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FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures

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Safety Announcement

[10-13-2010] The U.S. Food and Drug Administration (FDA) is updating the public regarding information previously communicated describing the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis. This information will be added to the *Warnings and Precautions* section of the labels of all bisphosphonate drugs approved for the prevention or treatment of osteoporosis.

Bisphosphonates are a class of medicines that can be effective at preventing or slowing the loss of bone mass (osteoporosis) in postmenopausal women, thus reducing the risk of common osteoporotic bone fracture. Osteoporotic fractures can result in pain, hospitalization, and surgery.

Atypical subtrochanteric femur fractures are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% of all hip and femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.

The bisphosphonates affected by this notice are only those approved to treat osteoporosis, including [Fosamax](#), [Fosamax Plus D](#), [Actonel](#), [Actonel with Calcium](#), [Boniva](#), [Atelvia](#), and [Reclast](#)¹ (and their generic products).

This notice does not affect bisphosphonate drugs that only are used to treat Paget's disease or high blood calcium levels due to cancer (i.e., [Didronel](#), [Zometa](#), [Skelid](#), and their generic products).

Although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term term bisphosphonate use. FDA will require a new Limitations of Use statement in the *Indications and Usage* section of the labels for these drugs. This statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis.

A Medication Guide will also be required to be given to patients when they pick up their bisphosphonate prescription. This Medication Guide will describe the symptoms of atypical femur fracture and recommend that patients notify their healthcare professional if they develop symptoms.

These actions are part of an ongoing safety review of bisphosphonate use and the occurrence of atypical subtrochanteric and diaphyseal femur fractures, as previously announced in a [Drug Safety Communication on March 10, 2010](#)².

Additional Information for Patients

If you currently take a bisphosphonate, you should:

- Continue to take your medication unless you are told to stop by your healthcare professional.
- Talk to your healthcare professional if you develop new hip or thigh pain (commonly described as dull or aching pain), or have any concerns with your medications.
- Report any side effects with your bisphosphonate medication to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Be aware of the possible risk of atypical subtrochanteric and diaphyseal femur fractures in patients taking bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing bisphosphonates.
- Discuss the known benefits and potential risks of using bisphosphonates with patients.
- Evaluate any patient who presents with new thigh or groin pain to rule out a femoral fracture.
- Discontinue potent antiresorptive medications (including bisphosphonates) in patients who have evidence of a femoral shaft fracture.
- Consider periodic reevaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for over 5 years.
- Report any adverse events with the use of bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Any information provided to MedWatch should be as detailed as possible and include information concerning fracture location/configuration, magnitude of trauma, fracture details (complete or incomplete, bilateral, or comminuted), presence and duration of prodromal thigh or groin pain, duration of bisphosphonate use, relevant medical history, and concomitant use of other medications.

Data Summary

FDA has reviewed all available data, including data summarized in the American Society for Bone and Mineral Research (ASBMR) Task Force report regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures¹, released on September 14, 2010. These atypical femur fractures can occur anywhere in the femoral shaft, from just below the lesser trochanter to above the supracondylar flare, and are transverse or short oblique in orientation without evidence of comminution. The fractures can be complete (involving both cortices) or incomplete (involving the lateral cortex only), and may be bilateral. Many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. The exact incidence of atypical femoral fractures is unknown but appears to account for less than one percent of hip and femoral fractures overall. Therefore, atypical fractures are very uncommon. Although atypical femoral fractures have been predominantly reported in patients taking bisphosphonates, they have also been reported in patients who have not taken bisphosphonates.

The optimal duration of bisphosphonate treatment for osteoporosis is unknown. Bisphosphonate medications approved for the prevention and/or treatment of osteoporosis have clinical trial data supporting fracture reduction efficacy through at least 3 years of treatment and, in some cases, through 5 years. The FDA is continuing its evaluation of data supporting the safety and effectiveness of long term use (greater than 3 to 5 years) of bisphosphonates for the treatment and prevention of osteoporosis and will provide additional guidance at the completion of our review.

In summary, FDA is continuing its ongoing safety review of bisphosphonate use and the occurrence of atypical femur fractures. As of this notice, the FDA is notifying patients and healthcare professionals of new *Warnings and Precautions* information that is being added regarding this risk to the labels of all bisphosphonate products approved for the prevention or treatment of osteoporosis. A new Limitations of Use statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis. In addition, the FDA will require that a Medication Guide be included with all bisphosphonate medications approved for osteoporosis indications to better inform patients of the risk for atypical femur fracture.

References:

1. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research [published online ahead of print]. *Journal of Bone and Mineral Research*. 2010; <http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf>³. Accessed September 17, 2010.

Related Information

- [Bisphosphonates \(marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa\) Information](#)⁴
- [FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures](#)⁵

- [Possible Fracture Risk With Osteoporosis Drugs](#)⁶
- [FDA: Possible increased risk of thigh bone fracture with bisphosphonates](#)⁷
- [Risk Evaluation and Mitigation Strategies \(REMS\) Letters to Sponsor/Applicants Requesting Labeling Changes](#)⁸

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- 1-800-FDA-0178 Fax

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Rockville, MD 20857

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2. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm23891.htm>
3. <http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf>
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