FDA ALERT [1/7/2008]: FDA is highlighting the possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates. Although severe musculoskeletal pain is included in the prescribing information for all bisphosphonates, the association between bisphosphonates and severe musculoskeletal pain may be overlooked by healthcare professionals, delaying diagnosis, prolonging pain and/or impairment, and necessitating the use of analgesics.

The severe musculoskeletal pain may occur within days, months, or years after starting a bisphosphonate. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete resolution. The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.

This severe musculoskeletal pain is in contrast to the acute phase response characterized by fever, chills, bone pain, myalgias, and arthralgias that sometimes accompanies initial administration of intravenous bisphosphonates and may occur with initial exposure to once-weekly or once-monthly doses of oral bisphosphonates. The symptoms related to the acute phase response tend to resolve within several days with continued drug use.

Healthcare professionals should consider whether bisphosphonate use might be responsible for severe musculoskeletal pain in patients who present with these symptoms and consider temporary or permanent discontinuation of the drug.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report/hcp.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

Recommendations and Considerations

- **Healthcare providers should consider whether a patient's severe musculoskeletal pain might be due to bisphosphonate use.** The PRECAUTIONS sections of the full prescribing information for all bisphosphonates includes information about the potential for severe incapacitating bone, joint, and/or muscle pain. Pain is commonly reported in people over the age of 65 years, but a review of the patients' medical and drug therapy history may uncover a temporal association between the onset of severe musculoskeletal pain and bisphosphonate use. Prescribers should consider discontinuing the bisphosphonate if severe pain symptoms occur.

- **Monitor patients who have severe musculoskeletal pain.** Musculoskeletal symptoms may resolve quickly, slowly, or not at all following discontinuation of the bisphosphonate. Alternative causes of the musculoskeletal pain should be considered if symptoms do not lessen or resolve following withdrawal of the bisphosphonate.

- **Consider the benefits and risks of bisphosphonate use.** Bisphosphonates provide benefit in treating and preventing osteoporosis and treating hypercalcemia of malignancy, Paget's disease, and patients with multiple myeloma and bone metastases from solid tumors.

Information for the patient: *Physicians who prescribe bisphosphonates should discuss with their patients:*

- If you develop severe bone, joint, and/or muscle pain while taking a bisphophonate, promptly contact your doctor.

Background Information and Data

Musculoskeletal pain has been reported in clinical trials of bisphosphonates, although the severity of the pain was not always documented. The prescribing information for all bisphosphonates contains information in the Precautions section about severe incapacitating bone, joint, and/or muscle (musculoskeletal) pain. This severe musculoskeletal pain is in contrast to the acute phase response, characterized by fever, chills, bone pain, myalgias, and arthralgias that sometimes accompanies initial administration of intravenous bisphosphonates and may occur with initial exposure to once-weekly or once-monthly doses of oral bisphosphonates. The symptoms related to the acute phase reaction tend to resolve within several days with continued drug use.[1, 2]

In 2005, FDA published findings from a post-marketing case review of bone, joint, and /or muscle pain of a serious nature associated with alendronate and risedronate.[3] The range of time to onset of pain after starting alendronate was 1 day to 52 months (mean = 91 days; median = 14 days). As described in this review, the pain was not isolated to a particular anatomical site. Some patients reported initial focal pain that developed into diffuse pain. In the most severe cases, pain was described as extreme, disabling, or incapacitating, and for some patients the pain was so severe that they were unable to continue their normal activities and required aids for walking. In a search for a cause of the musculoskeletal pain, many patients underwent numerous diagnostic tests with mostly normal findings. Pain was treated with a variety of analgesics including opioids. Many patients experienced relief after the bisphosphonate was discontinued. While relief was immediate after drug discontinuation in some patients, others experienced a slower, partial resolution.

The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.

FDA is further evaluating reports of severe musculoskeletal pain associated with bisphosphonate use. This evaluation will take about 6 months to complete after which FDA will provide to healthcare professionals any new information helpful to the identification and management of severe musculoskeletal pain.

References

1. Adami S, Bhalla AK, Dorizzi R, Montesanti F, Rosini S, Salvagno G, et al. The acute-phase response after bisphosphonate administration. Calcified Tissue International 1987;41:326-331.

2. Bock O, Boerst H, Thomasius FE, Degner C, Stephan-Oelkers M, et al. Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention. Journal of Musculoskeletal and Neuronal Interactions 2007;7:144-148.

3. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. Archives of Internal Medicine 2005;165: 346-347.