

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

PID# D030552

DATE: November 21, 2003

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SUBJECT: Reaction: Osteonecrosis
Drugs: Pamidronate (Aredia) and Zoledronic Acid (Zometa)

EXECUTIVE SUMMARY

This memorandum concerns a consult request of Nancy Scher, M.D., Medical Reviewer, DODP, regarding zoledronic acid-associated osteonecrosis. Interest in this adverse event was stimulated from a cluster of reports submitted recently to FDA's postmarketing database. Additionally, Novartis Pharmaceuticals, the Sponsor for zoledronic acid, recently submitted a "Special Supplement-Changes Being Effected" to include a *Post-Marketing Experience* subsection of the *Adverse Reactions* section of Zometa's package insert to provide information on osteonecrosis. For completeness, pamidronate is also reviewed as it is given intravenously and is from the same therapeutic class, namely bisphosphonate-mediated bone resorption inhibitors.

Using the FDA's Adverse Event Reporting System database, a search was undertaken to determine the number of osteonecrosis cases associated with zoledronic acid and pamidronate using the MedDRA High Level Term (HLT) Bone Disorders. Cases were included per physician diagnosis of osteonecrosis. The data lock-points are from the date of marketing for the two bisphosphonates, October 31, 1991 for pamidronate and August 20, 2001 for zoledronic acid, until October 6, 2003.

A total of 53 cases, 30 with pamidronate use, 6 with zoledronic acid use, and 17 with both zoledronic acid and pamidronate use, were found in AERS. All cases, except for two, were domestic. No patients experienced serious sequelae resulting in hospitalization or death.

Because both medications are from the same therapeutic class and it was difficult to determine primary suspect drug, the cases are analyzed together according to medication receipt (see Table 1).

In cases in which the patient received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid.

Though only cases with use of intravenous bisphosphonates were evaluated here, we also intend to reviewing cases involving oral bisphosphonates and osteonecrosis to determine whether this is a drug class effect.

Our postmarketing data indicate a safety concern exists for zoledronic acid and pamidronate, in reference to osteonecrosis, despite the confounders in these cases. The zoledronic acid and pamidronate labeling should be amended to note that there have been postmarketing cases of osteonecrosis associated with these medications. Additionally, the labeling should state that the recovery time is not immediate, even after discontinuing the bisphosphonates as the half-lives are long. Prescribers should alert patients to report any jaw pain and referral to a dentist or oral surgeon for appropriate treatment is necessary, once bone metastases is ruled out.

BACKGROUND

This memorandum concerns a consult request of Nancy Scher, M.D., Medical Reviewer, DODP, regarding zoledronic acid-associated osteonecrosis. Interest in this adverse event was stimulated from a cluster of reports submitted to the FDA recently.

Additionally, Novartis Pharmaceuticals, the Sponsor for pamidronate and zoledronic acid, recently submitted a “Special Supplement-Changes Being Effected” to include a *Post-Marketing Experience* subsection of the *Adverse Reactions* section of Zometa’s package insert to provide information on the adverse reaction as follows:

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 co-morbid risk factors (e.g., anemia, infection, pre-existing oral disease).

Regarding their pharmacologic action, pamidronate and zoledronic acid are classified as bisphosphonates that act on the bone to inhibit resorption. As stated per the Sponsor’s package inserts for both bisphosphonates, several factors are thought to contribute to this action, although their antiresorptive mechanism is not completely understood.^{1,2} *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone.¹ Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. Hence, these actions interrupt the normal homeostasis of bone turnover and resorption.

LABELING

Currently, osteonecrosis is not labeled as an adverse reaction in neither Aredia’s nor Zometa’s package insert.

METHODS

Selection of Cases from AERS

An AERS database search was undertaken to determine the number of osteonecrosis cases associated with zoledronic acid and pamidronate use using the MedDRA High Level Term (HLT) Bone Disorders. Cases were included per physician diagnosis of osteonecrosis.

The data lock-points are from the date of marketing for the two bisphosphonates, October 31, 1991 for pamidronate and August 20, 2001 for zoledronic acid, until October 6, 2003.

RESULTS

Table 1 summarizes the characteristics of 53 zoledronic acid and pamidronate cases. These cases are presented in one table because their efficacy is linked to the same mechanism. Additionally, many patients received both bisphosphonates; thus, difficulty lies in classifying the cases according to bisphosphonate use as the half-lives of the bisphosphonates are long.^{1,2}

Table 1. Demographics for Pamidronate and Zoledronic Acid Cases

<u>Selected Characteristics</u>	N=53
<u>Approval date</u>	
Pamidronate	10/31/1991
Zoledronic acid	8/20/2001
<u>Reporting year</u>	2001-2003
<u>Country of origin</u>	
Domestic	51
Foreign	2
<u>Reporter</u>	
Dentist	5
Oral surgeon	42
Oncologist	4
Healthcare professional	2
<u>Age</u>	N=47
Range (years)	40-82
Mean	65
Median	65
<u>Sex</u>	N=51
Female	34
Male	17
<u>Cancer type</u>	
Breast	19
Multiple myeloma	20
Chronic myelocytic leukemia	1
Colon	1
Prostate	3
Uterine	1
None	1
Unknown	6
<u>Bisphosphonate treatment</u>	
Pamidronate only	30
Zoledronic acid only	6
Pamidronate & zoledronic Acid	17
<u>Reaction onset</u>	
Pamidronate only	N=12
Range (days)	272-1722
Mean	981
Median	898
Zoledronic acid only	n=4
Range (days)	163-441
Mean	318
Median	333
<u>Site of osteonecrosis</u>	
Dental cavity	52
Femoral head	1

Table 1. Demographics for Pamidronate and Zoledronic Acid Cases (Continued)

<u>Confounding factors*</u>	N=39
Chemotherapy	20
Radiation	5
Steroids	16
Extraction	15
Bone marrow transplant	3
<u>Treatment modalities</u>	N=30
Debridement	3
Debridement with tooth extraction	1
Surgery (maxillectomy, mandibulectomy, or sequestrectomy)	23
Oral antral fistula	3
<u>Outcome*</u>	
Hospitalized	0
Death	0
Non-Serious	53
Not recovered	5

* Not mutually exclusive

Summary of Cases

A total of 53 cases, 30 with pamidronate use only, 6 with zoledronic acid use only, and 17 with both zoledronic acid and pamidronate use, were found in AERS. All cases, except for two, were domestic. No patients experienced serious sequelae resulting in hospitalization or death.

Because both medications are from the same therapeutic class and there was difficulty in determining the primary suspect drug, the cases are analyzed together. In cases in which patients received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid.

Pertaining to patient demographics, the average patient age was elderly at 65 years, and the ratio of females to males was 2:1. For the two largest treatment groups, 20 (38%) patients received either bisphosphonate for osteolytic lesions secondary multiple myeloma and 19 ((36%) for bone metastases arising from breast cancer. Uterine, prostate, and colon cancers and chronic myelocytic leukemia comprised the remaining malignancies.

All reporters, except in four cases, were oral surgeons or dentists. With respect to their medical specialty, all cases, except for one, stated the site of osteonecrosis was the jaw. The one exception was a foreign case that described osteonecrosis of the femoral head. For the cases involving the jaw, the cases often came to the attention of an oral surgeon or dentist for nonhealing of bone following dental extractions. No cases mentioned dental caries as a cause of osteonecrosis.

As shown in Table 1, about three-quarters of the patients had received another treatment besides bisphosphonates, such as bone marrow transplant, chemotherapy, radiation, or steroids (dexamethasone and prednisone) for their cancer.

Only one patient in our case series received a bisphosphonate for a noncancerous indication, namely post-menopausal osteoporosis. This patient received treatment previously with alendronate.

Below are three index narratives, two pertain to osteonecrosis of the oral cavity and one to osteonecrosis of the femoral head:

Index narrative: 4187827-9, Domestic

A 72-year old female was placed on zoledronic acid (dose and frequency not specified) for postmenopausal osteoporosis on May 11, 2003 and developed osteonecrosis of the right mandible on August 20, 2003. Her diagnosis was confirmed through two biopsies, CT scan and X-ray. Restorative treatment consisted of multiple surgeries and antibiotic treatment and her care was ongoing at the time of the report. The patient had a wisdom tooth extraction and dental implants. Her medical history also included hypothyroidism which was treated with levothyronine, gastroesophageal reflux disease which was treated with esomeprazole, hyperlipidemia which was treated with simvastatin, and osteoarthritis for which treatment not stated. For osteoporosis, she has received alendronate, raloxifene, hormone replacement therapy, and salmon calcitonin.

Index narrative 4148113-6, Domestic

A 42-year old female started receiving pamidronate 90 mg (no frequency or stop date provided) for metastatic breast cancer in February 2000. After a dental extraction (date unspecified), the

patient failed to heal in December 2001, despite debridement and antibiotics. An examination by an oral surgeon revealed exposed bone of the right posterior mandible and reported osteonecrosis of the mandible. The patient was not treated with any radiation, but did receive steroid therapy (no dates, duration, or name of steroid were provided). In March 2002, she initiated treatment with zoledronic acid. As of May 19, 2003, the patient continued to have some numbness of the jaw and had trouble opening her mouth wide because of the numbness. Her other medications included anastrozole for breast cancer.

Index narrative 3830380-7, Foreign

A female patient of unknown age was treated with pamidronate 90 mg every four weeks since 1998 (exact date unspecified) for metastatic colon carcinoma. Her CT scan demonstrated normal findings of the femoral head “at this time”. In June 2001, treatment was changed to zoledronic acid 4 mg every 4 weeks without any problems or adverse drug reactions. In November 2001, another CT scan revealed total necrosis of the femoral head. No other medical history or medications were stated.

DISCUSSION

Unlike most case series in which the cases were from numerous reporters, this case series was unique in that most of cases were reported by oral surgeons and dentists. One oral surgeon, in particular, submitted almost half of the cases in this review.³ Another oral surgeon, who submitted several cases, recently published on this issue. Because of the reporter’s occupation, the site of osteonecrosis detected in all cases, except for one, was the jaw. These cases often came to the attention of an oral surgeon or dentist for nonhealing of bone following dental extractions, exposed bone in oral cavity, osteomyelitis, chronic maxillary sinusitis secondary to necrotic bone, and fistulae of various types. Patients often complained of jaw pain, and upon presentation, the bone did not bleed when traumatized appropriately for diagnostic purposes. In some cases, necrotic bone was diagnosed based on radiographic, clinical, and histopathologic evidence. No mention of bone metastases as the cause of jaw pain was made.

It is interesting that the sites of osteonecrosis were in the oral cavity and were diagnosed by oral surgeons and dentists per complaints of jaw pain by patients in almost all of the cases. An explanation for this is that the oral cavity is the site most often exposed to the external environment via the teeth and oral mucosa.³ With disturbance of the dental environment by periodontal inflammation, abscesses, and dental extractions, the rate of bone turnover increases as part of the repair process. Over one-third of these cases were a result of nonhealed dental extractions.

The sequelae of the osteonecrosis were severe in a number of cases. Once detected, treatment in all cases was necessary. In some cases, debridement or a course of antibiotics were sufficient to treat necrotic area, but many patients underwent extensive surgical procedures, such as resection of the mandible or maxilla, or sequestrectomy. In five cases that reported this information, the necrotic area still had not healed, presumably because of impaired bone turnover and resorption. The recovery time can be prolonged and painful as the half-lives of the bisphosphonates in the bone are long.^{1,2}

Analysis of the osteonecrosis cases with zoledronic acid and pamidronate use suggests that there is a causal association between the adverse event in question and the medications, despite incomplete medical histories on the patients and confounders, such as radiation, chemotherapy,

and steroid use.^{4,5,6} Although the etiologic cause may be multifactorial as almost all of these patients had cancer and received chemotherapy, radiation and steroids, the common denominator is that these patients were treated with bisphosphonates. These therapies can either impair the immune system response by increasing the risk for infection or disturb the integrity of the bone matrix.

Our one noncancerous case involving post-menopausal osteoporosis suggests that zoledronic acid and pamidronate may be causally associated with osteonecrosis. Not included in our analysis as it was communicated orally, one reporter, an oral surgeon, stated that he was aware of three patients, without malignancy and no receipt of chemotherapy, who experienced osteonecrosis associated with bisphosphonate use. Two patients received zoledronic acid treatment and one patient was administered alendronate. Although it is not discussed here, we have noted alendronate cases associated with osteonecrosis in our AERS database and we intend to review oral bisphosphonates for cases of osteonecrosis to determine whether this may be a drug class effect.

CONCLUSIONS

Our postmarketing data indicate a safety concern exists for zoledronic acid and pamidronate, in reference to osteoporosis, though there are confounders in these cases. The zoledronic acid and pamidronate labeling should be amended to note that there have been postmarketing cases of osteonecrosis associated with these medications. Additionally, the labeling should state that the recovery time can be prolonged, even after discontinuing the bisphosphonates as the half-lives are long. Prescribers should alert patients to report any jaw pain and once bone metastases is ruled out, referral to a dentist or oral surgeon for appropriate treatment is necessary.

We also intend to review oral bisphosphonates for cases of osteonecrosis to determine whether this may be a class effect.

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¹ Zometa product label. East Hanover, N.J.: Novartis Pharmaceuticals, 2002. (Accessed November 1, 2003, at <http://www.us.zometa.com/info/about/index.jsp>.)

² Aredia product label. East Hanover, N.J.: Novartis Pharmaceuticals, 2002. (Accessed November 1, 2003, at <http://www.pharma.us.novartis.com/products/name/aredia.jsp>.)

³ Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg.* 2003 Sep;61(9):1115-7.

⁴ Sung EC, Chan SM, Sakurai K, et al. Osteonecrosis of the maxilla as a complication to chemotherapy: a case report. *Spec Care Dentist.* 2002 Jul-Aug;22(4):142-6.

⁵ Larson DL, Lindberg RD, Lane E, Goepfert H. Major complications of radiotherapy in cancer of the oral cavity and oropharynx. A 10 year retrospective study. *Am J Surg.* 1983 Oct;146(4):531-6.

⁶ Mirzai R, Chang C, Greenspan A, Gershwin ME. The pathogenesis of osteonecrosis and the relationships to corticosteroids. *J Asthma.* 1999;36(1):77-95.

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/s/

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