

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee Meeting
March 4, 2005

Aredia/Zometa

Questions to the Committee

Background

Pamidronate (Aredia) and zoledronic acid (Zometa) are potent intravenous bisphosphonates. Pamidronate injection is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic metastases of breast cancer and osteolytic lesions of multiple myeloma, as well as hypercalcemia of malignancy (HCM) and Paget's Disease. Zoledronic acid injection is indicated for the treatment of HCM and for the treatment of patients with multiple myeloma and patients with documented metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. Aredia received approval for HCM in 1991, for multiple myeloma in 1995, and for osteolytic bone metastases from breast cancer in 1996. Zometa was approved for HCM in August 2001 and for a broad bone metastasis indication in February 2002.

In 2002, the FDA received 9 spontaneous reports of osteonecrosis of the jaw (ONJ) in patients with malignancy whose treatment regimens included intravenous bisphosphonates. In 2003, the first published reports of ONJ in patients treated with intravenous bisphosphonates appeared in the literature. In a high proportion of cases, there was an association with a recent dental procedure. These patients had no history of radiation therapy to the head and neck.

The Zometa package insert was updated in October 2003 to include information about ONJ in the adverse events section. The Aredia package insert was updated in November 2003. In August 2004, changes were made to the Precautions section of the Zometa label, followed by parallel changes to the Aredia label, regarding ONJ. Novartis issued a Dear Doctor letter in September 2004 regarding ONJ.

Below are excerpts from the current approved product labeling for Zometa and Aredia that include information on osteonecrosis of the jaw in the PRECAUTIONS and ADVERSE REACTIONS sections of the package inserts.

• PRECAUTIONS: Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

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(Questions to the Committee Continued)

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

• **Adverse Events: Post-Marketing Experience**

For Zometa:

Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaws has multiple well-documented risk factors including a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g., anemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged. (See PRECAUTIONS.)

For Aredia:

Cases of osteonecrosis (primarily of the jaws) have been reported since market introduction. Osteonecrosis of the jaws has other well documented multiple risk factors. It is not possible to determine if these events are related to Aredia or other bisphosphonates, to concomitant drugs or other therapies (e.g., chemotherapy, radiotherapy, corticosteroid), to patient's underlying disease, or to other comorbid risk factors (e.g., anemia, infection, preexisting oral disease). (See PRECAUTIONS.)

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Discussion Points

1. Discuss the information content communicated by the FDA and Novartis regarding osteonecrosis of the jaw (ONJ) in patients receiving Zometa and Aredia. Should any other information be communicated?
2. It is known that the potent intravenous bisphosphonates, Zometa and Aredia, bind to bone for many months after infusion. Discuss whether there are data or a strong rationale to support discontinuation of bisphosphonate therapy in patients having invasive dental procedures.
3. For patients who develop ONJ, are there data suggesting that temporary interruption or discontinuation of therapy is indicated?
4. Discuss the potential value of establishing a Registry of patients receiving bisphosphonate to obtain additional information regarding ONJ associated with bisphosphonate use.
5. Discuss additional approaches or studies that should be done to evaluate ONJ and its management.