ASBMR®
The American Society for Bone and Mineral Research

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Kalyani Bhatt
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue, WO31-2417
Silver Spring, MD 20993-0002

Dear Ms. Bhatt,

The American Society for Bone and Mineral Research (ASBMR) commends the Food and Drug Administration for looking closely at the benefits and risks of the long-term use of bisphosphonates for the treatment and prevention of osteoporosis. ASBMR is the leading scientific research organization on bone health in the United States. Our nearly 4,000 members include scientific researchers, physicians and other health care practitioners.

Osteoporosis, one of the most devastating chronic diseases of aging that we face today, currently affects more than 10 million Americans. Another 34 million women and men have low bone mass, which may progress to osteoporosis. In all, osteoporosis costs $19 billion annually in hospitalizations, treatment and emergency room visits for fractures, which are the main symptom of osteoporosis. Without treatment, one in two women and one in four men age 50 and above will experience a fracture due to osteoporosis. Among seniors with osteoporosis, one in five who break a hip will die within a year from complications related to the break. With the aging of the American population, these numbers are expected to increase exponentially over the next 20 years and beyond. It is crucial for our aging society that we improve the diagnosis and treatment of osteoporosis. An important approach to this goal is to understand better the benefits and risks of the long-term use of bisphosphonates, which play a central role in prevention of osteoporotic fractures.

I will represent ASBMR on September 9th to provide testimony to the FDA's joint meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. We thank you for this opportunity. I am past-president of ASBMR and an endocrinologist and professor of Medicine at Columbia University in New York with more than 25 years of experience caring for patients with osteoporosis. Additionally I served as co-chair of two ASBMR scientific task forces on bisphosphonate use.

Background on ASBMR Task Forces on Bisphosphonates
ASBMR convened a task force on bisphosphonate use and osteonecrosis of the jaw (ONJ) in 2007 and a second task force on bisphosphonates and atypical femur fractures in 2010, in the wake of concerning reports of these conditions in patients using these drugs. Both task forces were international and multidisciplinary and included experts in clinical bone disease, basic bone biology, epidemiology and radiology. In addition, the ONJ task force included experts in dentistry and oral surgery and the atypical femur fracture task force included experts in orthopedic surgery. Each reviewed all published cases and unpublished data on both issues,

representing the most comprehensive scientific reports to date on these topics. In addition, the task force co-chairs conducted interviews with representatives of pharmaceutical companies that market drugs to treat osteoporosis and, in the case of the atypical femur fracture task force, with representatives of the Food and Drug Administration.

ASBMR Task Force on Osteonecrosis of the Jaw – Summary of Findings
In 2007, the ASBMR task force on osteonecrosis of the jaw examined the link between bisphosphonates and ONJ (Khosla et al., J Bone Miner Res. 2007;22:1479-91). It found the risk of ONJ to be low for people taking low dose oral bisphosphonates (between 1 in 10,000 and <1 and 100,000 patient-treatment years). Although a recent report, based on a mail survey of bisphosphonate users, found the incidence to be higher, the study design may be affected by selection bias (Lo et al., J Oral Maxillofac Surg 2010;68:243-53). In contrast, the risk of ONJ is greater for people receiving high-dose intravenous bisphosphonates for cancer (affecting 1% to 10% of patients). In both settings, the risk increases with duration of treatment.

ASBMR Task Force on Atypical Femur Fractures – Summary of Findings
In 2010, the ASBMR task force on atypical femur fractures examined all available cases of atypical femur fractures (Shane et al. J Bone Miner Res 2010;25:2267-94). Studies that included review of fracture x-rays to assess for the specific radiographic characteristics of atypical femur fractures show that there is an increased relative risk of atypical femur fractures with bisphosphonate therapy for osteoporosis (Shane et al. J Bone Miner Res 2010;25:2267-94; Schilcher et al., New Engl J Med 2011;364:1728-37). However, the absolute risk appears low. Atypical femur fractures account for less than one percent of all hip and femur fractures. At the same time, the overall risk appears to be higher among patients who have been taking bisphosphonates for more than five years. However, the risk of common hip fractures (femoral neck and intertrochanteric fractures) is far higher and decreased by bisphosphonate therapy (Park-Wyllie et al., JAMA 2011;305:783-9; Schilcher et al., New Engl J Med 2011;364:1728-37).

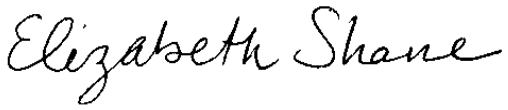
Summary of Task Force Recommendations
Based on these two task force reports, as well as literature published after the reports, ASBMR believes that osteonecrosis of the jaw and atypical femur fractures are serious potential side effects of bisphosphonates, particularly with long-term use. However, ASBMR also believes that bisphosphonates are effective drugs that lower the risk of common osteoporotic fractures. In patients receiving oral bisphosphonates in the doses typically used for treatment of osteoporosis, these potential side effects are relatively rare compared to common osteoporotic fractures prevented by bisphosphonates. In addition, although bisphosphonates are associated with these entities, they have not been shown to cause them. The vast majority of patients who take bisphosphonates for osteoporosis do not develop ONJ or atypical femur fractures and some patients develop them even though they have never taken bisphosphonates.

However, because the risk of ONJ and atypical femur fractures may increase with long-term use, it is important for health professionals to reserve bisphosphonates for patients with osteoporosis who are at high risk of having a fracture, patients with certain cancers, and other bone diseases. Although the risks are very low, health professionals should know the warning signs of osteonecrosis of the jaw and atypical femur fractures and should assess annually whether bisphosphonates are appropriate for each patient. Patients should not stop taking bisphosphonates because of concerns about these potential side effects, but should consult with their health care providers.

Following publication of the atypical femur fracture report, the FDA revised its product labeling to provide more information about potential side effects. We commend this change and believe it will help ensure that patients and physicians better understand the risks and warning signs. Additionally, ASBMR is calling for the creation of new diagnostic and procedural codes for atypical femur fractures to improve the quality of case reporting and facilitate future epidemiological research, and the establishment of an international registry of patients experiencing atypical femur fractures to track cases and facilitate future research.

We thank you for the opportunity for providing these comments in advance of the September 9th Advisory Committee meeting. Our hope is that the Advisory Committee recommendations will help patients and their health care providers better understand both the important benefits and risks of these widely prescribed drugs.

Sincerely,



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