DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**ODS POSTMARKETING SAFETY REVIEW**	
TO: **Richard Pazdur, M.D., Director, Division of Oncology Drug Products (DODP), HFD-150**	**FROM:** **Jennie Chang, Pharm.D. , Safety Evaluator, Division of Drug Risk Evaluation (DDRE), HFD-430**	**ODS PID #** **D040283** **August 25, 2004**
DATE REQUESTED: May 6, 2004	**REQUESTOR/Phone #:** **Nancy Scher, M.D., DODP, HFD-150** **(301) 594-5745**	
DATE RECEIVED: May 6, 2004		
DRUG (Est): Pamidronate, zoledronic acid, alendronate, risedronate	**NDA/IND #** **21-223, 20-036, 20-560, 20-835**	**SPONSOR**: **Novartis Pharmaceuticals, Merck, Proctor and Gamble Pharmaceuticals**
DRUG NAME (Trade): Aredia (pamidronate) and Zometa (zoledronic acid), Fosamax (alendronate), Actonel (risedronate)	**THERAPEUTIC CLASSIFICATION: Bisphosphonates**	
EVENT: Osteonecrosis and osteomyelitis		

Executive Summary:

This memorandum is an update of a consult that was completed on November 21, 2003 (see DFS for consult) by the Office of Drug Safety regarding osteonecrosis associated with two intravenous bisphosphonates, pamidronate and zoledronic acid.[1] Interest in this adverse event was stimulated from a cluster of reports submitted recently to FDA's postmarketing database in 2003. Additionally, Novartis Pharmaceuticals, the sponsor of zoledronic acid, 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.

In this consult, we reviewed new cases of osteonecrosis associated with pamidronate and zoledronic acid that have been submitted since the previous consult. Osteomyelitis cases were included as a significant number of patients presented with a mixed osteonecrosis and osteomyelitis diagnosis. We also evaluated cases of osteonecrosis associated with oral bisphosphonates, namely alendronate and risedronate to determine if this is a therapeutic class effect.

Using the FDA's Adverse Event Reporting System database, a search was undertaken to determine the number of osteonecrosis cases associated with the four bisphosphonates using the MedDRA High Level Term (HLT) Bone Disorders. Cases were included per physician diagnosis of osteonecrosis and osteomyelitis. For pamidronate and zoledronic acid cases, the data lock-points are from October 6, 2003 (data termination point of the previous consult), until May 24, 2004. These cases that were analyzed during this time period were added to ones from the previous consult; thus, a cumulative review of the osteonecrosis cases is presented herein. The alendronate and risedronate cases were also reviewed for the time period from their marketing approvals, September 29, 1995 and March 27, 1998, respectively, until May 24, 2004.

As with the previous consult, the pamidronate and zoledronic acid cases were analyzed together because both bisphosphonates are indicated for the same patient population and most patients received the two bisphosphonates. In cases in which the patient received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid, except for one patient who received two bisphosphonates on an alternating schedule.

A total of 139 cases, 47 (34%) with pamidronate use, 33 (24%) with zoledronic acid use, and 59 (42%) with both zoledronic acid and pamidronate use, were found in AERS. Less than ten percent of the cases were from foreign sources. For the oral bisphosphonates, 12 alendronate cases were related to osteonecrosis, and only one case was identified for risedronate. It should be noted that many cases did not provide complete information as to other confounding factors for osteonecrosis and osteomyelitis, treatment types for osteonecrosis and osteomyelitis, or outcomes.

Our search yielded mostly cases of osteonecrosis, but there was also a fraction (6%) of patients who had developed osteomyelitis secondary to pamidronate and zoledronic acid use and about one-quarter of the patients who had presented with a

mixed picture of osteomyelitis and osteonecrosis. For the alendronate and risedronate cases, all patients presented with osteonecrosis at time of diagnosis. Table 1 summarizes the characteristics of 139 zoledronic acid and pamidronate cases and Table 2 describes the osteonecrosis cases associated with alendronate use.

Since this issue was first reviewed, our update has identified more cases of osteonecrosis and osteomyelitis associated with pamidronate and zoledronic acid. Additionally, our AERS search has yielded osteonecrosis cases involving oral bisphosphonates, specifically alendronate and risedronate. The previous consult only focused on intravenous bisphosphonates.

Of interest, one reporter, an oral surgeon, provided us with a substantial number of cases associated with zoledronic acid and pamidronate use, which have since been published.[2] This same reporter submitted nine alendronate cases and the one risedronate case, all involving osteonecrosis of the jaw. As with the previous consult, most of the cases were submitted to us by oral surgeons.

Our postmarketing data indicate a safety concern exists for zoledronic acid and pamidronate, in reference to osteonecrosis, despite the confounders in these cases. It appears that osteonecrosis may be a class effect as exhibited by alendronate cases, in addition to zoledronic acid and pamidronate. Based on our recommendations from the previous consult[1], changes to the product label for zoledronic acid have been made to include language about osteonecrosis, but more language is necessary to highlight this adverse event because it is associated with the therapeutic class of bisphosphonates, as evidenced by our case analysis. This language should also be included in the other bisphosphonate product labels, namely those of alendronate, risedronate, and pamidronate. The case analysis of the intravenous bisphosphonates also revealed that some of the patients presented with a mixed diagnosis of osteomyelitis and osteonecrosis and in some cases, only osteomyelitis. Thus, language about this should be included in the *Post-Marketing Experience* subsection of the *Adverse Reactions*.

Search Date: From their respective marketing approval dates until May 24, 2004. The various marketing approval dates for the bisphosphonates are as follows:

alendronate	September 29, 1995
pamidronate	October 31, 1991
risedronate	March 27, 1998
zoledronic acid	October 6, 2003

Search Criteria: Using the AERS database, the following MedDRA term was applied: High Level Term (HLT) Bone Disorders. The cases were then individually reviewed and included in the analysis if a diagnosis of osteonecrosis was recorded.

Search Results:

A total of 139 cases, 47 (34%) with pamidronate use, 33 (24%) with zoledronic acid use, and 59 (42%) with both zoledronic acid and pamidronate use, were found in AERS. Less than 10% of the cases were from foreign sources. For the oral bisphosphonates, 12 alendronate cases pertained to osteonecrosis, and only one case was found for risedronate. It should be noted that many cases did not provide complete information as to other confounding factors for osteonecrosis, treatment types for osteonecrosis, or outcomes.

Intravenous Bisphosphonates: Pamidronate and zoledronic acid

Table 1 summarizes the characteristics of 139 zoledronic acid and pamidronate cases. Following the same format as the previous consult, 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] In cases in which patients received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid, except for one case in which the patient alternated between zoledronic acid and pamidronate. A significant number of zoledronic acid and pamidronate cases were submitted, but the data collected by the sponsor was incomplete for a number of variables (see Novartis' briefing package submitted on June 21, 2004).

Pertaining to patient demographics for the pamidronate and zoledronic acid cases, the average patient age was 63 years, and the majority of the patients were of female gender. For the two largest treatment groups, 60 (43%) patients received either bisphosphonate for osteolytic lesions secondary multiple myeloma and 52 (37%) for bone metastases arising from breast cancer. Lung, uterine, prostate, and colon cancers, and chronic myelocytic leukemia comprised the other malignancies. Only one patient in our case series received a bisphosphonate for a noncancerous indication, which was post-menopausal osteoporosis. This patient received treatment previously with alendronate.

Slightly more than two-thirds of the patients were diagnosed with osteonecrosis and about one-quarter had a mixed diagnosis of osteomyelitis and osteonecrosis. Only six percent of the patients presented with osteomyelitis. The reaction onset in these patients extended past one year, with the duration of onset longer for pamidronate than zoledronic acid. The duration of onset of osteonecrosis and osteomyelitis was about six years for pamidronate and 14 months for zoledronic acid. For patients receiving both bisphosphonates, the average duration of reaction onset was over three years. Site of osteonecrosis/osteomyelitis was the jaw for all cases, except for one which was the femoral head.

Factors which may have contributed to osteonecrosis/osteomyelitis include chemotherapy, radiation, steroids, thalidomide, and bone marrow transplant. Over half of the patients received chemotherapy. Although 19 (14%) patients were radiated at their tumor site, only one patient was radiated in the jaw, specifically, the mandible. About half of the patients had received steroids.

Development of osteonecrosis/osteomyelitis occurred in 57 (41%) patients after a dental procedure consisting of a tooth extraction or root canal. Detection of osteonecrosis occurred after spontaneous tooth loss in four patients.

There were only five cases in which the patient reported as recovered from the event. Fourteen patients had improved outcomes, but had not fully recovered at the time of report. Two patients expired, but the cause of death was not stated in one case, which was reported by a foreign source. In the second case, one patient died from cardiac failure, not related to bisphosphonate treatment. For the remainder of the other cases, outcomes were not provided. The treatment modalities of osteonecrosis varied. Some patients received antibiotics and debridement, but others received more invasive types of treatment, including surgical resections, as shown in Table 1.

Oral bisphosphonates: Alendronate and Risedronate

The demographics and clinical characteristics of the alendronate cases are presented in Table 2. For risedronate, there was only one case reported. The AERS search yielded only one case of risedronate, it is presented below. For alendronate, 12 cases were identified, nine of which were from domestic sources and were reported by an oral surgeon who had treated these patients in his practice. This oral surgeon also identified a large number of pamidronate and zoledronic acid cases. Treatment indication for alendronate therapy was osteoporosis for all cases. All patients were elderly, as the average age was 70 years and most patients were of female gender. Outcomes and concomitant medications were not provided. Three-quarters of the patients received sequestrectomies for treatment of their osteonecrosis.

One osteonecrosis case involving risedronate was identified. An 80 year-old female had received risedronate (dose and duration, and outcome were not stated) for osteoporosis and subsequently developed necrotic bone of the left mandible following tooth extraction. Of note, the reporter is the same oral surgeon who reported all of the domestic alendronate cases.

Discussion:

This consult is an update of a prior consult; thus, please refer to the discussion points raised previously.[1]

Since this issue was first reviewed, our update has identified more cases of osteonecrosis associated with pamidronate and zoledronic acid. Additionally, our AERS search has identified osteonecrosis cases involving oral bisphosphonates, specifically alendronate and risedronate. The previous consult only focused on intravenous bisphosphonates. One reporter, an oral surgeon, submitted all nine domestic alendronate cases and one risedronate case, all involving osteonecrosis of the jaw. Of interest, this same reporter provided us with a substantial number of cases associated with zoledronic acid and pamidronate use, which have since been published.[2] As with the previous consult, most of the cases were submitted to us by oral surgeons.

The cases involving oral bisphosphonates suggest that this adverse event may be a class event, rather than limited to intravenous bisphosphonates. Despite the fact that in the majority of the cases, osteonecrosis was detected in the jaws and the cases were submitted by the same reporter, the common factor of alendronate treatment dismisses the idea that other variables may have influenced this adverse event. It should be noted that oral bisphosphonates are not as potent as the intravenous bisphosphonates, but they share the mechanism of action.

Although the issue involving the preponderance of the number of cases reported by oral surgeons and dentists was discussed in the prior consult, there remains a concern that reporter bias may affect the validity of the reports. The seriousness of the cases, along with the morbidity, does serve to discount this concern. Furthermore, we have received cases from other sources, such as dentists, oncologists, other oral surgeons. A fraction of these cases were also submitted by foreign reporters.

Conclusion:

Our postmarketing data indicate a continuing safety concern exists for the oral and intravenous bisphosphonates, despite the confounders in these cases. Based on our recommendations from the previous consult[1], changes to the product label for zoledronic acid have been made to include language about osteonecrosis, but more language is necessary to highlight this adverse event as this is associated with the therapeutic class of bisphosphonates, as evidenced by our case analysis. This language should also be included in the other bisphosphonate product labels, namely those of alendronate, risedronate, and pamidronate. The case analysis of the intravenous bisphosphonates also revealed that some of the patients presented with a mixed diagnosis of osteomyelitis and osteonecrosis and in some cases, only osteomyelitis. Thus, language about this should be included in the *Post-Marketing Experience* subsection of the *Adverse Reactions*.

Reviewer's Signature / Date:	
Team Leader's Signature / Date:	**Division Director's Signature / Date:**

Table 1. Demographics for Pamidronate and Zoledronic Acid Cases from Marketing Approval until May 24, 2004

Selected Characteristics	n=139
Approval date	
Pamidronate	10/31/1991
Zoledronic acid	8/20/2001
Reporting year	2001-2004
Geographic region of reporting source	
Domestic	120 (92%)
Foreign	19 (8%)
Age	N=132
Range (years)	34-88
Mean	63.2
Median	65
Gender	
Female	79 (57%)
Male	58 (42%)
Unknown	2 (1.4%)
Cancer type	
Breast[1]	52 (37%)
Multiple myeloma[3]	60 (43%)
Prostate	11 (8%)
Lung	2 (1%)
Chronic myelocytic leukemia	1
Colon	1
Lymphoma	1
Uterine	1
None	1
Unknown	9 (4%)
Diagnosis	
Osteonecrosis	97 (70%)
Osteomyelitis	9 (6%)
Mixed, osteomyelitis and osteonecrosis	33 (24%)
Bisphosphonate treatment	
Pamidronate only	47 (34%)
Zoledronic acid only	33 (24%)
Pamidronate & zoledronic Acid	59 (42%)
Reaction onset	
Pamidronate only (n=45)	n=23
Range, days	272-4211
Mean	2233
Median	2233
Zoledronic acid only (n=22)	n=14
Range, days	60-703
Mean	459
Median	441
Pamidronate and zoledronic acid together	n=34
Range, days	180-2433
Mean	1267
Median	1180
Site of osteonecrosis	
Jaw	138
Femoral head	1

[1] One patient had a concurrent diagnosis of ovarian cancer.
[2] One patient was receiving an experimental medication.
[3] One patient had a concurrent diagnosis of prostate cancer.

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

Contributory factors*	
Chemotherapy	78 (56%)
Radiation[1]	19 (14%)
Steroids	67 (48%)
Thalidomide	17 (12%)
Bone marrow transplant	6 (4%)
Dental procedure leading to osteonecrosis	
Tooth extraction, root canal	57 (41%)
Spontaneous tooth loss	4 (3%)
Treatment modalities*	
Antibiotics	18 (13%)
Maxillectomy	6 (4%)
Debridement	15 (11%)
Oral surgery, unspecific	10 (7%)
Tooth extraction	10 (7%)
Sequestrectomy	9 (6%)
Mandibulectomy	9 (6%)
Oxygen	1
Oral antral fistula	3
Ostectomy	1
Root canal	2
Outcome*	
Improved	14
Recovered	5
Unknown	97
Not recovered	21
Death	2

* Not mutually exclusive

[1] Only one patient had radiation to the oral cavity (mandible).

Table 2. Demographics for Alendronate Cases[a]

Selected Characteristics	n=12
Approval date	9/29/1995
Reporting year	1997-2004
Country of origin	
Domestic	9
Foreign	3
Age	
Range (years)	59-82
Mean	70.3
Median	70
Gender	
Female	10
Male	2
Treatment indication	
Osteoporosis	12
Site of osteonecrosis	
Dental cavity	9
Femoral head	2
Vertebrae	1
Treatment modalities	
Sequestrectomy	9
Unknown	3
Concomitant medications	
Unknown	12
Outcome	
Unknown	11
Recovered	1

[a] One patient was also receiving zoledronic acid concomitantly.

cc: NDA 21-223, 20-036, 20-560, 20-835
HFD-150 Pazdur / Scher / Staten / Ibrahim
HFD-510 Orloff / Colman / Hedin / Stadel
HFD-430 Avigan / Chang / Green / Birdsong

[1] Chang J. Consult: Pamidronate- and zoledronic acid- osteonecrosis. DFS entry on November 21, 2003.

[2] Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 62:527-534, 2004.

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/s/

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DRUG SAFETY OFFICE REVIEWER

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