

Clarify Duration of Bisphosphonate Use, FDA Panel Says

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September 9, 2011 — An advisory panel to the US Food and Drug Administration (FDA) has voted 17 to 6 to recommend that the labeling for bisphosphonates for the treatment of osteoporosis become more specific about how long the drugs should be used.

"Do you recommend that the label should further clarify the duration of use for bisphosphonates?" was the only voting question for members of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee.

But up for discussion were 5 other issues, including the strength of the available — and growing — evidence that bisphosphonates increase the risk for atypical subtrochanteric and femoral fractures, osteonecrosis of the jaw, and esophageal cancer, and whether recommending that patients take a holiday from using bisphosphonates is a good idea.

Bottom Line: Bisphosphonates Prevent Fractures

The panel heard presentations from the manufacturers of the 4 currently approved bisphosphonates: alendronate (*Fosamax*, Merck), risedronate (*Actonel*, Warner Chilcott), zoledronic acid (*Reclast*, Novartis), and ibandronate (*Boniva*, Roche).

The bottom line from these presentations was that bisphosphonates prevent fractures and reduce mortality.

Elizabeth Shane, MD, a past-president of the American Society for Bone and Mineral Research, spoke in favor of the bisphosphonates. She acknowledged concerns about the "rare but serious" side effects of osteonecrosis of the jaw and atypical femur fractures but concluded in her testimony before the joint committee that "many high-quality clinical trials have established that bisphosphonates prevent most types of serious fractures and thus are of benefit to millions of patients in the US and worldwide."

According to the FDA, 10 million people in the United States have osteoporosis, and another 34 million have osteopenia. Bisphosphonates are widely used, but there is growing uncertainty about how long they should be used, and even how effective they are in warding off fractures in people with osteoporosis.

Atypical Fracture Victims Plead for Black Box Warnings

The Open Public Hearing of the meeting lasted for close to an hour, during which 18 people, mostly victims of atypical fractures, told their stories. Most of them asked that a black box warning about the risk for atypical fracture be added to the labels of the drugs and also that the drugs be used only for people with osteoporosis, not osteopenia.

Also during the open hearing, many women mentioned that they had suffered metatarsal fractures before experiencing a femoral fracture and asked that the FDA begin to document such fractures.

The joint panel spent considerable time debating the overall risks and benefits of continuous long-term use, which the FDA defined as greater than 3 to 5 years.

We May Be at the Distal End of the Bell Curve

"I'm still not sure that we are understanding what is going on," said Lewis Nelson, MD, from New York School of Medicine, New York City.

"We may not be seeing the full risk when it comes to any of these issues, given the fact that cancer has a 15-year lead time, and that there are probably people who are more sensitive to fractures and other risks who are presenting early with these issues. If we left the general population on this medication for more and more years we might actually see much more of these adverse effects. We may be at the distal end of a bell curve of atypical fractures and we have to be very careful."

Almut Winterstein, PhD, from the University of Florida in Gainesville, insisted that risks vs benefits could not be evaluated "given that the data are insufficient and the efficacy remains questionable."

Asked whether a drug holiday from bisphosphonates might be beneficial, many panel members voiced uncertainty, again citing lack of definitive data.

Julia Johnson, MD, from the University of Massachusetts Medical School, Worcester, said that a trial to test the utility of a drug holiday is needed.

"Patients are hearing about these adverse effects and are coming to us after 3 years and saying that they want to stop," she said. "We don't have the data to tell us what to do, so let's do trials of drug holidays and follow patients with mild osteoporosis to see if we can determine the optimal length of the holiday."

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