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**Appendix 7:
Package Insert Revisions
re: Osteonecrosis of the Jaw**

Zometa[®] (zoledronic acid) Injection

and

Aredia[®] (pamidronate disodium) Injection

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Oncologic Drugs Advisory Committee Meeting

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1 Zometa package insert revisions re: osteonecrosis of the jaw

1.1 Package insert dated September 2003

The following paragraph was added under Post-Marketing Experiences in the Adverse Events section:

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 Zometa 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).

1.2 Package insert dated March 2004

The paragraph added in September 2003 was revised in the package insert dated March 2004 to read:

Cases of osteonecrosis (primarily of 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.

1.3 Package insert dated August 2004

A statement re: Osteonecrosis of the jaw was added in the Precautions section and reads as follows:

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.

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.

2 Aredia package insert revisions re: osteonecrosis of the jaw

2.1 Package insert dated October 2003

The following paragraph was added under Post-Marketing Experiences in the Adverse Events section:

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 Zometa or other bisphosphonates, to concomitant drugs or other therapies (e.g., chemotherapy, radiotherapy, corticosteroid), to patients' underlying disease, or to other comorbid risk factors (e.g., anemia, infection, preexisting oral disease).

2.2 Package insert dated August 2004

A statement re: Osteonecrosis of the jaw was added in the Precautions section and reads as follows:

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.

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.