replaced, or whether these ancillary measures are adequate.

Overview of Safety: Safety is comparable to that with the marketed alendronate for postmenopausal osteoporosis, except for concerns about fractures in bones that are not predominantly trabecular bone. Both spine and ribs are made up of a high proportion of trabecular bone. I have applied the term non-trabecular to all other bones, but recognize that they do contain trabecular bone which is a smaller proportion of the total bone than is present in vertebae and ribs. Thus I have used "trabecular" to mean vertebral and rib, and used "non-trabecular to mean all other bones fractured."

The number of fractures in vertebrae and ribs is compatible with a benefit from alendronate therapy. The number of fractures in non-trabecular bones is suggestive of excess fractures in the treated groups: two in the placebo group, 5 in the 5 mg/d group, and 7 in the 10 mg/d group. These fractures in non-trabecular bones are disturbing even though they are less numerous than fractures of the trabecular bones, because they are more serious, more painful, and more incapacitating. These fractures are mostly in the appendicular skeleton and result in much greater disability.

The rationale for use of alendronate in CIOP is weak, and essentially is just that it worked in post-menopausal osteoporosis, so it should work in CIOP. However, the pathophysiology of post-menopausal osteoporosis is increased turnover of bone, whereas in CIOP, it is largely decreased osteoblast activity so that bone is resorbed but not rebuilt. Suppressed osteoblasts mean that the osteoclast-produced excavations do not get refilled with bone, so suppressing the osteoclasts may help to reduce the unfilled excavations and to increase bone density. However, adding a drug that suppresses osteoclast activity to a condition characterized by suppressed osteoblasts is not intuitively understood to result in stronger bone. Because osteoclasts initiate bone remodeling, it is reasonable to presume that both resorption and rebuilding of bone are decreased. This may be all right in the short term, and may eventually result in increased numbers of appendicular fractures. Bone does become slightly more dense but may be lacking in normal matrix and may become more brittle, less

resilient. According to Bockman and Weinerman of Cornell University (Page 20 of this review, Appendix A), among the direct effects of glucocorticoids on bone cells, "there is **inhibition of osteoblast synthesis of matrix proteins…**" This suggests a means by which bone becomes more dense, but not more resistant to fractures. The **effect of alendronate on BMD** in MN and US **is less than the effect observed in post-menopausal osteoporosis**, where lumbar spine BMD increased more than 5%. This difference might be telling us that it acts differently on the CIOP population than on the post-menopausal osteoporosis population.

The strength of the bone is not addressed by measurement of BMD. That would require fracture studies. **Fracture studies** are difficult because fractures are not experienced by all glucocorticoid-treated patients especially if adequate calcium and vitamin D are ingested. However, the magnitude of the differences experienced in the MN and US trials (approximately a 3 fold difference in the number of fractures in non-vertebral bone between drug and placebo groups) suggests that it would not require a very much larger study to detect a difference. It would, however be important to detect somewhat less difference, say a 50% increase.

11. **Labeling Review:** No review is made at this time, because the drug should not be approved until some reassurance is received on the safety for non-trabecular bone.

12. **Conclusions:**
    1. Alendronate has been shown to prevent bone loss (decrease in BMD) in patients on glucocorticoids.
    2. Alendronate has been shown to be reasonably safe when administered to patients on glucocorticoids.
    3. BMD has not been shown to be a valid surogate for fractures in patients on glucocorticoids.
    4. Fractures observed in the trials (MN and US) indicate a trend (in treated vs placebo patients) toward fewer fractures in bones of high trabecular content (spine and ribs) and a trend toward more fractures in other (appendicular) bones.
    5. The surrogate endpoint of BMD must be validated for CIOP before it can be accepted as adequate to establish efficacy for prevention of osteoporosis in patients on glucocorticoid therapy.

6. Acceptable validation of BMD will require a fracture study that does not rely on vertebral and rib fractures.

13. **Recommendations:** Alendronate is not approvable for prevention of glucocorticoid-induced osteoporosis.

14. **Further Thoughts:**

a. The **M & E Advisory Committee** is expected to discuss requirements for approval of a drug for glucocorticoid-induced osteoporosis in mid May. They will not be discussing this or any other specific application, and since it is my opinion that this application cannot be approved as is, the data in this NDA will not be public information. If there is any way that the **information about fracture rates** in trabecular and non-trabecular bone can be made available to the Committee, it should be done. It may be that the number of fractures and the rate of fractures in each treatment group and in the combined treatment groups can **be discussed without identifying the source.** Or perhaps it would be possible to provide the Committee with the data without making it available publicly. I doubt the latter would be acceptable unless the sponsor was told that we would do this, so they could rebut the implications with whatever they found acceptable to reveal. However, I think that having the public discussion with the Committee without informing them might result in a recommendation that was not adequately informed to protect the public health.

b. It is possible that **the sponsor could support an argument** that, because fractures are more frequent in trabecular bone, the benefits of decreasing them outweigh the increase in fractures in other bones. There were 14 vertebral and 5 rib fractures (8.8 and 2.5% of patients on pbo), 4 and 1 (2.5 and 0.6% on 5 mg), and 8 and 1 (5.1 and 0.6% on 10 mg). Adding vertebral and rib fractures together, there were 19, 5, and 9 trabecular bone fractures, and 2, 5 and 7 fractures of non-trabecular bone. Twice the number of subjects in placebo is equal to the sum of the number in the two treated groups. The mean of non-trabecular fractures in drug groups is 6 and the number in placebo patients is 2; the excess of fractures in treated patients = 4. The mean number of vertebral/rib fractures is 6 in treated and 14 in placebo patients; the excess of fractures in

untreated patients = 8. Thus, the patients who take drug might have one non-trabecular fracture for each 2 trabecular fractures prevented. This is making too much out of a small number of fractures, and I know it cannot be relied on, but I am trying to indicate the relative magnitude of the fracture risk from taking or not taking the drug, and this is all we have. I believe more information is needed to make a meaningful assessment of the benefits and risks of this drug used for this purpose.

c. If the Advisory Committee recommends that drugs for CIOP be approved on the basis of BMD only, as I think they are likely to do if the bone fracture data from these studies is not available to them, we probably would have to approve the drug, because of the efficacy in preventing vertebral and rib fractures. Then the data would become public and could be used in the package insert to indicate serious concern about risk of fractures in bones other than spine and ribs.

d. The sponsor met with us and promised to submit further information, including a calculation of study size necessary to determine whether non-trabecular bone fracture rates are increased. They were also going to provide us with further information to convince us to accept the BMD data without demonstration of fracture efficacy. Those data are reviewed below.

In addition notes from recent literature make up Appendix A.

/S/ [redacted]

Gloria Troendle

APPEARS THIS WAY ON ORIGINAL

Appendix A NDA 20560, Merck, Supplemental Application 20 March, 1998

MEDLINE: Glucocorticoids and Fractures

Adachi, NEngJMed 1997, Aug 7, 337:382-7. 12-mo, randomized, placebo trial of intermittent etidronate 400 mg/d x 14 d and calcium 500 mg/d x 76 d, 4 cycles. 141 men and women who recently started **high-dose corticosteroid therapy**. Primary endpoint is **change in bone density of lumbar spine**; secondary endpoint is BMD radius, trochanter and femoral neck and rate of vertebral fractures. Differences in etidronate and placebo change from baseline in lumbar spine and trochanter BMD were 3.72 and 4.14%. Changes in femoral neck and radius were not significant. There were 1 and 7 fractures in 32 postmenopausal women on etidronate and 31 placebo patients ($p = 0.05$.).

Shane, AmJMed 1996 Sep, 101:262-9. BMD of 70 patients with **lung transplant** and end-stage pulmonary disease was determined and expressed as standard deviations below mean peak bone mass. Spine x-rays were taken on 50 of the patients. **30% of patients had BMD score of -2.5** standard deviations or less at the lumbar spine and 49% at the femoral neck. 29% of COPD and 25% of cystic fibrosis had **vertebral fractures.**

Pichette, AMJKidneyDis 1996 Jul, 28:105-14. BMD in 70 **kidney transplant** recipients (KTR) at mean 8.1 years post transplant. DXA was repeated in 55 pts after mean 22mo. Although vertebral fractures "are relatively infrequent in long-term survivors of renal transplantation, osteopenia is a frequent finding." Fractures were found in 4 men.

Houssiau BrJRheumatol 1996 Mar,j 35:244-7. DXA in 47 **premenopausal women with systemic lupus erythematosis** showed low BMD in lumbar spine, hip, total body, trabecular and cortical. Bone loss was greater in those who had taken glucocorticoids compared to those who never did, but those who never took glucocorticoids had lower hip BMD compared to controls, "suggesting that **the disease per se might induce some bone loss.**"

Peris, BrJRheumatol 1995 Oct, 34:936-41. 81 osteoporotic men from rheumatology clinic had measurement of markers of bone turnover. 18 had **primary osteoporosis, 12 hypogonadism, 10 corticosteroid therapy and 10 alcoholism.** In 69 patients, back pain was the chief complaint. In 45, the pain was chronic (50% had vertebral fractures), and in 24 subacute episodes.

Reid, BaillieresClinRheumatol 1993 Oct, 7:573-87. Glucocorticoids produce osteoporosis via a number of mechanisms, the most important of which is probably **inhibition of bone formation.** This results in bone reduction 10-20% at common sites, 30-40% in **predominantly trabecular bone.**

Luengo Thorax 1994 Nov, 49:1099-102. In two-year trial of intranasal calcitonin in 22 women, the calcitonin group increased bone density 2.7% first year while Ca group lost 2.8% in the first year. In the second year, there was no bone loss in calcitonin patients, but those on Ca only lost another 7.8%. There were **3 new fractures in each group** and there were no changes in biochemical parameters. "...the **lack of effect of calcitonin on the rate of vertebral fractures does not permit its recommendation for routine use in preventing steroid-induced osteoporosis.**"

Khosla Bone 1994 Sep, 15:551-5. All 22 residents of Olmsted County MN 20-44y when first diagnosed with osteoporosis in 1976-90. 12 were steroid-induced, 3 postmenopausal, 2 delayed puberty, 2 anticonvulsant-induced, 2 gastrointestinal, 2 alcoholic, 1 anorexic and 7 other etiologies. Two were idiopathic. Further, 56 patients with idiopathic osteoporosis from the Mayo Clinic experience were identified. There was **a preponderance of cancellous bone fractures, vertebral 81%, rib 37%, wrist** 13%. Also, 13% had hip fractures. Biopsies were available in 18. Compared to controls matched for age and sex, the osteoporotic subjects had a reduction in trabecular bone volume, cortical thickness and mean wall thickness, suggesting an abnormality of osteoblast function.

Literature of interest:

Bockman & Weinerman, Orthopedic Clinics NA 1990, 21:97. Review. "The clinical presentation of cortisol excess is one of progressive demineralization, primarily of trabecular bone, resulting in **fractures of the vertebral bodies and ribs.** Bone dissolution...can result in the loss of up to 20 per cent of trabecular bone in the first year." "Histologically, one finds...increased bone resorption with an increase in osteoclast number and activity, along with decreased bone formation and mineralization rate." "Chronic glucocorticoid exposure leads to a decrease in bone DNA content, which is thought to reflect the inhibition of osteoblastic precursor proliferation and differentiation." "To summarize the direct effects of glucocorticoids on bone cells, there is **inhibition of osteoblast synthesis of matrix proteins and enhancement of osteoblastic resorption.**"

Indirect effects include decreased intestinal absorption of calcium. "The role of vitamin D in the pathophysiology of steroid induced decreased calcium absorption is further confused by the data showing that pharmacologic doses of calcidiol or calcitriol will prevent steroid-related bone loss."

Shane, et al., AmJMed 1993, 94:257-264. 40 cardiac transplant patients received prednisone and cyclosporin A. Osteopenia was present in 28% at lumbar spine and 20% at femoral neck. **Vertebral fractures were present in 35% of patients.** Serum **osteocalcin was elevated in 60% of patients, in contrast to other patients receiving glucocorticoids.** Osteopenia of the femoral neck appeared to be a better indicator of vertebral fracture prevalence than low vertebral BMD.

Meunier, NEngJMed 1993, 328:1781-2. Editorial. **"risk of hip fracture is 50 percent higher in patients receiving long-term corticosteroid therapy and 30 to35 percent of these patients have vertebral fractures."** Sambrook et al. report that 0.6 mcg calcitriol and 1000mg calcium for one year prevented bone loss in the lumbar spine but not at the femoral neck or distal radius. **Hypercalcemia developed in 25% of patients receiving calcitriol.** Calcifediol and calcium had a beneficial effect with much less risk of hypercalcemia.

Reid, et al., JAsthma 1994, 31:7-18. Review. **Fractures have been noted in about one third of patients** with Cushing's, and similarly **in patients requiring long-term, high-dose steroids. Backache and height loss** are common. Adinoff and Hollister studied two groups of patients requiring high-dose steroids and found rib or vertebral fractures in 11 and 45% of patients. Most **fractures were symptomatic**, and there were no fractures in asthma patients not receiving steroids. In treated patients, vertebral fractures were seen in 34% of treated asthmatics by Luengo, et al. Laan, et al. reported that postmenopausal women with rheumatoid arthritis treated with prednisone for 8 years had an average of 0.4 vertebral fractures, more than twice the number found in similar patients not receiving prednisone. This is consistent with a case-control study in rheumatoid patients indicating that the **use of steroids is associated with a doubling in the incidence of hip fractures** (Cooper, et al.). Lo Cascio found 40% decrease in trabecular bone volume of the iliac crests of steroid-treated patients.

Canalis, JClinEndocrinolMetab 1996, 81:3441-7. "In vitro **glucocorticoids have an acute stimulatory effect on bone resorption, but in long term cultures they are inhibitory.** The stimulation may be due to an increase in osteoclast activity, and is in accordance with effects observed in vivo. The mechanism...could involve the induction of interleukin-6 receptors in skeletal cells. IL-6 is...known to induce osteoclast recruitment and to play a central role in bone resorption. The inhibition of bone resorption appears to play a minor role in vivo and is due to a decrease in osteoclast number...that may be secondary to a suppression of IL-6 synthesis." "An **impairment in bone formation is a predominant result of glucocorticoid excess** and is associated with **a decrease in serum levels of osteocalcin**, a marker of osteoblastic function." An additional component could be...inhibition of gonadotropin and sex steroid production.

Abstracts: Osteoporosis and Related Bone Diseases-National Resource Center, National Osteoporosis Foundation, December 1996

Buckley, J Rheumatol 1995, 22:1055-9. **Low dose steroids** (5-9 mg/d) were associated with low BMD lumbar spine, but not of the femoral neck.

Laan, Calcif Tissue Int 1993, 52:5-9. 120 postmenopausal women with **rheumatoid arthritis** were classified current users of steroids, ex-users, and never users. 7966 age matched controls were also examined. Never users were significantly decreased compared to controls at distal radius, calcaneus and hip indicating **RA caused bone loss.**

Shane, JclinEndocrinolMetab 1996, 81:1740-6. 34 men and 13 postmenopausal women were studied pre and post cardiac transplant. All were supplemented with 1000mg/d calcium and 400IU Vit D. 7 women and 10 men had fractures in the first year, 85% in the first 6 months after transplant. Bone loss at femoral neck was greater in men with fracture, and femoral neck BMD was lower in women with fracture. 1,25OH2 vit D was lower and PTH higher in men who did not fracture.

Reid, NEngJMed 1997, 337: 420-1. Editorial. In glucocorticoid-treated patients, "loss of bone results in **fractures in about one third of patients after 5-10 years of treatment.** Fractures are predominantly at sites rich in trabecular bone, such as the vertebral bodies and ribs, but the **risk of hip fracture is also tripled.**"

NDA 20560/SEI-012 BM
Merck
Alendronate (Fosamax)
Dated 3-6-98 and stamped 3-9-98
Received 3-16-98
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This submission is in response to questions asked of the sponsor by the Division.

Section I describes the possible **animal models** of glucocorticoid-induced osteoporosis (GIOP). Their conclusion is that no suitable animal is adequately validated.

Section II responds to our request for information on which they rely to conclude that **GIOP is sufficiently similar to post-menopausal osteoporosis** (PMOP) that validation in PMOP can be extrapolated to GIOP.

Similarities:

1. **Bone resorption** relative to formation results in net bone loss.
2. Excessive **osteoclastic bone resorption** relative to osteoblastic bone formation is the key pathophysiologic mechanism underlying the bone loss.
3. **Negative bone balance** is attributable to 3 factors: 1) effects on osteoblasts lead to decreased bone formation, 2) secondary hyperparathyroidism due to decreased intestinal absorption and decreased renal tubular reabsorption of calcium leads to increases in both resorption and formation, and 3) gonadal hormone deficiency results in increased resorption and formation.
4. **Bone resorption is increased** in both GIOP and PMOP, and the cellular mechanisms are the same: mediated by the osteoclast.
5. Many **small studies** demonstrate the efficacy of bisphosphonates in male osteoporosis, immobilization, hyperthyroidism, idiopathic juvenile osteoporosis and osteogenesis imperfecta, indicating that beneficial effects on bone mass relate to specific effects of bisphosphonates as inhibitors of bone resorption **irrespective of mechanism of stimulating bone resorption.**
6. Alendronate **has consistent effects on bone mineral density.**
7. Absorptiometric measurements are **predominantly measures of cortical bone quality.**

8. Bone turnover is more rapid in cancellous bone, so **changes in bone density can be seen first at more cancellous sites.**
9. Bone mineral density **GIOP data are consistent with PMOP** data, as are data for men and pre and post menopausal women and data for the different GIOP underlying illnesses. Data are presented for PMOP phase III, FIT, EPIC and GIOP studies for spine and hip.
10. Effects (excess bone resorption) of **bone markers** are consistent for GIOP and PMOP.
11. **Bone turnover** (BSAP and NTx) is **greater in women who fracture** regardless of use of alendronate.
12. **Histomorphometry** does not reveal any failure of mineralization (osteoid volume, mineral apposition rate, mineralizing surface).

Items 1-8 above were very difficult to understand, so I may not have gotten them straight. They did not seem to make much sense in the context of whether BMD is a valid surrogate for fractures in GIOP. Mostly, they assert that BMD is similar in GIOP and PMOP without any reasonable backup in GIOP data. Of course, we are convinced that, in PMOP, BMD is correlated with spinal fracture rate, and bisphosphonates reduce the risk of vertebral fractures. However, **non-vertebral fractures in patients with GIOP** are the cause of our concern. No validation of BMD in GIOP is offered. In 9 and 10 above, the data compare BMD results of GIOP and PMOP trials, but **provide no basis for extrapolating results from PMOP to GIOP or from BMD to non-vertebral fractures in GIOP patients.** Number 11 seems to say again that turnover is increased, and alendronate will reduce it--not helpful. It is whether reducing turnover further when formation is already suppressed is making bone stronger. Number 12 is no help, because we agree that bone is mineralized, particularly axial bone, a point that can be inferred from the BMD data.

Section III is an analysis of GIOP fracture data, which is acceptable, but does not address the issue **of excess non-trabecular fractures** in alendronate-treated subjects in the GIOP trials. They do include **a list of non-vertebral fractures,** information which we already have.

Appendix 2 is referenced in this section. It consists of a **table of non-vertebral fractures,** which includes rib fractures. According to this list, there were 6 patients with rib fractures (ages 76, 67, 61, 57, 47, 46), one of whom also had the sternum fractured. There was one rib fracture in each of the treatment groups.

Non-vertebral, non-rib:

Sex age	Treatment	Fracture site	Trauma
F25	PBO	humerus	skiing accident
F59	PBO	elbow	due to trauma
F51	5mg	tibia	stress fracture
F76	5mg	ankle	fell on ice
F75	5mg	pelvis	fell onto coffee table
M40	5mg	ulna	knocked while playing
F79	5mg	humerus	fell on ice
F69	10mg	knee	knocked down by dog
F59	10mg	wrist	fell
F58	10mg	foot	no trauma
F32	10mg	elbow	fell
F71	10mg	hip	no trauma
F56	10mg	foot	trauma
F47	10mg	ankle	tripped while walking

This analysis seems to support our concern. It is hard to judge the amount of trauma, but it seems most of those who fractured just fell from a standing position. One skiing accident was in the placebo group.

Section IV discusses **the calculations of study size and trial feasibility**. Based on the GIOP placebo group, a fracture incidence of 4% and 10%/year is assumed. In all patients rate was 3.7%; in patients with 3 yr exposure to glucocorticoids it was 4.2%/year; and in patients with prevalent fractures it was 9.1%/year. The drop out rate was presumed to be 20%. To have 90% chance, in a one-year study, to detect a 50% reduction in fracture rate in patients with a vertebral fracture at baseline, sample size would have to be almost 700.

They also calculate detecting 30 or 40% increase in fracture rate (1156 to 5745 subjects for subjects with and without prevalent fracture). I would like to see some information on the size study required to **detect a 100% increase in non-vertebral, non-rib fracture rate**, because my concern is that the 3-fold increase in the GIOP studies might be real.

I believe that the **vertebral fractures detected in this study were largely symptomatic**, because there was not a plan to determine baseline and incident vertebral fractures. The investigator or other health care provider had to get an xray of the spine because of symptoms or as a routine screening in order for a fracture to be reported as an adverse event. It might be reasonable to count all symptomatic fractures including the spine and ribs, because there is more benefit to prevention of symptomatic fractures, but it would still be difficult to equate some vague backaches to hip or limb fractures. Only **one study**

with one treatment group and placebo would be required. More than one year should be considered, even though patients are not on glucocorticoids that long. The sponsor seems to argue that there are many fractures when pressing to have this valuable drug approved to prevent fractures, but that there are very few who have osteoporosis more than a few months to one year. It seems that patients do go on and off of glucocorticoids, but it is hard to keep them off for long periods of time, if they have a responsive illness.

There is nothing that causes me to change my mind about the approvability of alendronate for prevention of fractures in patients with GIOP.

Recommendation: Not Approvable

/S/ [redacted]

Gloria Troendle
Orig NDA 20560
Div File
HFD-510/GTroendle/RHedin

NDA 20-560/S-012
Fosamax (alendronate sodium)
Merck Research Laboratories

Safety update is included in the medical officer's review.