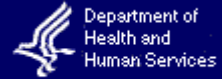


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Early Communication of an Ongoing Safety Review

Bisphosphonates: Alendronate (Fosamax, Fosamax Plus D), Etidronate (Didronel), Ibandronate (Boniva), Pamidronate (Aredia), Risedronate (Actonel, Actonel W/Calcium), Tiludronate (Skelid), and Zoledronic acid (Reclast, Zometa)

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

Publications in a recent issue of *The New England Journal of Medicine* have raised the question about the association of atrial fibrillation with the use of bisphosphonates. FDA has reviewed some safety data and requested additional data to further evaluate the risk of atrial fibrillation in patients who take bisphosphonates.

An article and an accompanying letter to the editor in the May 3, 2007, issue of *The New England Journal of Medicine* describe increased rates of serious atrial fibrillation (defined by the authors as life-threatening or resulting in hospitalization or disability) in two different studies of older women with osteoporosis treated with the bisphosphonates, Reclast and Fosamax. In both studies, more women who received one of the bisphosphonates (Reclast-1.3% or Fosamax-1.5%) reportedly developed serious atrial fibrillation as compared to women who received placebo (Reclast study-0.5%, Fosamax study-1.0%). In both studies, the rates of all atrial fibrillation (serious plus nonserious) were not significantly different between groups treated with bisphosphonate versus placebo.

What does FDA know about this concern?

The FDA reviewed spontaneous post-marketing reports of atrial fibrillation reported in association with oral and intravenous bisphosphonates and did not identify a population of bisphosphonate users at increased risk of atrial fibrillation. In addition, as part of the data review for the recent approval of once-yearly Reclast for the treatment of postmenopausal osteoporosis, the FDA evaluated the possible association between atrial fibrillation and the use of Reclast. Most cases of atrial fibrillation occurred more than a month after drug infusion. Also, in a subset of

patients monitored by electrocardiogram up to the 11th day following infusion, there was no significant difference in the prevalence of atrial fibrillation between patients who received Reclast and patients who received placebo.

Atrial fibrillation is a heart rhythm disorder common in individuals 65 years old and older, the same age range of many of the patients studied in the article published in *The New England Journal of Medicine*. Upon initial review, it is unclear how these data on serious atrial fibrillation should be interpreted. Therefore, FDA does not believe that healthcare providers or patients should change either their prescribing practices or their use of bisphosphonates at this time.

This early communication is in keeping with FDA's commitment to inform the public about its ongoing safety reviews of drugs. FDA is seeking additional data to allow for an in-depth evaluation of the atrial fibrillation issue for the entire class of bisphosphonates. It may take up to 12 months to complete the evaluation at which time FDA will communicate the conclusions and any resulting recommendations to the public. Moreover, FDA is continuing to monitor spontaneous post-marketing reports of atrial fibrillation reported in patients who have taken bisphosphonates.

Bisphosphonates are a class of drugs used primarily to increase bone mass and reduce the risk for fracture in patients with osteoporosis. Bisphosphonates are also used to slow bone turnover in patients with Paget's disease of the bone and to treat bone metastases and lower elevated levels of blood calcium in patients with cancer. There are 7 FDA-approved bisphosphonates: alendronate (Fosamax, Fosamax Plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel W/Calcium), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa).

The FDA urges both healthcare professionals and patients to report side effects from the use of bisphosphonates to the FDA's MedWatch Adverse Event Reporting program.

- on-line at www.fda.gov/medwatch/report.htm
- by returning the postage-paid FDA form 3500 (available in PDF format at www.fda.gov/medwatch/getforms.htm) to 5600 Fishers Lane, Rockville, MD 20852-9787
- faxing the form to 1-800-FDA-0178
- by phone at 1-800-332-1088

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