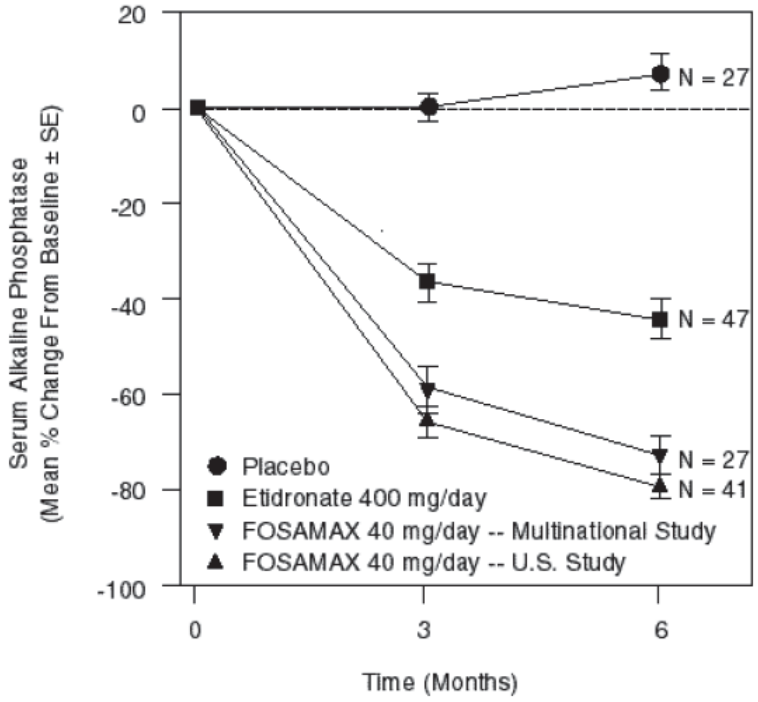
Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively.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

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

Paget's disease of bone

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

Studies in Paget's Disease of Bone
Effect on Serum Alkaline Phosphatase of FOSAMAX
40 mg/day Versus Placebo or Elidronate 400 mg/day



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group.

FOSAMAX was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

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

ANIMAL PHARMACOLOGY

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

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women

- For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics.*)
- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be Important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to in greater in patients who lie down after taking FOSAMAX and/or who fail to swallow it with the recommended amount of water, and/or who continue to take FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

Because of possible irritant effects of FOSAMAX on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been post-marketing reports of gastric and duodenal ulcers, some severe and with

complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs includes

FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan

or each patient based on individual benefit/risk assessment.

Low-Energy Femoral Shaft Fracture

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. **[1]** Some patients experienced prodromal pain in the affected area often associated with imaging features of stress fracture weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate. **[2]** Patients with suspected stress fractures should be evaluated including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse) and receive appropriate orthopedic care. **[3]** Interruption of bisphosphonate therapy in patients with stress fractures **[4]** should be considered pending evaluation of the patient, based on individual benefit/risk assessment. **[3]**

COMMENTS/SUPPORT

1. [Sec. 2.5: p. 5]
2. [Sec. 2.5: p. 7]
3. [Sec. 2.5: p. 5]
4. [Sec. 2.5: p. 8]

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in

postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

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

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

Dosing Instructions

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

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6–8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet

because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn)they should stop taking FOSAMAX and consult their physician.

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

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

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies,*

Concomitant use with estrogen/hormone replacement therapy (HRT) and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

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

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3,

and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/ m^2. The relevance of this finding to humans is unknown.

Perafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/ m^2. The relevance of this finding to humans is unknown.

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

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and

lumbar), skull, and sternebral bones. The above doses ranged from 0.26 limes (1 mg/k) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/cay (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

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

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

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

Nursing Mothers

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

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4–18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4. 5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1. 3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling)

or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies, Osteogenesis Imperfects*.)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX

usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49–54% had a history of gastrointestinal disorders at baseline and 54–89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

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

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

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

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1□ of Patients		
	Once Weekly FOSAMAX 70 mg □ (n=519)	FOSAMAX 10 mg/day □ (n=370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men

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

Osteoporosis Studies in Men
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2 of Patients

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

Prevention of osteoporosis in postmenopausal women

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

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

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

Osteoporosis Prevention Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or
Definitely Drug Related by the Investigators and
Reported in ≥1□ of Patients

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

Concomitant use with estrogen/hormone replacement therapy

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

Treatment of glucocorticoid-induced osteoporosis

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

One-Year Studies in Glucocorticoid-Treated Patients
Adverse Experiences Considered Possibly, Probably, or
Definitely Drug Related by the Investigators and
Reported in ≥1□ of Patients

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

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

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3–12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

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

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with

FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

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

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8. 0 mg/dL (2.0 mM) and serum phosphate to ≥2.0 mg/dl (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in

association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*); joint swelling; low-energy femoral shaft fracture (see PRECAUTIONS, *Low-Energy Femoral Shaft Fracture*).

COMMENTS/SUPPORT

Addition of Post-Marketing Adverse Reaction "low-energy femoral shaft fracture," based on the WAES reports listed on paged 37, 38.

Nervous system: dizziness and vertigo.

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

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

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

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

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less

than 30 minutes, or taking FOSAMAX with food. beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6–8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes *and* until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one bottle of 70 mg oral solution once weekly

or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

or

- one bottle of 70 mg oral solution once weekly

or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal woman (*see* INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patents who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

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

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100

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

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

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

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

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

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

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

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

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

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

Storage

FOSAMAX Tablets:

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

FOSAMAX Oral Solution:

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

Low-energy femoral shaft fractures

Previously Submitted :o FDA*

WAES Number			
00087273	0602USA00223	0703USA04033	0801SGP00016
99021496	0602USA00297	0703USA04034	0802USA02803
0203USA03318	0606USA00160	0705COL00005	0802USA02809
0205USA02234	0608USA06608	0707PHL00001	0802USA02811
0311USA00524	0610SGP00008	0707PHL00003	0802USA02812
0311USA00841	0610USA06249	0707PHL00004	0803USA00534
0311USA01839	0611SGP00006	0707PHL00005	0804BEL00009
0312USA00476	0612SGP00002	0707SGP00001	0804CHE00016
0403USA00626	0702SGP00005	0708TUR00008	0804CHE00017
0403USA02294	0702SGP00006	0708USA02909	0804USA02067
0408USA01969	0702SGP00007	0709SGP00002	0804USA02068
0411USA00196	0702SGP00008	0709SGP00003	0805ESP00038
0412FRA00067	0702SGP00009	0709SGP00007	0806AUS00019
0412USA00096	0702SGP00010	0709SGP00011	0806USA02011
0503USA04454	0702SGP00011	0709USA00505	0806USA02300
0506AUS00061	0702USA04448	0712HKG00008	0806USA02648
0506USA01525	0703SGP00016	0801SGP00008	0806USA02727
0506USA03125	0703USA03215	0801SGP00009	0806USA02856
0507MYS00005	0703USA03744	0801SGP00010	0806USA02857
0508MYS00006	0703USA03988	0801SGP00011	0806USA03308
0508USA01401	0703USA03989	0801SGP00012	0806USA03310
0508USA02056	0703USA03990	0801SGP00013	0806USA03311
0512USA00384	0703USA03991	0801SGP00014	
0512USA00518	0703USA03992	0801SGP00015	

** Previously submitted io FDA as either "expedited 15-day reports" or as "periodic reports" (pursuant to 21 CFR 314.80 or 21 CFR 600.80).*

Not Previously Submitted to FDA**

WAES Number			
0610SGP00001	0703SGP00005	0801SGP00001	0804USA01295
0610SGP00002	0703SGP00006	0803USA03222	0804USA01296
0610SGP00003	0703SGP00007	0804USA01287	0804USA01297
0610SGP00006	0703SGP00008	0804USA01288	0804USA01298
0610SGP00007	0703SGP00009	0804USA01289	0804USA01299
0611SGP00007	0703SGP00010	0804USA01290	0807USA00254
0611SGP00008	0703SGP00011	0804USA01291	0807USA00255
0611SGP00010	0709SGP00004	0804USA01292	99073649
0702SGP00012	0709SGP00005	0804USA01293	
0703SGP00003	0710AUS00006	0804USA01294	

*** The reports referenced above have not been previously submitted to FDA and belong to one of the following two categories: reports which meet the criteria for submission to FDA (pursuant to 21 CFR 314.80 or 21 CFR 600.80) and are scheduled for a future "periodic adverse experience report" or an "expedited 15-day report"; or reports which do not meet the criteria for submission to FDA (including non-US non-expedited reports, non-expedited literature reports, initial MedWatch reports received directly from FDA, and initial reports received through the Freedom of Information Act). Reports not previously submitted but meeting criteria for submission will be sent to FDA as either "expedited 15-day reports" or as "periodic reports" with future scheduled "periodic adverse experience report" submissions, as appropriate.*

Patient Information
FOSAMAX® (FOSS-ah-max)
(alendronate sodium) Tablets

Read this information before you start taking FOSAMAX*. Also, read the leaflet each time you refill your prescription, just in case anything has changed. This leaflet does not take the place of discussions with your doctor. You and your doctor should discuss FOSAMAX when you start taking your medicine and at regular checkups.

What is the most important information I should know about FOSAMAX?

- **You must take FOSAMAX exactly as directed to help make sure it works and to help lower the chance of problems in your esophagus (the tube that connects your mouth and stomach). (See "How should I take FOSAMAX?").**

- **If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking FOSAMAX and call your doctor. (See "What are the possible side effects of FOSAMAX?").**

What is FOSAMAX?

FOSAMAX is a prescription medicine for:

- The treatment or prevention of osteoporosis (thinning of bone) in women after menopause. It

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*Registered trademark of MERCK & CO., Inc.

reduces the chance of having a hip or spinal fracture (break).

- Treatment to increase bone mass in men with osteoporosis.
- The treatment of osteoporosis in either men or women who are taking corticosteroid medicines (for example, prednisone).

Improvement in bone density may be observed as early as 3 months after you start taking FOSAMAX even though you won't see or feel a difference. For FOSAMAX to continue to work, you need to keep taking it.

FOSAMAX is not a hormone.

There is more information about osteoporosis at the end of this leaflet.

Who should not take FOSAMAX?

Do not take FOSAMAX if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in four blood
- Are allergic to FOSAMAX or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before using FOSAMAX?

Tell your doctor about all of your medical conditions, including if you;

- **have problems with swallowing**
- **have stomach or digestive problems**

- **have kidney problems**
- **are pregnant or planning to become pregnant.** It is not known if FOSAMAX can harm your unborn baby.
- **are breastfeeding.** It is not known if FOSAMAX passes into your milk and if it can harm your baby.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take FOSAMAX?

- Take 1 FOSAMAX tablet once a day, every day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX while you are sitting or standing.
- Swallow your FOSAMAX tablet with a full glass (6-8 oz) of plain water only.

Do **not** take FOSAMAX with:

Mineral water
Coffee or tea
Juice

FOSAMAX works only if taken on an empty stomach.

Do not chew or suck on a tablet of FOSAMAX.

After swallowing your FOSAMAX tablet, wait at least 30 minutes:

- before you lie down. You may sit, stand or walk, and do normal activities like reading.

- before you take your first food or drink except for plain water.
- before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down until after first food of the day.

- It is important that you keep taking FOSAMAX for as long as your doctor says to take it. For FOSAMAX to continue to work, you need to keep taking it.

What should I do if I miss a dose of FOSAMAX or if I take too many?

- If you miss a dose, do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.
- If you think you took more than the prescribed dose of FOSAMAX, drink a full glass of milk and call your doctor right away. Do not try to vomit. Do not lie down.

What should I avoid while taking FOSAMAX?

- Do not eat, drink, or take other medicines or supplements **before** taking FOSAMAX.
- Wait for at least 30 minutes **after** taking FOSAMAX to eat, drink, or take other medicines or supplements.
- Do not lie down for at least 30 minutes **after** taking FOSAMAX. Do not lie down until **after** your first food of the day.

What are the possible side effects of FOSAMAX?

FOSAMAX may cause problems in your esophagus (the tube that connects the mouth

and stomach). (See "What is the most important information I should know about FOSAMAX?".) These problems include irritation, inflammation, or ulcers of the esophagus, which may sometimes bleed. This may occur especially if you do not drink a full glass of water with FOSAMAX or if you lie down in less than 30 minutes or before your first food of the day.

- **Stop taking FOSAMAX and call your doctor right away if you get any of these signs of possible serious problems of the esophagus:**
    - **Chest pain**
    - **New or worsening heartburn**
    - **Trouble or pain when swallowing**
- Esophagus problems may get worse if you continue to take FOSAMAX.
- Mouth sores (ulcers) may occur if the FOSAMAX tablet is chewed or dissolved in the mouth.
- You may get flu-like symptoms typically at the start of treatment with FOSAMAX.
- You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
- FOSAMAX may cause jaw-bone problems in some people. Jaw-bone problems may include infection, and delayed healing after teeth are pulled.
- The most common side effect is stomach area (abdominal) pain. Less common side effects are nausea, vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, eye pain, rash that may be made worse by sunlight, hair loss,

headache, dizziness, a changed sense of taste, joint swelling or swelling in the hands or legs, and bone, muscle, or joint pain.

- **Call your doctor if you develop severe bone, muscle, or joint pain.**
- Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh.

COMMENTS/SUPPORT

Side effect added for consistency with the revision in the USPC.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with FOSAMAX. Ask your doctor or pharmacist for more information.

How do I store FOSAMAX?

- Store FOSAMAX at room temperature, 59 to 86°F (15 to 30°C).
- Safely discard FOSAMAX that is out-of-date or no longer needed.
- **Keep FOSAMAX and all medicines out of the reach of children.**

General information about using FOSAMAX safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use FOSAMAX for a condition for which it was not prescribed.

Do not give FOSAMAX to other people, even if they have the same symptoms you have. It may harm them.

FOSAMAX is not indicated for use in children.

This leaflet is a summary of information about FOSAMAX. If you have any questions or concerns about FOSAMAX or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about FOSAMAX written for health care providers. For more information, call 1-877-408-4699 (toll-free) or visit the following website: www.fosamax.com.

What are the ingredients in FOSAMAX?

FOSAMAX contains alendronate sodium as the active ingredient and the following inactive ingredients:

cellulose, lactose, croscarmellose sodium and magnesium stearate. The 10 mg tablet also contains carnauba wax.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids.

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around (mobility).

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- Are going through or who are past menopause

Men who:

- Are elderly

People who

- Are white (Caucasian) or oriental (Asian)
- Are thin
- Have family member with osteoporosis
- Do not get enough calcium or vitamin D
- Do not exercise
- Smoke
- Drink alcohol often
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What can I do to help prevent or treat osteoporosis?

In addition to FOSAMAX, your doctor may suggest one or more of the following lifestyle changes:

- **Stop smoking**. Smoking may increase your chance of getting osteoporosis.
- **Reduce the use of alcohol**. Too much alcohol may increase the risk of osteoporosis and injuries that can cause fractures.
- **Exercise regularly**. Like muscles, tones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin any exercise program.
- **Eat a balanced diet**. Having enough calcium in your diet is important. Your doctor can advise you

whether you need to change your diet or take any dietary supplements, such as calcium or vitamin D.

Rx only

* * *

2.5.1 Product Development Rationale

Not applicable

2.5.1 Product Development Rationale

Not applicable

2.5.2 Overview of Biopharmaceutics

Not applicable

2.5.3 Overview of Clinical Pharmacology

Not applicable

2.5.4 Overview of Efficacy

Not applicable

2.5.5 Overview of Safety

The following label change (new text is in italic) is proposed for the alendronate sodium and alendronate sodium/cholecalciferol Company Core Data Sheet (CCDS) under Precautions and Side effects:

Section V. PRECAUTIONS:

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low and

stress fractures with similar clinical features have also occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g. vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes well tins, chronic alcohol abuse), and receive appropriate orthopedic care, interruption of bisphosphonate therapy in patients with stress fractures should be considered pending evaluation of the patient, based on individual benefit/risk assessment.

Section XL Side Effects

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see PRECAUTIONS); joint swelling, *low-energy femoral shaft fracture (see PRECAUTIONS).*

This revision is based upon review of spontaneous adverse experience reports from the Merck Worldwide Adverse Experience System (WAES) database. A substantial number of the spontaneous reports are sourced from the literature. A summary of the spontaneous reports follows below.

Introduction

A low-energy fracture is defined as one that is caused by the equivalent of a fall from standing height or less. A stress fracture (also known as an insufficiency fracture) is defined as a partial or complete fracture occurring with either normal or increased activity, but without an identifiable external traumatic event. Stress fractures are included in the larger group of low-energy fractures. Stress fractures arc seen mainly

in postmenopausal osteoporotic women and are becoming more common with the increase of elderly population and its increasing involvement in relatively intensive physical/fitness activities [Ref. 5.4: 6622, 6630, 6634]. Osteoporosis is a systemic skeletal disease and bone is abnormal due to both loss of bone mass and microarchitectural deterioration of the remaining bone. Insufficiency stress fractures are also increasingly recognized in patients with other systemic and localized metabolic conditions including rheumatoid arthritis, systemic lupus erythematosus, osteomalacia, Paget's disease, diabetes mellitus, fibrous dysplasia, pyrophosphate arthropathy, osteogenesis imperfecta, hyperparathyroidism, osteonecrosis, and endogenous or iatrogenic Cushing's syndrome [Ref. 5.4: 6622, 6623, 6626, 6628, 6629, 6630, 6632, 6633]. The proximal femur is one of the most commonly affected sites for insufficiency fractures, as are the pelvis, distal tibia and metatarsals [Ref. 5,4: 6630]. In addition to abnormally decreased bone mineral density (BMD) associated with osteoporosis, long-term immobilization/disuse, and use of glucocorticoids, the presence of joint deformity, leg-length discrepancies, muscle weakness, and spasm with resulting alteration in force distribution across the joints is likely to be very important in the development of insufficiency fractures [Ref. 5. 4: 6627, 6631]. A sudden increase in activity after joint replacement surgery and poor aerobic fitness may also be contributory factors (Ref. 5.4: 6624]. Moreover, some traumatic fractures may have a clinical presentation of a stress fracture as a patient may not tell the physician about a fall (or other external

trauma) that resulted in an incomplete fracture weeks before persistent pain lead to medical evaluation.

Several authors have reported cases of low-energy subtrochanteric/femoral shaft fractures in patients treated with alendronate [Ref 5.4: 5399, 5705, 6175, 6536, 6540, 6605, 6606, 6607, 6608]; of these, 52% were reported to be stress fractures. The published cases listed above have been entered into WAES database and arc included in the review below.

Spontaneous reports

Merck & Co., Inc.'s Worldwide Adverse Experience System database was searched for spontaneous reports with a large range of MedDRA preferred terms[1] from healthcare professionals (HCP), including regulatory agencies, in patients treated with alendronate sodium and/or alendronate sodium/cholecalciferol from market introduction (16-Jul-1993 and 10-Mar-2005, respectively) through 30-Jun-2008.

A total of 132 reports [Ref. 5.3.6: 6603] describing low-energy subtrochanteric/mid femoral shaft fractures were identified. Of these, 60% were reported as stress fractures. Forty-six (35%) of the 132 reports were from literature (5 - Odvina et al.; 15 - Lenart, Lane et al; 9 - Goh et al; 9 - Kwek et al; 3 - Visckruna et al; and single case reports by Schneider, Demiralp et al, Cheung et al, Lee et al., and Husada et al) [Ref, 5.4: 5399, 5705, 6175, 6536, 6540, 6568, 6605, 6606, 6607,

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[1] Bone development abnormal, bone formation decreased; fracture delayed union, fracture malunion, fracture nonunion, low turnover osteopathy, pathological fracture, stress fracture, multiple fractures, femur fracture, hip fracture, and femoral neck fracture.

6608], and 24 (52%) of these were identified as stress fractures.

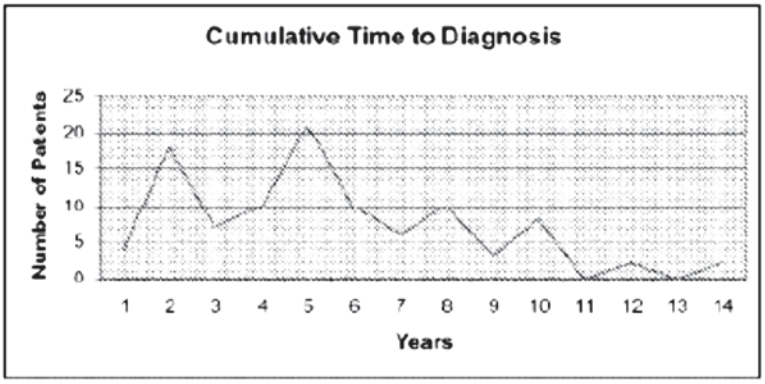
The 132 reports originated from 14 countries with half from the US (n=66, 50%), followed by Singapore (n=45, 34%), and 16% from the remaining 12 countries: Philippines (n-4), Australia (n=4), Malaysia (n=), Japan (n=), Switzerland (n=2), and 1 each from Hong Kong, France, Sweden, Turkey, Colombia, Belgium and Spain. Ninety-seven percent were female patients. he mean and median ages were both 67 years with a range from 37 to 84 years. Sixty-seven percent were aged greater than or equal to 64 years.

In these reports, alendronate therapy was given for the treatment of: osteoporosis (45%), osteopenia (11%), osteoporosis prophylaxis (4%), glucocorticosteriod-induced osteoporosis (4%) and unknown indications (37%). Of note, baseline BMD values were not typically provided to confirm the presence of osteoporosis or otherwise low bone mass prior to initiation of alendronate therapy; in 2 reports (WAES 0606USA00160 and 0610SGP00006) with reported indication of osteoporosis and osteoporosis prophylaxis respectively, the BMD values were within normal limits. The prescribed alendronate dose was not reported in a majority of the reports; however, the weekly 70 mg dose was most commonly used, which is a reflection of the current worldwide distribution pattern. Two patients (WAES 0801SGP00015 and 0804USA020G8) were receiving risedronate – one for 6 years following 4 years therapy with alendronate and the other using alendronate and risedronate concomitantly for 4 years.

The 132 reports were examined for evidence of the time after initiation of treatment with alendronate to the diagnosis of fracture. In 101/132 reports there was sufficient information (either onset and start therapy dates provided or information in the narrative indicating the approximate duration) to estimate the time to diagnosis of fracture after initiation of treatment with alendronate. [Figure 2.5: 1] is a plot of these data. The earliest time was approximately 3 months and the latest time was approximately 14 years [Note: data are presented as reported to the Company]. The mean time to diagnosis was 5.3 years; the median time was 5 years. In one patient (WAES 0709SGP00004), the fracture occurred 1 year after discontinuation of alendronate therapy.

Figure 2.5:1

Cumulative Time to Diagnosis of the Fracture after Starting Treatment With Alendronate



The reports were evaluated for fracture risk factors, including those specifically tied to stress fracture. Seventy of 132 reports (53%) provided information on patient's medical history/concurrent conditions and/or

concomitant medications sufficient to identify stress fracture risk factors [2]. Musculoskeletal disorders, including most commonly osteoarthritis (spine, hip and knee) and rheumatoid arthritis, were reported in 38 of the 70 patients (54%). The presence of joint deformities, muscle imbalance, leg-length discrepancies, and change in activity was common for this subgroup of patients. Other musculoskeletal disorders included systemic lupus erythematosus, hypermobility syndrome; fibromyalgia, myasthenia gravis, mild collagen disorder. Twenty-eight of the 70 patients (40%) had a history of fracture (25% stress fractures, 21% femur fractures; the remaining were vertebral fractures and fractures of bones of the foot), Ten of the 70 patients (14%) sustained subtrochanteric fracture following joint replacement/surgeries. Seventeen patients (24%) had endocrine/metabolic disorders including diabetes mellitus, hypothyroidism and obesity. Use of glucocorticoids was reported in 14 patients (20%) and estrogen therapy in 10 patients (14%). Malignant disease was reported in 10 patients (14%). Three patients (4%) were smokers and 5 patients (7%) had malabsorption due to gastrointestinal disease. In the remaining 47% of the 132 reports there was no information on medical history/concurrent conditions, and/or concomitant therapies precluding evaluation of possible risk factors.

Of the 132 reports of low-energy subtrochanteric/femoral shaft fracture, 80 (60%) were considered as stress/insufficiency fractures based on diagnostic results (e.g., radiographic, and/or bone scan, and/or MRI) or solely clinician's assessment with no

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[2] A patient may have had more than 1 risk factor.

diagnostic verification provided. The remaining 52 (40%) reports did not provide data to allow classification/assessment of the fracture except for 1 report where the fracture was characterized as "spiral with thin cortices".

Prodromal pain in the affected leg mainly on weight-bearing, with duration ranging from 1 week to 2 years, was reported in 48 (36%) of the 132 patients; for the remaining patients this information was not provided. Prodromal pain was reported in 51% (41/80) of the reports of stress fracture. In five of these 41 patients, limited weight bearing led to relief of the pain and healing of the stress fracture in 4 of them.

In this series of 132 reports, radiography was the most frequently used diagnostic method with common findings of cortical thickening localized to the lateral cortex of the proximal femur, periosteal reaction, cortex regeneration, fracture line and callus, described in 43 (54%) of the 80 reports of stress fracture; in very few reports generally thick femoral cortices were noted. Other diagnostic tests that were less frequently reported included bone scintigraphy and MRI with results typically indicating increased bone uptake at the fracture site.

Clinical and laboratory evaluations for known causes of stress fractures (e.g., osteomalacia, collagen disorders, Paget disease, etc.) were described in 21 (16%) of the 132 reports. A mild collagen disorder was suspected in one patient, and Paget disease in another. While bone biopsy results (provided only in 9/132; 7% reports) indicated low bone turnover, no data were presented that indicate that the rate of bone turnover was lower than that typically found during

bisphosphonate therapy. Biochemical markers of bone turnover were within normal range in the reports with this information (14/132; 11%). In two patients, the serum osteocalcin was noted to be low with all other markers within the normal range; the scrum bone-specific alkaline phosphatase was increased in 1 patient and slightly decreased in another. Vitamin D level was within normal limits except for 1 report where it was on the low borderline. It should be noted that generally the clinical and laboratory evaluations were poorly documented often with missing lab and/or reference values.

Based on 65 reports with information on fracture management, the most common treatment was surgical (in 59/65; 91%). Six (9%) patients with incomplete stress fractures were treated conservatively with restricted weight-bearing.

Outcome was reported in less than half of the reports (62/132; 47%). Furthermore, most of the reports with outcome did not provide sufficient data anchor a cl equate follow-up period to allow appropriate evaluation of fracture outcome (e.g., healed fracture, fracture nonunion, fracture delayed union). Review of the fracture outcome in relation to the fracture management and action taken with alendronate therapy is summarized in [Table 2.5:1].

Table 2.5:1

Fracture Outcome Related to Fracture Treatment and Action Taken With Alendronate Therapy

Outcome	Fracture Treatment		Action Taken with Alendronate Therapy	
	Surgical N=59	Non-surgical N=6	Discontinued N= 50	Continued N= 18
Fracture healed	24 (41%)	4 (67%)	26 (52%)	9 (50%)
Fracture not healed	11 (19%)	1 (17%)	12 (24%)	5 (28%)
Unknown	24 (41%)	1 (17%)	12 (24%)	4 (22%)

Comment

In summary, the following features can be noted for the post-marketing reports of low-energy subtrochanteric/femoral shaft fractures:

- Incomplete data in many reports precludes an appropriate assessment;
- The presence of advanced age, female gender, and osteoporosis as well as other important underlying conditions/risk factors are known to predispose the patients to insufficiency fractures and hinder the healing process. The presence of joint deformities, muscle imbalance, leg-length discrepancies, and a change in physical activities was noted in a significant number of patients;
- The duration of alendronate therapy relative to onset of the fracture was 5.3 years mean and 5 years median with a range from 3 months to 14 years;
- A significant number of reports represent published case reports/case series [Ref. 5.4; 5399, 6175, 6568, 6607]; however, little information is available about many of the cases selected by the authors, and inadequate data are available on the

period preceding the start of alendronate treatment; the possibility that other underlying metabolic bone disorders may have been responsible for the fractures, and may have existed prior to the start of alendronate therapy, should also be considered;

- Sixty percent of the 132 low-energy subtrochanteric/femoral shaft fractures were stress (insufficiency) fractures. Fifty-one percent of the stress fracture reports were associated with prodromal leg/hip pain suggestive of incomplete stress fracture;
- In many cases, there was either missing information or inadequate follow-up of the fracture outcome; however, based on the available data, a higher proportion of the fractures were reported to be healing or have healed.
- The data on the outcome relative to action taken with alendronate therapy in response to event are incomplete and do not allow for any conclusions;
- The review of the post-marketing reports describing low-energy subtrochanteric/femoral shaft fractures does not demonstrate a causal link with alendronate therapy.

In conclusion, the spontaneous reports in this review represent low-energy fractures, some described as stress/insufficiency fractures, at the subtrochanteric region of the femoral shaft. While these fractures arc less common than other osteoporotic low-energy fractures (representing about 6% of fractures of the femur), they occur in a similar population of elderly individuals and have been reported prior to the availability of bisphosphonates. It is not possible with

the present data to establish whether treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft fractures. Nevertheless, considering the clinical importance of these fractures in patients with osteoporosis and their temporal association with bisphosphonate use, the Company believes that it is important to include an appropriate statement about them in the product information and precautions needed to identify and manage such fractures. This may further increase physicians' awareness of possible fractures in some osteoporotic patients at risk and allow early intervention thus possibly preventing the progression to complete fracture and/or other complications.

The Company will continue to closely monitor the reports describing low-energy subtrochanteric/femoral shaft fractures and ensure the adequacy of the safety information in the product label.

2.5.6 Benefits and Risks Conclusions

Review of the spontaneous reports of low-energy subtrochanteric femoral fractures supports the proposed label communication under Precautions and Side Effects sections of the CCDS for alendronate sodium and alendronate sodium/cholecalciferol.

Based on the extensive experience with alendronate in patients with osteoporosis of [REDACT] patient-years of treatment, the number of the spontaneous reports of low-energy subtrochanteric/femoral shaft fractures which have been received is very small [REDACT] per 100,000 patient treatment years). The benefit to risk balance for alendronate in the treatment of osteoporosis remains favorable considering that

bisphosphonates reduce the risk of most common hip fractures by approximately 50% in osteoporotic postmenopausal women.

The MAH will continue to monitor reports of low-energy subtrochanteric/ femoral shaft fractures in patients receiving alendronate therapy as part of routine pharmacovigilance activities.

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shaft fractures. Clinical Orthopaedics and Related Research 2000;372:241–9.

[Exhibit 64 to Confoy Declaration]

Linda S. Hostelley
Vice President
Worldwide Product Safety
and Quality Assurance

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March 18, 2009

Food and Drug Administration
Center for Drug Evaluation & Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Sir or Madam:

Enclosed please find, in duplicate, "courtesy copies" of a Periodic Safety Update Report prepared for Fosamax® (alendronate sodium tablet and oral buffered solution, MSD). This report includes information received from 16-July-2008 through 15-January-2009.

Please be advised that this report is being provided to you for information until which time 21 CFR 314.80 is changed and a Periodic Safety Update Report replaces the required annual periodic adverse drug

experience report submissions to NDA 20-560 and 21-575.

Thank you for your attention to this matter.

Sincerely,

/s/ Linda S. Hostelley
Linda S. Hostelley
Vice President
Worldwide Product Safety & Quality Assurance

Enclosures

cc: S. Blumenthal
WORF
File

[Exhibit 65 to Confoy Declaration]

Regulatory Liaison Telephone Conversation Record

To	***Application or Project***	***Drug/Biologic/Compound***
[Direct Supervisor}	[Insert Application Type and # or project if appropriate.]	[Insert Trade, Generic or MK#]
David Altarac	NDA 20-560 NDA 21-762 NDA 21-575	Fosamax Tablets, Fosamax Plus, Fosamax Oral solution

Agency [Name of Agency Contacting]	***Agency Contact(s) / Title / Affiliation with the Agency*** [List each contact/ attendee. Use a hard carriage return (¶) to move to the next line.]
FDA	Dr. Scott Monroe, Divisional Director Reproductive and Urologic Products

Date(s) of Conversation(s)	***Merck Contact***
[dd-mmm-yyyy, e.g. 06-May-2006]	[List Merck Primary contact/ title. Insert add'l attendees at bottom of page]

9 April 2009 Charlotte B. Merritt

Subject:

Follow up on Labeling Supplements

Executive Summary [Note: Limit this field to 500 characters. Action should be captured in the Executive Summary.]

On April 7, I placed a call to Dr. Scott Monroe, Division Director for Reproductive and Urologic Products, to discuss with him the status of two outstanding submissions for the alendronate products. He returned my call on April 9. We first discussed Supplement 051 for FOSAMAX Tablets, which provided an update to the ONJ labeling. Dr. Kehoe (Medical Officer, Team Leader), who participated in the call with Dr. Monroe, indicated that FDA would be in the position to provide us a revised draft of the labeling in a few weeks following feedback from an internal consultation with dental experts. The subsequent discussion of Supplement 054 for FOSAMAX Tablets (which added language to the label related to subtrochanteric fractures) resulted in a suggestion by Dr. Monroe that, as an interim measure, we could amend the post-marketing section of the label only to include these data. The conversation ended cordially with my promise to get back to him shortly with our plans.

Detailed Summary [Note: This field has an unlimited number of characters.]

On April 7, I placed a call to Dr. Scott Monroe, Division Director for Reproductive and Urologic Products, to discuss with him the status of two

outstanding submissions for the alendronate products. He returned my call on April 9 and with him was Dr. Theresa Kehoe (Medical Officer, Team Leader). I thanked Dr. Monroe for returning my call and shared with him that Merck was anxious to understand FDA's timelines for completing their review of two labeling supplements and that this information had not been forthcoming from the Project Manager.

We discussed Supplement 051 for FOSAMAX Tablets, which provided an update to the ONJ labeling. The PDUFA data for this supplement was November 9, 2007. There have been several interactions with FDA and Merck on this supplement, but we had anticipated feedback on our latest response prior to the current time and would like to bring the interactions to completion so that we can print an updated label with the most current information. Dr Kehoe indicated that part of the delay was related to our request to add osteomyelitis (term added to draft labeling in April 2008 and all reports submitted in June 2008). In addition, she indicated that they have recently engaged some Dental colleagues and are expecting a recommendation from them in the next week or so. They will provide a revised draft of the labeling to us after this time, which can be the basis for a teleconference. Their goal is to craft separate class labels for oral and IV bisphosphonates.

We then discussed Supplement 054 for FOSAMAX Tablets, which added language to the label related to subtrochanteric fractures. Dr. Monroe indicated the duration of review was related to our elevation of this issue to a precaution in the labeling. He indicated that they could agree quickly to language in the post-marketing section of the labeling. FDA would like to

approach the issue of a precaution from the prospective of all bisphosphonates and are working with the Office of Safety and Epidemiology to do so. The conflicting nature of the literature does not provide a clear path forward, and more time will be need for FDA to formulate a formal opinion on the issue of a precaution around these data.

Prior to concluding our discussion, Dr. Monroe suggested that as an interim measure we may want to include a request to add text relating to subtrochanteric fractures to the post-marketing section of the label as part of our response to FDA's recent request (received April 6) to include Barrett's esophagus as an example of an active upper GI condition in which caution should be used when administering alendronate. I thanked him for this option and indicated that I would take this suggestion back to the team and would get back to him shortly. I also suggested that, if FDA was able to get back to us in a few weeks on the ONJ supplement, perhaps we could finalize that labeling as well in time to allow for a single printing including all three issues. Finally, Dr. Monroe reminded me that we also need to respond to their request for PLR by June. I indicated that I was aware of that request.

The conversation ended cordially with my promise to get back to him shortly with our plans. Alternatively, we agreed that Jim Adams may contact the Project Manager to follow up.

[Complete this section if actionable items have been identified.]

[If applicable, provide name only. Separate additional name]

[Exhibit 73 to Confoy Declaration]

FDA **U.S. Food and Drug Administration**

Protecting and Promoting Your Health

Drugs

Podcast for Healthcare Professionals: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures

Podcast[1]

Welcome, my name is Catherine Chew, a pharmacist in the Division of Drug Information. Today I am updating you about an ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures.

Healthcare professionals may have questions about oral bisphosphonate medications and atypical subtrochanteric femur fractures – fractures in the bone just below the hip joint.

Recent news reports have raised the question about whether there is an increased risk of this type of fracture in patients with osteoporosis using these medications. At this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures.

Based on published case reports of atypical subtrochanteric femur fractures occurring in women with osteoporosis using bisphosphonates, FDA, in June 2008, requested information from all

bisphosphonate drug manufacturers regarding this potential safety signal. All available case reports and clinical trial data were requested. FDA's review of these data did not show an increase in this risk in women using these medications.

In addition, FDA reviewed a December 2008 article in the *Journal of Bone and Mineral Research* by Abrahamsen and co-authors that analyzed data from two large observational studies in patients with osteoporosis. The authors concluded that atypical subtrochanteric femur fractures had many similar features in common with classical osteoporotic hip fractures, including patient age, gender, and trauma mechanism. The data showed that patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures relative to classical osteoporotic hip fractures.

The agency will continue to review new information as it becomes available and is working closely with outside experts, including members of the recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue.

Once additional information is available, FDA will update the public about this issue.

At this time, FDA recommends that healthcare professionals:

1. Be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking oral bisphosphonates.

2. Continue to follow the recommendations in the drug label when prescribing oral bisphosphonates.

3. Discuss with patients the known benefits and potential risks with using oral bisphosphonates.

4. Report any adverse events with the use of oral bisphosphonates to FDA's MedWatch program at www.fda.gov/medwatch.

Thank you for listening. The FDA is committed to keeping healthcare professionals informed of the latest safety information. If you have questions about this safety communication, you can reach the Division of Drug Information at the following email address: druginfo@fda.hhs.gov.

Related Information

- Podcast for Healthcare Professionals: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures - mp3 (MP3 - 7.1MB)[2]
- FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures[3]

Contact FDA

Toll Free
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(301) 796-3400
druginfo@fda.hhs.gov
Human Drug Information
Division of Drug Information (CDER)
Office of Communications

Feedback Form[4]

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Page Last Updated: 03/17/2010

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