

## Testimony Regarding Bisphosphonates

September 9, 2011

### Testimony to Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee Sammy Almashat, M.D., and Sidney Wolfe, M.D., Public Citizen's Health Research Group

My name is Dr. Sammy Almashat, staff researcher at Public Citizen's Health Research Group. I am testifying on behalf of myself and Dr. Sidney Wolfe, director of the Health Research Group. We have no financial conflicts of interest.

#### ATYPICAL FEMORAL FRACTURES AND OSTEONECROSIS OF THE JAW: STRONG ASSOCIATIONS WITH BISPSPHONATE USE

We agree with the Food and Drug Administration's (FDA) assessment that, "Atypical fractures... [as] defined by the A[merican] S[ociety] for B[one] and M[ineral] R[esearch] Task Force appear to have a strong association with bisphosphonates."<sup>[1]</sup> These rare stress fractures have almost certainly been under-reported due to the lack of a discrete case definition until recently. With the ASBMR definition, however, a consistent and very strong association with bisphosphonate use was found across three studies, with two of the studies finding a duration-response effect.<sup>[2]</sup>

Osteonecrosis of the jaw is another dangerous adverse reaction unique to, and defined by, bisphosphonate exposure and found to occur in 1 of 952 survey respondents treated with oral bisphosphonates in the FDA Predicting Risk of Osteonecrosis of the Jaw with Oral Bisphosphonate Exposure (PROBE) cross-sectional study.<sup>[3]</sup>

#### NO BENEFIT OF THERAPY IN AT LEAST TWO PATIENT POPULATIONS

Given these, and other, serious risks, bisphosphonates should be restricted to patients who will actually benefit from therapy. However, there are at least two patient populations in which the drugs have not been shown to decrease fracture risk: 1) post-menopausal women with osteopenia, and 2) all patients remaining on the drugs beyond 5 years.

#### FOR 34 MILLION WOMEN WITH OSTEOPENIA, SERIOUS RISKS WITH NO CLINICAL BENEFIT

Osteopenia is a condition that was heavily promoted to expand the market of Fosamax to millions of otherwise healthy women.<sup>[4]</sup> Yet, all randomized trials of bisphosphonates in women without osteoporosis have only shown an improvement in a surrogate marker, bone mineral density (BMD) – and not fracture risk, the only relevant clinical endpoint.<sup>[5]</sup>

Furthermore, bisphosphonates are currently approved to treat not only all osteopenic patients, regardless of fracture risk, but virtually all post-menopausal women. According to the Fosamax label, treatment can be considered in postmenopausal women with a "thin body build" and those of "Caucasian or Asian race," thus including in its indicated population almost all postmenopausal American women.<sup>[6]</sup>

By contrast, the National Osteoporosis Foundation recommends bisphosphonate use only in osteopenic patients with a 10-year risk of >3% for hip fracture or >20% for major osteoporotic fracture.<sup>[7]</sup>

#### BISPSPHONATES SHOULD BE STOPPED AFTER FIVE YEARS

The landmark Fracture Intervention Trial Long-term Extension (FLEX) study also showed no benefit of Fosamax in almost all patients beyond 5 years of use, even in high-risk women with osteoporosis and a history of vertebral fracture.<sup>[8]</sup> This lack of any benefit on fracture incidence extends to all other oral bisphosphonates, as found in the FDA's pooled analysis.<sup>[9]</sup> The FDA staff concluded correctly that, "These results suggest no significant advantage of continuing drug therapy beyond 5 years."<sup>[10]</sup>

Prolonged use greater than 5 years exposes patients to serious risks, as the rates of both atypical femoral fractures and osteonecrosis of the jaw have been shown to increase 3-4 fold beyond this point.<sup>[11]</sup>

#### THE FDA MUST ACT IMMEDIATELY TO RESTRICT UNNECESSARY, DANGEROUS USE OF BISPSPHONATES

Thus, the use of bisphosphonates in these two populations needlessly exposes patients to serious risks with no evidence of any clinical benefit. This risk:benefit profile is completely unacceptable. Therefore, we urge the Committee to recommend the following to the FDA:

- 1) Long-term use of bisphosphonates for the prevention of osteoporotic fractures must be limited to 5 years.
- 2) The indication for bisphosphonate treatment for osteopenic women must be

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removed, unless the patient has a significant 10-year fracture risk as determined by the World Health Organization's (WHO) FRAX algorithm.<sup>[12]</sup>

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[1] Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Page 26. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.

[2] Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Pages 22-23. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.

[3] Lo JC, O'Ryan FS, Gordon NP, et al. Predicting Risk of Osteonecrosis of the Jaw with Oral Bisphosphonate Exposure (PROBE) Investigators. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg.* 2010 Feb;68(2):243-53. Epub 2009 Sep 24.

[4] Spiegel A. How A Bone Disease Grew To Fit The Prescription. Dec. 21, 2009. National Public Radio. Available at: <http://www.npr.org/templates/story/story.php?storyId=121609815> Accessed on September 8, 2011.

[5] McClung MR, Wasnich RD, Hosking DJ, et al. Early Postmenopausal Intervention Cohort Study. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab.* 2004 Oct;89(10):4879-85. Also see relevant bisphosphonate labels, listing clinical trials conducted for approval to prevent osteoporosis in osteopenic patients.

[6] Addendum to the Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document Addendum]. Page 14. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.

[7] Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Page 8. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.

[8] Ott SM. What is the optimal duration of bisphosphonate therapy? *Cleve Clin J Med.* 2011 Sep;78(9):619-30.

[9] Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Page 38. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.

[10] Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Page 39. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.

[11] Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Pages 19, 23. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.

[12] Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Page 8. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270957.htm> Accessed on September 8, 2011.