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BACKGROUND INFORMATION
FOR
Oncologic Drugs Advisory Committee Meeting
March 4, 2005

Zometa® (zoledronic acid) Injection

and

Aredia® (pamidronate disodium) Injection

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Table of contents

List of tables

List of Appendices

Appendix 9: Dear Doctor Letter

Appendix 10: Advisory Board Attendees

Appendix 11: Expert Panel Recommendation for the Prevention, Diagnosis and Treatment of Osteonecrosis of the Jaw

1 Executive summary

Osteonecrosis of the jaw (ONJ) is a vaguely defined and poorly understood clinical entity. The etiology and pathogenesis of ONJ are not clear, but multiple risk factors are involved, 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). The management of ONJ can be challenging, though patients' discomfort can be reduced with appropriate medical intervention.

ONJ in cancer patients treated with bisphosphonates was first reported to Novartis in December 2002. Novartis took immediate action to collect detailed information on the reported cases in an effort trying to understand ONJ. Subsequently, Novartis took various steps to enhance the awareness of ONJ among healthcare professionals and patients, including revision of patient informed consent for clinical trials, dissemination of a patient brochure on ONJ and distribution of a Dear Doctor letter (Appendix 9). Novartis also revised the package inserts for both Aredia® and Zometa® to provide information on post-marketing reports of ONJ and guidance on the prevention and treatment of this condition.

Novartis has carefully reviewed and analyzed the available data on ONJ, which are included in this submission. The background rate of ONJ in cancer patients not treated with a bisphosphonate is unknown. In addition, the number of ONJ cases in clinical trials is small. The majority of information on this condition is derived from uncontrolled case series. Therefore, a causal relationship between bisphosphonate therapy and ONJ cannot be established.

In order to protect patients, there is a need to continue efforts to understand this condition in cancer patients, including the identification of risk factors for ONJ. In addition, clinical data may be required for healthcare professionals to develop treatment plans for patients at risk for ONJ, to optimize management of patients with ONJ while on bisphosphonate therapy, and to guide physicians on how to change treatment plans if patients encounter risk factors such as a need for dental extraction during bisphosphonate treatment.

Zometa and Aredia provide significant benefit to patients with multiple myeloma and bone metastases from solid tumors by reducing the risk of serious skeletal complications. When assessing benefit/risk, it is important to consider the critical difference between Zometa and Aredia in that Zometa has a broader range of activity in tumors where Aredia is inactive. Novartis is committed to further the safety of these patients by continuing to investigate ONJ and educate patients and healthcare professionals about this condition and its management. We hope the meeting with the FDA and Advisory Committee Members will provide us with additional insight and guidance for our future activities in understanding ONJ in cancer patients.

2 Background on Zometa

Zoledronic acid (Zometa®) is a third generation nitrogen-containing bisphosphonate developed to treat patients with multiple myeloma or solid tumor and bone metastases, where skeletal complications frequently occur due to bone lesions (Coleman 1997). Bone metastases are either osteolytic (osteoclastic) or osteosclerotic (osteoblastic). Osteolytic metastases are caused by tumor associated cytokine activation of osteoclasts leading to increased bone resorption, bone lesion, and eventually bone complications (Mundy 2001; Mundy 2002). The pathogenesis underlying osteosclerotic metastases is less well defined but tumor related endothelin secretion has been implicated as an important pathogenetic factor (Guise 2004; Mundy. 2003). Tumor cells activate osteoclasts, which cause excessive bone resorption leading to bone lesions and subsequently skeletal complications. It is worth noting the osteolytic process is also active in the osteoblastic lesions as evidenced by increased bone resorption markers in patients with osteoblastic lesions (Demers et al, 2000), and an increase in the number of osteoclasts at sites of invasion by prostate cancer cell into the bone (Yonou et al, 2004). Zometa acts primarily by inhibiting osteoclasts by inducing apoptosis and preventing the maturation and activation of osteoclasts, thus causing suppression of bone resorption (Green 2002).

Bone lesions occur in almost all patients with Durie-Salmon stage III multiple myeloma and in the majority of patients with advanced breast or prostate cancer, where bone metastases occur in 65-75% of the patients (Coleman 1997, Coleman 2002). These patients frequently experience bone complications known as skeletal related events (SREs), which include pathological or clinical fractures, spinal cord compression, surgery to bone and hypercalcemia of malignancy (HCM). Approximately half of the patients experience one or more SREs during their disease course (Theriault 1999; Lipton 2000), which constitutes a significant clinical problem, as the SREs are painful and sometimes debilitating complications that can seriously limit patient mobility and cause deterioration in patients' quality of life (Coleman 1997).

While several therapeutic options exist for the management of bone metastases such as local radiation and systemic hormonal or chemotherapy, patients with multiple myeloma or bone metastases continued to experience skeletal complications prior to the introduction of bisphosphonate, which has now become the mainstay for the prevention of skeletal complications in these patients. Randomized clinical trials with 90 mg pamidronate (Aredia) demonstrated significant clinical benefit of this agent showing reduction of skeletal morbidity in patients with multiple myeloma (Berenson et al, 1996), breast cancer patients undergoing chemotherapy (Protocol 19, Hortobagyi et al, 1996) or hormonal therapy (Protocol 18, Theriault et al, 1999). In the multiple myeloma study (Protocol 12), Aredia 90 mg infused over 4 hrs monthly for 9 cycles reduced the proportion of patients with any SRE from 41% to 24%, significantly delayed the time to fist SRE, decreased patient's pain scores, and maintained the quality of life in these patients (Berenson et al, 1996). In the breast cancer trials (Protocol 18 and 19), Aredia 90 mg infused over 2 hrs for 12 cycles also reduced the proportion of patients with any SREs from 65% 46% (Protocol 19) or from 67% to 56% (Protocol 18). The treatment also significantly delayed the time to first SRE by nearly 7 months (P19) or 3 months (P18). Both studies demonstrated a decrease in patient's pain scores and analgesic consumption, and [Study 0019] also showed a better ECOG performance

status in the Aredia group than the placebo group (Hortobagyi 1996, Hortobagyi 1998; Theriault 1999, Clinical Study Report for P18 and P19 – core+extension). Data from these clinical trials established Aredia as the standard of care for patients with multiple myeloma bone metastases from breast cancer with bone metastases as recommended by ASCO guidelines (Hillner 2000, Hillner 2003; Berenson 2002).

The phase III program for Zometa consists of 3 large randomized clinical trial involving > 3,000 patients with multiple myeloma or breast cancer [Study 0010], prostate cancer [Study 0039], or lung cancer and other solid tumors [Study 0011]. These trials were the basis for documenting effectiveness in bone metastases that led to its marketing authorization globally. [Study 0010] demonstrates that 4 mg Zometa infused over 15 min every 3-4 weeks was at least as effective as 90 mg Aredia in terms of proportion of patients with any SREs (Rosen et al, 2001). Exploratory multiple-event analyses with the Anderson-Gill approach suggested that Zometa reduces the risk of developing one or more SREs by an additional 20% as compared to Aredia in the subset of patients with breast cancer (Rosen et al, 2003a). Furthermore, a retrospective analysis of [Study 0010] in the subset of breast cancer patients with one or more lytic lesions indicated that Zometa is more effective than Aredia in this patient population, reducing the proportion of patients with any SRE by an additional 10% (48% for Zometa and 58% for Aredia patients, p=0.058); and reducing the risk of developing one or more SREs by an additional 30% in comparison with Aredia (p=0.01) (Rosen et al, 2004).

Clinical trials with Zometa have also demonstrated for the first time that the efficacy of a bisphosphonate in prostate cancer (Saad et al, 2002). Clinical trials for Aredia failed to demonstrate clinical benefit in this patient population (Small et al, 2003), where Zometa was shown to reduce the proportion of patients with any SRE from 49% to 38%, and delay the time to first SRE by more than 5 months (Saad et al, 2004). In patients with in lung cancer and solid tumors other than breast or prostate cancer, Zometa reduced the proportion of patients with SRE from 46% to 39%, and delayed the time to first SRE by more than 2 months ([Study 0011], Rosen et al, 2003b). Additionally, these trials show that Zometa significantly reduced the risk of developing one or more SREs by >30% in these patients (Saad 2004, Rosen 2003b). The key efficacy data of the placebo-controlled trials are shown in Table 2-1 and Table 2-2.

In summary, the clinical trials of Zometa clearly demonstrate its efficacy in patients with multiple myeloma and bone metastases from solid tumors. The clinical data not only show that Zometa is at least as effective as Aredia in multiple myeloma and breast cancer, but also suggest that Zometa may be more effective than Aredia for patients with breast cancer, particularly those with lytic lesions. Moreover, Zometa demonstrated efficacy in prostate cancer where Aredia failed to show efficacy, as well as in lung cancer and other solid tumors where Aredia has not been investigated in clinical trials. Thus, Zometa has expanded the spectrum of clinical activity of bisphosphonates, and offers additional benefit to patient populations previously not treated with bisphosphonates. Together with the convenience of a 15 minute infusion, Zometa provides significant clinical benefit to patients with a wide range of malignancies, which has enabled Zometa as the new standard of care for patients with bone lesions from malignancies. Today, Zometa is the most widely used bisphosphonate in oncology.

Table 2-1 Efficacy summary of Zometa in patients with prostate cancer [Study 0039]

	Proportion of patients with an SRE, %*	Time to first SRE, median days (hazard ratio)**	Mean skeletal morbidity rate, events/year**	Multiple-event analysis, hazard ratio**
ZOMETA 4 mg N = 214	38	488 (0.677)	0.77	0.64
Placebo N = 208	49	321	1.47	
P value	0.028	0.009	0.005	0.002

*Hypercalcemia of malignancy (HCM) excluded as an SRE

**HCM included as an SRE

Table 2-2 Efficacy summary of Zometa in patients with lung cancer and other solid tumors [Study 0011]

	Proportion of patients with an SRE, %*	Time to first SRE, median days (hazard ratio)**	Mean skeletal morbidity rate, events/year**	Multiple event analysis, hazard ratio**
ZOMETA 4 mg N = 257	39	236 (0.703)	1.74	0.693
Placebo N = 250	46	155	2.71	
P value	0.127	0.009	0.012	0.003

*HCM excluded as an SRE

**HCM included as an SRE

3 Osteonecrosis (ON) – background information

3.1 Introduction

Osteonecrosis (ON), also known as aseptic vascular necrosis of the bone (AVN), refers to the death of bone, which occurs as a result of impaired blood supply to the affected areas. Other terms that are used to describe ON include ischemic necrosis, subchondral avascular necrosis, aseptic necrosis of bone, and osteochondritis dissecans (Assouline-Dayan et al, 2002). ON can occur in multiple locations of the skeleton, but the femoral head appears to be the most frequently involved site. Reports of ON at other sites such as humerus, shoulder, knee, as well as the jaw bone have been reported. Patients with ON usually present with pain, bone destruction, and functional disability. Diagnosis of ON is based on clinical findings and imaging studies using MRI, X-ray film, and sometimes bone scan. No curative treatment exists for ON, which is usually managed with either conservative anti-inflammatory treatment or surgery.

The causes of ON include trauma and non-traumatic factors that lead to interruption of circulation to bone. The mechanism for the reduction or loss of blood supply to the involved areas of bone includes intraluminal obstruction (thromboembolism, sludging of blood cells, or stasis), vascular compression (vasospasm), and the physical disruption of the vessel (Wolfe et

al, 2000). It is estimated that non-traumatic ON occurs at an incidence of ~ 10,000 to 20,000 new cases per year in the US (Mankin 1992). While the etiology and pathogenesis of ON are not well understood (Bouquot 2000; Wang 2003), a variety of medical conditions and a large number of risk factors have been associated with ON (Vail and Covington 1997), suggesting that the etiology of ON is multifactorial.

3.2 Risk factors for ON

Numerous medical conditions and risk factors have been associated with ON (Appendix 1), including several uncommon diseases such as connective tissue disorders, sickle-cell disease, Gaucher's disease, systemic lupus erythematosus (SLE) as well as some common medical conditions such as direct or indirect trauma, infection, coagulopathy, hyperlipidemia, anemia, immunocompromised states (e.g., HIV infection), and cancer (Jones 1997; Assouline-Dayan 2002). The pathogenetic pathways underlying the development of ON in patients with these conditions is complicated and not clear, but eventually the risk factors lead to compromised circulation to areas of the bone with subsequent death and necrosis of the involved area. Published literature suggests intravascular coagulation (IC) as a common intermediary event in the pathway leading to ON, as evidenced by a study showing that 82% of ON patients evaluated had at least one coagulation abnormality as compared to 30% of the controls (Jones et al, 2003). Therefore, defects in the coagulation mechanism may have some impact on the development of ON, as discussed in case reports of hypercoagulability in ON patients resulting from thrombophilia or hypofibrinolysis (Cheras 1997, Zalavras 2002).

ON has been associated with various drugs, notably, alcohol abuse, smoking and corticosteroids. Alcohol has clearly been associated with increased risk of ON with an odds ratio of > 13 for regular drinkers (Hirota et al, 1997). Similarly, smoking increases the risk of ON by > 4 fold (Hirota et al, 1997). Alcohol causes disturbances of circulation by inducing fat embolism, while smoking has been shown to have negative impact on the cardiovascular system, both of which could lead to vascular occlusion and development of ON (Hirota et al, 1997).

3.2.1 Corticosteroids as a risk factor for ON

Corticosteroids are a known risk factor for ON (Gebhard and Maibach 2001). In a study with patients on corticosteroid replacement therapy, ON occurred in 2.4% of the patients with a latency of 16 months to five years (Vreden et al, 1991). ON has also been reported in patients exposed to topical corticosteroids (Kubo 2001; Mistlin 2004), indicating a strong association of this risk factor with ON. In patients undergoing organ transplant, a rate of ON as high as 41% post-transplant was reported in an earlier literature (Hawking 1976), although recent reports quoted a lower rate of 4% occurring in patients within 6 months of a renal transplant (Lopez-Ben et al, 2004). The exact mode of action for corticosteroids to induce ON has not been fully investigated, although preclinical studies have shown that high-dose corticosteroids decrease blood flow and induce hypercoagulability, causing a decrease in blood flow to the bone (Drescher et al, 2004).

3.2.2 Coagulopathy as a risk factor for ON

Another risk factor for ON, especially in cancer patients, is the possible role of coagulopathy, which is known to occur commonly in cancer patients. Coagulopathy may manifest as venous thromboembolism (VTE) or deep vein thrombosis (DVT) (Baron 1998, Kakkar 2004, Zangari 2004). Glueck and colleagues have documented thrombophilia and hypofibrinolysis in several cohorts of patients with ON of the hip, which showed coagulopathy in ~ 75% of these ON patients (Glueck et al, 1997).

While one prominent risk factor or condition may be associated with the occurrence of ON in a particular patient, studies have shown that co-existence of multiple risk factors/conditions lead to a significantly higher incidence of ON. For example, ON developed in 44% of systemic lupus erythematosus (SLE) patients within 5 months of starting high dose steroid therapy (Oinuma et al, 2001).

3.3 ON in cancer patients

The incidence of ON in cancer patients has not been reported in the literature. Analysis of the UK General Practice Research Database (GPRD) by Novartis scientists suggests that the incidence of ON in cancer patients is estimated to be 1.31 per 10,000 person-yrs (95% CI: 0.72-2.21), which is more than four times that of general population. (Sablinkska 2003).

Risk factors for ON that are specific to cancer patients include cancer itself, radiation therapy, chemotherapy and therapeutic regimens that contain corticosteroids. Additionally, many cancer treatments can compromise patients' immune systems, rendering them more susceptible to infection. Malignancy itself is noted among the list of medical conditions that predispose patients to ON (Appendix 1).

Various reports of ON in cancer patients have been published with chemotherapy and steroids noted as possible risk factors (Dawson 2001, Winquist 2001, van den Berkmortel 2004, Cook 2001, Gogas 1996). Winquist et al (2001) summarized 15 published reports with a total of 41 cases of ON in cancer patients treated with a variety of chemotherapy regimens (Table 3-1), suggesting a possible role of chemotherapy in ON. It is noteworthy that the majority of these cases of ON involves the femoral head.

Table 3-1 Cases of osteonecrosis after chemotherapy for solid tumors (from Winquist et al, 2001)

Author (ref.)	No. of cases	Cancer diagnosis	Chemotherapy regimen(s)	Onset	Sites of ON
Obrist et al	1*	Breast	CMF	Subacute‡	Humeral head
Perloff et al	2	Breast Breast	CMFVP CMFVP	Delayed Delayed	Femoral heads Femoral head
Harper et al	1*	Testis	VeB + VAC, PVB	Subacute	Multiple including femoral head

Author (ref.)	No. of cases	Cancer diagnosis	Chemotherapy regimen(s)	Onset	Sites of ON
Ishii et al	2*†	Neuroblastoma Neuroblastoma	Cyclophosphamide, cisplatin+teniposide VAC	Subacute Subacute	Femoral head Femoral head
Marymont et al	1*	Breast,	FAC, Melphalan	Delayed	Femoral condyles
Kolin et al	1	Breast	CMFVP	Delayed	Femoral head
Meneghello et al	2	Testis Osteosarcoma	PVB VAC	Delayed Delayed	Femoral heads Femoral heads
Wuisman et al	1	Osteosarcoma	Multiple including intra-arterial cisplatin	Acute	Proximal tibia
Forrai et al	19	Testis	PVB	Subacute (2) Delayed (17)	Femoral head (6) Femoral head(13)
Jones	1	Small cell lung	EC, EP	Subacute	Multiple including femoral head
Gogas et al	1	Ovarian	Multiple	Delayed	Femoral heads
Besson et al	1	Breast	Multiple	Subacute	Humeral head, femoral heads
Geetha et al	1*†	Neuroblastoma	CAPE	Subacute	Femoral heads
Cook et al	5	Testis Testis Testis	BEP BEP BEP	Delayed Delayed Delayed	Femoral head Femoral head Femoral heads
Winquist et al	2	Testis Testis	PVB BEP	Delayed Delayed	Femoral heads Femoral heads

BEP, bleomycin, etoposide, cisplatin; CAPE, cyclophosphamide, doxorubicin, cisplatin, etoposide; CMF, cyclophosphamide, methotrexate, fluorouracil; CMFVP, cyclophosphamide, methotrexate, fluorouracil, vincristine, prednisone; EC, etoposide, carboplatin; EP, etoposide and cisplatin; FAC, fluorouracil, doxorubicin, cyclophosphamide; PVB, cisplatin, vinblastine, bleomycin; VAC, vincristine, dactinomycin, cyclophosphamide; VeB, vinblastine, bleomycin.

* Chemotherapy given without corticosteroids.

† Pediatric patient.

‡ Subacute, diagnosis of osteonecrosis nonacute during/within 6 months of chemotherapy.

Obrist R, Hartmann D and Obrecht JP (1978) Osteonecrosis after chemotherapy [letter]. Lancet; 1:1316.

Perloff M and Lesnick GJ (1980) Avascular necrosis of the femoral head: association with adjuvant chemotherapy for breast carcinoma. Cancer Treat Rep; 64:361–2.

Harper PG, Trask C and Souhami RL (1984) Avascular necrosis of bone caused by combination chemotherapy without corticosteroids. BMJ (Clin Res); 288:267–8.

Ishii E, Yoshida N and Miyazaki S (1984) Avascular necrosis of bone in neuroblastoma treated with combination chemotherapy. Eur J Pediatr; 143:152–3.

Author (ref.)	No. of cases	Cancer diagnosis	Chemotherapy regimen(s)	Onset	Sites of ON

Marymont JV and Kaufman EE (1986) Osteonecrosis of bone associated with combination chemotherapy without corticosteroids. Clin Orthop; 204:150–3.

Kolin E and Sherry H (1987) Avascular necrosis of the femoral head in patients being treated for malignancy. Mt Sinai J Med; 54: 516–21.

Meneghello A, Presacco D and Di Maggio C (1989) Aseptic necrosis of the femoral head in cancer patients affected with vincristine/vinblastine –induced neuropathy [in Italian]. Radiol Med (Torino); 77:626–30.

Wuisman P, Erlemann R, Roessner A, et al (1991) Case report 669. Skeletal Radiol; 20:294–8.

Forrai G, Baki M and Bodrogi I (1994) Incidence of osteoporosis and aseptic femoral head necrosis after complex cytostatic therapy in germ cell testicular cancer patients [in Hungarian]. Orv Hetil; 135: 1695–700.

Jones DN (1994) Multifocal osteonecrosis following chemotherapy and short-term corticosteroid therapy in a patient with small-cell ronchogenic carcinoma. J Nucl Med; 35:1347–50.

Gogas H and Fennelly D (1996) Avascular necrosis following extensive chemotherapy and dexamethasone treatment in a patient with advanced ovarian cancer: case report and review of the literature. Gynecol Oncol; 63:379–81.

Besson C, Stelianides S, Belmatoug N, et al (1998) Multifocal osteonecrosis after chemotherapy in a patient with breast cancer. J Rheumatol; 25:2479–80.

Geetha N, Kumary PK, Ramachandran K, et al (1998) Avascular necrosis of the femoral head in neuroblastoma: a case report. Pediatr Hematol Oncol; 15:443–6.

Cook AM, Patterson H, Nicholls J, et al (1999) Avascular necrosis in patients treated with BEP chemotherapy for testicular tumours. Clin Oncol (R Coll Radiol); 11:126–7.

Winquist EW, Bauman GS and Balogh J (2001) Nontraumatic osteonecrosis after chemotherapy for testicular cancer: a systematic review. Am J Clin Oncol; 24(6):603-6.

Corticosteriods are key components of therapeutic regimens for hematological malignancies such as acute lymphoblastic leukemia, and therefore patients with these types of malignancy may be exposed to high dose corticosteroids for prolonged periods of time. For example, the incidence of ON is estimated to be ~ 9-20% for children and young adults 10-20 years of age receiving intensive therapy for acute lymphocytic leukemia using regimens that contain high dose corticosteroids (Mattano et al, 2000). Additionally, patients undergoing stem-cell transplant are also exposed to high-dose steroids. The reported prevalence of ON ranges from 0.6 to 38% in patients with various hematological malignancies as summarized by Assouline-Dayan et al (2002) (Table 3-2).

Table 3-2 Selected studies of corticosteroid-induced osteonecrosis [adapted from (Assouline-Dayan et al, 2002)]

Condition or Disease	Type of Study	Patients (n)	Prevalence (%)	Glucocortico-steroid Dose	Mean Interval Between Treatment and Osteonecrosis	Reference
ALL	Prospective	24	38	NA	Within a few months	(Ojala et al 1999)[1]
Post-allogeneic BMT	Retrospective	272	6	Total dose 189 mg/kg (range 13-555 mg/kg)	13	(Weismann et al 1998)[2]
Hodgkin's	Retrospective	784	1	Total	35	(Enrici et al

Disease				Prednisone 2725-5250mg		1998)[3]
ALL	Retrospective	850	0.6	NA	29	(Vaidya et al 1998)[4]
Post-BMT	Case Control	1939	5	NA	26	(Fink et al 1998)[5]
Pediatric, ALL	Prospective	28	32	High-dose Dexamethasone	NA	(Ojala et al 1997)[6]
Post-BMT	Multicenter Retrospective	4388	4	NA	22	(Socie et al 1997)[7]

1. Ojala AE, Paakko E, Lanning FP, Lanning M (1999) Osteonecrosis during the treatment of childhood acute lymphoblastic leukemia: a prospective MRI study. Med Pediatr Oncol; 32:11-7.

2. Weismann A, Pereira P, Bohm P, et al (1998) Avascular necrosis of bone following allogeneic stem cell transplantation: MR screening and therapeutic options. Bone Marrow Transplant; 22:565-9.

3. Enrici RM, Anselmo AP, Donato V, et al (1998) Avascular osteonecrosis in patients treated for Hodgkin's Disease. Eur J Haematol; 61:204-9.

4. Vaidya S, Saika S, Sirohi B, et al (1998) Avascular necrosis of bone – a complication of aggressive therapy for acute lymphoblastic leukemia. Acta Oncol; 37:175-7.

5. Fink JC, Leisenring WM, Sullivan KM, et al (1998) Avascular necrosis following bone marrow transplantation: a case control study. Bone; 22:67-71.

6. Ojala AE, Lanning FP, Paakko E, et al (1997) Osteonecrosis in children treated for acute lymphoblastic leukemia: a magnetic resonance imaging study after treatment. Med Pediatr Oncol; 29:260-5.

7. Socie G, Chan JY, Carmelo J, et al (1997) Avascular necrosis of bone after allogeneic bone marrow transplantation: analysis of risk factors for 4388 patients by the Societe Francaise de Greffe de Moelle (SFGM). Br J Haematol; 97:865-70.

3.4 Osteonecrosis of the jaw (ONJ)

Jaw bones are unique in that they are the only bones in the body that are constantly exposed to the external environment due to the presence of teeth. Additionally, the jaw bones are subject to the risk of repeated trauma and injury from dental procedures such as routine cleaning or other necessary medical interventions. Thus, the jaw bones are more susceptible to infection, and are in need of mechanisms to deal with the chronic mechanical or infectious insults.

Osteonecrosis of the jaw (ONJ) has been reported since the 19th century, though the number of such reports as been small.

One of the variants of ONJ is known as neuralgia-inducing cavitational necrosis (NICO), which is defined as a chronic neurogenic pain syndrome caused by alveolar bone necrosis and the formation of intrabony cavities of significant size (Bouquot 1992a, Bouquot 1992b, Bouquot 1995, Bouquot 1997, Freedman 1998, Bouquot 2000, Shankland 2002). While there is still debate on whether "NICO" represents a true disease entity (Zuniga 2000, Bouquot 2003), histopathological features of NICO clearly indicate presence of bone necrosis, suggesting ischemia as a possible pathogenic mechanism (Bouquot 1995, Brontons 2003). It is likely that some reports of osteomyelitis, particularly when chronic and persistent in nature, are in fact cases of osteonecrosis, which may occur as a result of infection (osteomyelitis) of the jaw bone, or present as osteomyelitis due to infection of the dead bone.

Unlike ON of other sites, a clear set of diagnostic criteria is lacking for ONJ. The disease may present clinically as "facial pain", jaw pain, chronic osteomyelitis of the jaw, exposed jaw bone, cavitary alveolar osteopathy, sequestration of alveolar bone, and a number of other signs and symptoms (Brontons 2003). An example of the current diagnostic complexity and

the confusion regarding clear criteria of diagnosis for ONJ is a recent case report that refers to cases of "osteomyelitis" in the title, but these cases are in fact ONJ when one reads the description of the cases (Lugassy 2004).

The pathogenesis of ONJ is not understood. It is possible that some of the risk factors and the pathogenic pathways for ON at other sites may also contribute to the development of ONJ. Shroyer et al (1991) reported and reviewed cases of osteomyelitis of the mandible in patients with sickle cell disease, and Kavadia-Tsatala et al (2004) reported 6 cases of mandibular bone infarcts in 42 patients with sickle cell hemoglobinopathy which is known to cause vasoocclusive crises. Moreover, Glueck (1997a), Glueck (1997b) reported presence of coagulopathy in 73% of 124 ONJ patients, manifested as either thrombophilia or hypofibrinolysis or both. Shankland (2002) reviewed 500 cases of ONJ and found evidence of impaired blood flow in the jaw bone or teeth in >95% of these patients. Moreover, blood flow to the jaw bone was shown to be reduced by chronic osteomyelitis (Wannfors and Gazelius 1991). These findings strongly implicate impaired circulation in the pathogenesis of ONJ.

An infectious cause of ONJ has been suggested in patients suffering from trigeminal herpes zoster which can induce vasculitis leading to ischemia (Schwartz 1989, Arikawa 2004). ONJ was also reported in patients with HIV infection (Schwartz 1989).

3.5 ONJ in cancer patients

Prior to 2003, ONJ in cancer patients was described in two case reports (Schwartz 1982; Sung 2002). Schwartz (1982) reported two cases of ONJ in patients with head and neck cancer that occurred after chemotherapy. One of the patients had mucosal infection prior to bone infection (osteomyelitis) and ONJ, and the other had dentures producing irritation. The potential role for chemotherapy in ONJ was also suggested by Sung et al (2002) who reported ONJ in patients with acute myelogenous leukemia (AML) treated with chemotherapy without steroids. While cancer and chemotherapy are noted as risk factors for ON (Appendix 1), the background incidence of ONJ in cancer patients and the general population is unknown.

Osteoradionecrosis (ORN), a specific form of ONJ which occurs after radiation to patients with head and neck cancer, has a reported incidence varying between 0.4 – 56% (Jerecaek-Fossa and Orecchia 2002). The incidence has decreased due to preventive oral hygiene measures and careful dental evaluation before and after irradiation. A recent study reported an ORN incidence of 8.2% in these patients (Reuther et al, 2003). Besides radiation itself, the risk factors for ORN are similar to those described for ON in cancer patients, and the patients remain at indefinite risk of ORN after radiation (Jerecaek-Fossa and Orecchia 2002). The mechanism for ORN involves radiation-induced damage to vasculature and bone tissues, and like ON in general, ischemia is hypothesized to be the ultimate immediate cause of death of bony tissue. The study of Bras et al (1990) showed obliteration by radiotherapy of the inferior alveolar artery that supplies portions of the mandible, providing strong evidence for ischemia as a mechanism of bone necrosis in ORN.

ONJ in cancer patients treated with a bisphosphonate was first reported by Marx (2003). Several reports have been published subsequently describing ONJ in patients receiving bisphosphonates. These reports are summarized in Section 4.

In summary, multiple risk factors and medical conditions are associated with ON, which occurs more frequently in cancer patients, presumably due to the underlying diseases and their therapy (Appendix 2). The pathogenesis of ON is not clearly understood, but impaired blood supply to the bone may be the final common pathway prior to death of bone tissues. ON causes significant morbidity and disability, and necessary measures should be taken to prevent or reduce the occurrence of ON in patients who have the known risk factors mentioned above. Additionally, ONJ is a specific form of ON that has specific local risk factors because of the unique properties of the jaw bone, and risk factors known to cause ON in general may also come into play in the pathogenesis of ONJ.

3.6 Preclinical data on bisphosphonates and osteonecrosis

The primary pharmacologic action of bisphosphonates such as pamidronate and zoledronic acid is to reduce osteoclastic bone resorption by inhibiting a key intracellular enzyme for lipid metabolism (farnesyl diphosphate synthase) in the osteoclast, which subsequently induces apoptosis (Rogers 2003). As bisphosphonates are highly charged, hydrophilic compounds that rapidly bind to bone, only endocytic cells in bone such as osteoclasts are normally exposed to pharmacologically active concentrations of drug. Osteonecrosis of the jaws or any other skeletal site was not observed in any of the in vivo profiling studies with zoledronic acid and pamidronate, nor have there been any reports of it in the preclinical literature for other bisphosphonates. In two rat models of aseptic osteonecrosis of the femoral head, zoledronic acid has been shown to exert a beneficial effect and thus was proposed as a clinical therapy for this condition (Little 2003a, Little 2003b). Recently there have been several publications on inhibition of angiogenesis in soft tissue and bone tumors by bisphosphonates, including pamidronate and zoledronic acid (Wood 2002, Fournier 2002, Croucher 2003, Fournier 2003, Giraudo 2004) but there have been no reports of a corresponding anti-angiogenic effect in normal bone that is being newly formed, remodeled or undergoing fracture repair – processes that are all dependent on angiogenesis (Hunziker et al 2000). Bisphosphonates have been extensively studied in animals models of periodontal disease, and, despite dental interventions such as tooth ligation, osteonecrosis of the jaws has not been reported in association with bisphosphonate treatment (Brunsvold 1992, Weinreb 1994, Reddy 1995, Shoji 1995, O'uchi 1998; Shibutani 2001).

A comprehensive preclinical safety assessment has been performed for pamidronate and zoledronic that included a wide range of oral and parenteral toxicology studies in multiple animal species at doses comparable to and at many multiples of those typically administered to the oncology patient (90 mg pamidronate, 4 mg zoledronic acid). No findings comparable to ONJ were observed in the bone specimens collected and evaluated from any of the animal studies. Moreover, a careful search of the literature did not reveal any known association between bisphosphonate administration and ONJ in animals. Animal experiments to study the possible role of bisphosphonates (including pamidronate and zoledronic acid) in the etiology and pathogenesis of ONJ were considerd. However, it was concluded that the design and conduct of such studies would be inordinately complex considering its multifactorial etiology, and traumatic (e.g. tooth evulsion studies in the canine) yielding what could at best be considered equivocal results.

4 Reported cases of osteonecrosis of the jaw

4.1 Cases of ONJ reported in the literature

ONJ in cancer patients treated with IV bisphosphonates was first reported by Marx et al (2003) in the September 2003 issue of the Journal of Oral and Maxillofacial Surgery. A collection of case reports was published by Ruggiero et al (2004) in the same journal in 2004. The sixty three (63) patients described in this paper had been treated with either IV or in a few cases with oral bisphosphonates.

During the latter half of 2004, there was some discussion of ONJ, as summarized in Table 4-1.

Table 4-1 References 2004

Author	No of ONJ Pts Reported	Journal	Methodology
(de Almeida, de Araujo and Pires 2004)	5	Rev Bras Oncologia Clinica (Brazil)	Case Report
(Bagan et al 2004)	10	J Oral Pathol Med	Case Report, Manuscript
(Curreli et al 2004)	1	MASCC/ISOO Symposium*	Case Report, Abstract
(Durie et al 2004)	62	Blood	Abstract, Anonymous web based survey
(Kut et al 2004)	No cases found	Blood	Abstract
(Lugassy et al 2004)	3	The American Journal of Medicine	Case Report, Letter to the Editor
(McMahon et al 2004)	No cases discussed	Journal of Oral and Maxillofacial Surgery	Letter to the Editor
(Schuster and Dymek 2004)	2	Blood	Case Reports, Abstract
(Thakkar et al 2004)	14	Blood	Case Reports, Abstract
(Van Poznack et al 2004)	6	San Antonio Breast Cancer Symposium	Clinical Database Review, Abstract

Though these various reports provide information for additional consideration, they are subject to a variety of limitations. For example, there is no standard definition of ONJ applied across these reports. ONJ was used to describe a variety of diagnoses and pathologies, including osteomyelitis, osteonecrosis, suspicious findings for osteonecrosis, ischemic bone disease, cavitational osteonecrosis, and bone marrow edema among others. Further, the amount of clinical data upon which the case reports are based is inconsistent. The Durie web-based survey is based on data collected from anonymous respondents. At the December 2004 ASH Meeting Durie et al (2004) presented findings from their web-based survey of 1,203 anonymous respondents. Respondents were recruited using the International Myeloma Foundation (IMF) email lists/website plus "ACOR" myeloma and breast listservs (e-mail), Nexcura (e-mail) and Y-Me National Breast Cancer Organization (web-based). The information was supplied anonymously by the respondents and therefore could not be validated against medical records. The bias associated with this survey methodology may be significant and has the potential to substantially affect the generalization of the study conclusions, including that ONJ occurs earlier with Zometa than with Aredia use, and that other therapies do not significantly increase the likelihood of ONJ.

In addition to bisphosphonates, the publications in Table 4-1 lists other factors that could contribute to the risk of ONJ, including chemotherapy, corticosteroids, thalidomide, surgical procedures in the oral cavity, transplantation, immune suppression, and inflammation/infection. Many of the cases reported were noted following tooth extraction.

4.2 Cases of ONJ reported to Novartis

ONJ in patients treated with intravenous pamidronate (Aredia) or zoledronic acid (Zometa) was first reported to Novartis in December 2002 (a spontaneous report).

Table 4-2 shows cases of osteonecrosis of the jaw in patients treated with Zometa and/or Aredia reported to the Novartis Clinical Safety and Epidemiology Department as of December 7, 2004. The current tally of the type of reports is as follows: 531 spontaneous reports and 79 literature cases for a total of 610 reports. It is estimated that up to November 2004 approximately 2.8 million patients have been treated worldwide with Aredia and/or Zometa.

Table 4-2 Reports of ONJ (including reportable cases from the literature) associated with the use of Zometa/Aredia (as of December 7, 2004)

	Cases under Aredia and/or Zometa	**N**	**%**
		610	**100 %**
Agent (suspect drug)	Zometa only*	374	61.3%
	Aredia only****	120	19.7%
	Both**	116	19.0%
Countries	US	440	72.1%
	Non-US	170	27.9%
Indication	Multiple Myeloma	218	35.7%
	Breast	125	20.5%

	Other	267	43.8%
Age***	Range Mean	27 – 93 years 62.6 (females) 66.4 (males)	
Gender	Female Male Unknown	340 231 39	56% 39% 6.4%
* 126 of these 374 cases had received prior treatment with Aredia ** The two drugs were given most frequently sequentially, but in a few cases the treatments were switched back and forth for unknown reasons. *** Age not reported in 142 cases **** One case received prior treatment with Zometa			

In 303 (50%) of the cases potential triggering events like dental surgery, local trauma, tooth extraction or dental infection preceded the diagnosis of ONJ. In 450 (74%) of the reports the patients had at least one of the risk factors for osteonecrosis.

Spontaneous report databases are known to be affected by multiple biases. In addition, the ONJ reports received are deficient with respect to medical and dental history, and concomitant medication information. Even after aggressive follow-up efforts by the sponsor, many cases can be considered to be only scantly described. The frequent lack of important case details leads to serious limitations to the analyses and interpretation of the findings from the spontaneous report database. However, the majority of cases for which some clinical details are available include significant risk factors for ON. Novartis is fully committed to continue the investigation of these cases.

Further epidemiologic data on these cases, including concomitant risk factors and duration of exposure to bisphosphonate treatment, are given in the Aredia and Zometa Comprehensive Medical safety Evaluation: Osteonecrosis of the Maxillofacial Area – December 2004 Overview [see (Appendix 3)].

Cases of osteonecrosis of the jaw (ONJ) in clinical studies

Since the specific term “osteonecrosis of the jaw” (ONJ) does not exist in the MedDRA dictionary (version 6.1), the clinical trial database for Zometa and Aredia was screened using 18 MedDRA terms that may identify cases related to ONJ. As of January 2005, we have searched 25 completed Zometa bone metastases studies (pivotal and non-pivotal), 3 pivotal Aredia bone metastases studies and 3 pivotal Zometa hypercalcemia trials involving more than 8,000 patients. Table 4-3 summarizes these studies, and details of these trials are presented in Appendix 4. Additional searches are being conducted for ongoing oncology studies of Zometa where databases are available.

The terms used in the search followed MedDRA 6.1. and include:

Bone debridment	jaw lesion excision
Jaw operation	mandibulectomy
Maxillofacial operation	oral surgery

Aseptic necrosis bone	bone infarction
Necrosis	osteomyelitis acute
Osteomyelitis chronic	osteomyelitis drainage
Osteomyelitis	osteonecrosis
Primary sequestrum	secondary sequestrum
Sequestrectomy	tertiary sequestrum

Table 4-3 Completed Zometa and Aredia studies included in the search for terms related to ONJ using MedDRA terms

Pivotal trials (Zometa + Aredia)	Treatment Group	No. of patients
Bone metastases Zometa		
[CZOL4460007+E]	Zometa	183
	Zometa/Aredia	30
	Aredia	75
[CZOL4460010+E]	Zometa	1,090
	Aredia	558
[CZOL4460011+E]	Zometa	523
	Placebo	250
[CZOL4460039+E]	Zometa	435
	Placebo	208
[CZOL4460704]	Zometa	204
	Placebo	201
Subtotal		**3757**
Bone metastases Aredia		
[CARD233AP12]	Aredia	203
	Placebo	189
[CARD233AP18	Aredia	182
	Placebo	189
CARD233AP19]	Aredia	185
	Placebo	197
Subtotal		**1145**
Hypercalcemia Zometa		
[CHJC1]	Zometa	33
[CZOL446036]	Zometa	94
	Aredia	50
[CZOL446037]	Zometa	87
	Aredia	51
Subtotal		**315**
Total for Pivotal Studies		**5217**
Non-Pivotal trials (Zometa)	**Treatment Group**	**No. of patients**

Bone metastases		
Phase I-III		
[CZOL4460001][1)]	Zometa	16
[CZOL4460002][1)]	Zometa	140
	Placebo	35
[CZOL4460003+E]	Zometa	59
[CZOL4460035+E]	Zometa	42
[CZOL4460503+E]	Zometa	36
[CZOL4460506+E]	Zometa	19
[CZOL4460510]	Zometa	20
[CZOL4460705]	Zometa	55
	Placebo	51
[CZOL446IA03]	Zometa	115
	Aredia	125
Subtotal		**713**
Phase IV		
[CZOL446EDE02]	Zometa	604
[CZOL446EIT01]	Zometa	312
[CZOL446EAU05]	Zometa	184
[CZOL446EAU07]	Zometa	11
[CZOL446GAU09]	Zometa	2
[CZOL446EGB01]	Zometa	101
[CZOL446EIN01]	Zometa	73
[CZOL446EPH01]	Zometa	70
[CZOL446GFR02]	Zometa	102
[CZOL446EUS16]	Zometa	638
[CZOL446EUS24]	Zometa	257
Subtotal		**2354**
TOTAL		**8,284**

4.2.1 Completed studies

The screen using the 18 MedDRA terms produced 24 matches. After medical review, 6 cases were determined to be consistent with a potential diagnosis of ONJ. Four of these were reported as osteomyelitis with jaw as the affected site. Although 3 of the 4 osteomyelitis cases did not report exposed or necrotic bone and thus cannot be definitively diagnosed as ONJ, we included them because of the lack of a clear case definition for ONJ and the fact that known ONJ cases have occasionally been reported as osteomyelitis (see Section 3).

The 6 cases of ONJ or osteomyelitis of the jaw (OMJ) were all found in the randomized pivotal studies (total of 11 trials, see Table 4-4). None of these were reported as serious or related to the study drug as assessed by the investigator. A summary of these 6 cases is presented in Table 4-5. Details of the 6 cases are summarized in Appendix 4.

The screening also identified 2 cases of osteomyelitis or osteonecrosis with unknown location, and involvement of the jaw has not been confirmed at this time (Appendix 4).

In addition, one case of osteoradionecrosis was identified in the Zometa 8/4 mg arm, and radiation injury was clearly described in this patient (Appendix 4).

Table 4-4 Summary of the ONJ cases in randomized pivotal clinical trials

Treatment	# of patients*	# of ONJ	# of Infusions	Tumor type
Zol 4 mg	1168	1	28	MM
Zol 8 mg	219	1	1[1)]	Head&Neck
Zol 8/4 mg	1227	2	20[2)] 17[3)]	PC MM
Aredia 90 mg	1334	2	14 28[4)]	MM MM
Placebo	1234	0		

* Patient number of study CHJC1(n=33) not included as dose regimen cannot be attributed to the categories presented in this table

[1)]HCM study

[2)]The patient received 7 infusions of Zometa 8 mg before switching to Zometa 4 mg 13 infusions)

[3)]The patient received 10 infusions of Zometa 4 mg before switching to Zometa 8 mg (7 infusions)

[4)]The patient received 10 infusions of Zometa 0.4 mg before switching to Aredia (18 infusions)

As shown in Table 4-4, ONJ was uncommon in randomized pivotal trials, with 6 cases out of 3,981 patients treated with either Zometa or Aredia (2,647 Zometa patients, and 1,334 Aredia patients). However, due to the small number of ONJ cases in pivotal clinical trials, an incidence by treatment group cannot be reliably calculated. Nevertheless, 1 case of ONJ was found in the 1,168 patients receiving 4 mg Zometa, and 2 cases of ONJ were observed in 1,334 patients receiving 90 mg Aredia, which are the dosage of Zometa and Aredia approved for clinical use. No cases of ONJ were found in the 1,234 placebo patients in these studies.

Review of the 6 ONJ or OMJ cases revealed multiple risk factors. Five patients had chemotherapy, and 4 of them also had concomitant corticosteroids in their treatment regimen. Various oral infections were present in 4 patients, one patient had tooth extraction and in one patient poor dentition was reported (Table 4-6, for details see Appendix 4).

ONJ was not found in non-pivotal or post-marketing studies that have been completed as of January 2005 (total of 20 trials, 3,067 patients, see Appendix 4).

Table 4-5 ONJ/OMJ cases reported in pivotal bone metastases and hypercalcemia trials: possible risk factors

Study No.	Tumor type	Diagnosis	Date of 1st infusion	Date of ONJ/OMJ diagnosis	No. infusions)	Possible risk factors

[CZOL446G 0007]	Multiple myeloma	ONJ	4Nov96	Mar99	28	Chemotherapy; cortico-steroids; candidal infection; tooth abscess
	Multiple myeloma	OMJ	24Oct96	9Apr98	17	Chemotherapy; cortico-steroids; radiolucency at mandible seen on a radiograph of the skull; jaw infection; osteoarthritis
[CZOL446G 0010]	Multiple myeloma	OMJ	10May99	5Mar01	28	Chemotherapy; cortico-steroids; ulcer mouth; cyst under chin; infection of the gum and teeth
[CZOL446G 0704]	Prostate cancer	OMJ	29Dec99	26Mar02	20	Dental abscess, tooth extraction; oral fistula; arthritis; hormone therapy
[CARD 233AP12]	Multiple myeloma	OMJ	20Aug91	21Oct92	14	Chemotherapy; cortico-steroids; dentition poor; denuded bone (mandible)
[CZOL446 0037]	SSC Head&Neck	ONJ	16Jul99	28Jul99	1	Chemotherapy

4.2.2 Ongoing studies

Three reports of serious adverse events consistent with findings suspicious of ONJ have been reported in ongoing Zometa oncology clinical trials involving more than 8,000 patients. Two of these serious adverse events were considered as not related to the study drug by the investigator. We have also received an additional report of ONJ that is considered non-serious by the investigator.

One of the patients had preexisting osteomyelitis of the jaw. Two patients had received chemotherapy and 1 corticosteroids in medical history or as current condition.

We do not have any currently ongoing studies with Aredia.

These cases are summarized in Table 4-6 (for details see Appendix 4).

Table 4-6 ONJ cases reported in ongoing Zometa bone metastases studies

Table .	Tumor Type	Diagnosis	Date of 1st infusion	Date of ONJ/OMJ diagnosis	No. infusions	Possible risk factors[2)]
[CZOL446G 2408]	Breast cancer	ONJ	26Jan04	Oct04[1)]	Max. 4	Chemotherapy; corticosteroids; gingival infection; dental extraction
[CZOL446E DE07]	Prostate cancer	OMJ	25Feb03	Already present at study entry[2)]	Max. 9	Preexisting osteomyelitis of the jaw
[CZOL446E DEKR02]	Breast cancer	ONJ	25Jul03	After 6Jan 04[3)]	Max. 4	Chemotherapy; chronic gingivitis
[CZOL446E DE01]	Multiple myeloma	ONJ	?	?	?	?

[1)]Patient received tooth extraction due to gingival infection on February 16, 2004. Tooth extraction site did not heal. Patient was treated by debridment of the jaw bone and curettage of necrotic bone.

[2)]Patient hospitalized on January 6, 2004 to receive local treatment and was discharged on January 11, 2004 having completely recovered.

[3)]Sequestrectomy was performed on April 20, 2004. According to follow-up reports (May 7, 2004 and June 1, 2004) patient's condition was improving.

4.3 Preliminary findings from retrospective chart review at MD Anderson Cancer Center

A research protocol (Appendix 5) was developed in conjunction with MD Anderson Cancer Center in Houston, Texas to collect information on the frequency of osteonecrosis of the jaw in all oncology patients treated with intravenous bisphosphonate therapy at this center during the preceding ten year time period. Additional objectives are to:

- Collect information on cases of altered/delayed healing in the oral cavity after oral surgery, miscellaneous trauma, or denture sores in patients treated with bisphosphonates.
- Develop a better definition of the diagnostic criteria, clinical presentation, and natural history of osteonecrosis of the jaw.
- Identify risk factors associated with osteonecrosis of the jaw in patients treated with intravenous bisphosphonates.
- Review records of patients seen in the dental clinics and diagnosed with osteonecrosis of the jaw who had been previously treated with bisphosphonates.

This initiative will result in the review of the charts of over 4,000 patients in the MD Anderson database who have been treated with a bisphosphonate at the center over the last 10 years. These charts were sorted by the pharmacy based on the number of infusions of bisphosphonates from highest to lowest received at the center and are being reviewed in this non-random order. The review is ongoing and we anticipate that it will be completed by the middle of 2005.

We requested an unplanned interim review of the data collected up to January 12, 2005 to provide information for the ODAC meeting. Of the first 963 patients' charts that were reviewed by that date, 18 cases of ONJ were identified. However, there is selection bias because 7 of the 18 cases were reviewed out of sequence, because the treating physician suspected the presence of ONJ in these 7 patients. In addition, caution should be used in interpreting these interim results because of the non-random nature of the chart review. The tumor types included in this review is shown in Table 4-7 and an overview of the 18 cases identified is presented in Table 4-8.

Table 4-7 Demographics of patients included in the review

Tumor	# of patients
Breast cancer	631
Multiple myeloma	148
Renal cell carcinoma	32
Prostate cancer	18

Lung cancer	17
Lymphoma	13
Others	89
Sub Total	**948**
Non cancer	**15**
Total	**963**

Table 4-8 Brief overview of 18 ONJ cases from MD Anderson Cancer Center

Characteristics	**N (%)**
Gender, n (%)	
Male	3 (17%)
Female	15 (83%)
Age (yrs)	
Mean (SD)	60.6 (10.9)
Median	60.5
Range	42-79
Cancer, n(%)	
Breast cancer	11 (61%)
Multiple Myeloma	6 (33%)
Medullary Thyroid Cancer*	1 (6%)
Time since cancer DX to ONJ (months)	
Median	62
Range	4(A) – 283(A,Z)
Bisphosphonate before ONJ	
A only	3 (17%)
Z only	4 (22%)
Z preceded by alendronate	1 (6%)
A, Z**	9 (50%)
Unknown	1 (6%)
Time since 1st BP to ONJ (months)**	
Median	33
Range	4(A) – 57(A,Z)

* Medullary Thyroid Cancer

**Missing or incomplete info for some cases. Data is not available on BP administration outside of MD Anderson cancer center.

As shown in Table 4-8, 11 cases of ONJ are breast cancer patients out of a total of 631 of these patients, while 6 cases of ONJ were identified among the 148 patients with multiple myeloma.

Among the 18 patients with diagnosed ONJ, various dental problems were noted in 16 o these patients. Dental extraction or trauma to the jaw were noted in 11 patients, and 5 patients had mandibular tori or infection. Fifteen of the 18 patients had received chemotherapy, and the other 3 patients had hormonal therapy. Details of the 18 ONJ cases are shown in Appendix 6.

It is noteworthy that 18 cases of osteonecrosis (ON) of other sites were identified in this review and seven of which had ON prior to bisphosphonate treatment and 10 had ON after bisphosphonate treatment. The other case had an unknown history of bisphosphonate treatment.

5 Regulatory background

The first spontaneous report of ONJ was received by Novartis in December 2002. Even though based on limited and often incomplete data, recognition of an increase in the post-marketing surveillance reports of ONJ in clinical safety database prompted Novartis to act in a timely and diligent manner to assure safety of the label and patients. As necessitated by the evolving data for both Zometa and Aredia, and in advisory consultation with the FDA, Novartis has made several changes to the Zometa and Aredia package inserts over the last 16 months. The first update was implemented in September 2003 for Zometa and November 2003 for Aredia. The revised package inserts included a paragraph concerning ONJ under Post Marketing Experience in the Adverse Reactions section (see Appendix 7).

After the first case series was published by Ruggiero et al (2004), that significant awareness of ONJ led to an increase in both the observation/recognition and reporting. Additional updates to the Zometa and Aredia package inserts were implemented by Novartis. In February 2004, revised labeling for Zometa was approved by the FDA based on approval of two NDA supplements which provided extension data from clinical studies. In this revised package insert, dated March 2004, the previous statement of September 2003 on the occurrence of ONJ appearing in the Adverse Reactions Section under Post-Marketing Experience was updated to reflect understanding of the event and its management (see Appendix 7).

In May 2004, FDA invited Novartis to a meeting held July 2004 to present current understanding of ONJ along with available data on risk factors from any formal assessment of literature including the company's safety database. This extensive scientific and clinical assessment also provided opportunity to reassess the package inserts for the two IV bisphosphonates. Even in the absence of any direct correlation or causation from mostly limited spontaneous reports data, this exercise led to further strengthening of the label to assure patient safety. In the briefing book prepared for the July 2004 meeting, Novartis took the initiative to propose a third labeling change to include information on ONJ in the Precautions section. The statement included in the [Zomedia Package Insert] and [Aredia Package Insert] is 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."

In addition, Novartis took additional steps to inform the medical community by mailing a Dear Doctor Letter on September 24, 2004. This letter was mailed to oral surgeons, medical oncologists, hematologists, and urologists informing them of the substantive change made to labeling of the product. This letter was also submitted to the Division of Oncology Drug Products and to Medwatch.

Similar changes were also made to the Aredia label (and usually followed the change in the Zometa labeling). In October 2004, the Aredia insert was updated with ONJ.

Along with changes to the labeling, it was agreed with the Division that better understanding of ONJ was needed to develop adequate designs for prospective studies, and in that light Novartis had already contacted MD Anderson Cancer Center to conduct a retrospective chart review (over the last 10 years) of all cases on ONJ on IV bisphosphonates. Most of these efforts have been supplemented with ongoing patient education programs, described elsewhere in this document as a part of the risk minimization goal.

6 Novartis initiatives concerning reports of ONJ

In response to the reported cases of ONJ, Novartis undertook a detailed program to collect and review clinical data. The presentation and documentation of risk factors and follow-up information were collected to aid physicians in the identification of patients at risk and to provide guidance for effective patient management.

6.1 Initiation of reporter communications

Many of the ONJ cases reported to Novartis were incomplete and required follow-up to obtain additional patient information. Reporters were contacted to obtain complete patient clinical and medication histories through the use of a specially designed questionnaire (Appendix 8). In many cases, individual patient data had to be collected from several sources including oral surgeons, oncologists, and sometimes other clinicians. The review of patient information revealed the following risk factors recognized in the medical literature:

See (Appendix 1) for a detailed list of risk factors.

Chemotherapy/hormonal antineoplastic therapy

Coagulopathies

Corticosteroid use

Dental procedures (especially tooth extractions)

Heavy nicotine use

Immunosuppression / status post-transplantation

Local cancerous invasion

Local radiation therapy

Oral herpes infection

Poor oral hygiene

Prior episodes of osteonecrosis / osteomyelitis

6.2 Review and changes of prescribing information

Novartis revised the package inserts for Aredia and Zometa to include information on osteonecrosis of the jaw described in post-marketing safety reports. To keep oncologists informed about these changes to the package inserts, all Novartis Oncology field personnel have been briefed about the revisions so that they can proactively bring them to the attention of the healthcare professionals whom they interact with on a daily basis. In addition, a Dear Doctor letter to health care providers concerning the recent revisions in the [Zometa Package Insert] and [Aredia Package Insert] was sent on September 24, 2004 (a copy of which is attached in (Appendix 9).

6.3 Advisory boards and patient management

To gain further insight into the prevention, diagnosis, and treatment of cancer patients with osteonecrosis of the jaw and to understand the potential role, if any, of bisphosphonates in these patients, Novartis conducted two advisory board meetings on December 5, 2003 and March 29, 2004. These meetings convened a panel of advisors in the fields of oral surgery, medical oncology, metabolic bone disease, and dentistry/oral health (Appendix 10).

The principal outcomes of the first advisory panel were:

1. Recognition of the multitude of ON risk factors impacting these patients
2. Recognition of the need for collecting additional information on ONJ in cancer patients receiving bisphosphonates as a component of their treatment
3. Recognition of the need for practical guidelines that would assist clinicians in both the medical oncology and dental/oral health communities in recognizing, diagnosing and managing cancer patients who might be at risk for ONJ or actually have ONJ.

A second meeting of the advisory panel was held specifically to develop recommendations for patient management. The recommendations are embodied in a white paper attached in (Appendix 11), and cover these key points:

1. Identification of risk factors and recommendations for the prevention of osteonecrosis of the jaw in cancer patients
2. Recommendations for the management of patients who require oral surgical procedures prior to or while on bisphosphonate therapy.
3. Recommendations for the management of cancer patients diagnosed with ONJ.

The white paper has been made available through Novartis Medical Services and Scientific Operations [distribution of this document began at the American Society of Clinical Oncology

(ASCO) Annual Meeting June 5-8, 2004]. A final draft manuscript expanding on these recommendations has been agreed to in principle by the members of the panel and will be submitted for publication in peer reviewed journals for medical oncologists, dentists, oral surgeons and allied health care professionals.

6.4 Change of informed consent

To ensure patients enrolled in or entering trials have access to all new information, the following addition to the informed consent was included for worldwide Novartis trials with Zometa effective April 1, 2004:

In advanced cancer patients receiving, among other anticancer treatments, a bisphosphonate (such as pamidronate/Aredia or zoledronic acid/Zometa), there have been reports of a condition known as osteonecrosis of the jaw. This means a portion of the jawbone becomes permanently damaged, may be painful, and may require dental treatment or removal of the damaged area. This condition occurs rarely, and may follow tooth extraction. Because many treatments (such as chemotherapy, corticosteroids and radiation) and medical conditions or dental procedures that can increase the risk of osteonecrosis of the jaw may be administered or occur concomitantly with bisphosphonate therapy, it is not clear if the reported cases of osteonecrosis of the jaw are related to the use of bisphosphonates or to these other treatments, medical conditions or dental procedures.

In addition, Novartis has advised all principal investigators of investigator initiated trials using Zometa to insert this wording in the informed consent section and to obtain patients re-consent at the next scheduled visit.

A similar procedure was implemented for the ongoing trials of zoledronic acid in benign indications. Novartis is not currently sponsoring or supporting clinical trials using Aredia.

7 Novartis continued due diligence

Novartis remains strongly committed to the safety and welfare of patients who are being treated with our products.

We will continue to monitor any additional reports of osteonecrosis of the jaw that may be referred from the medical and dental communities and to share any insights with health care professionals. These reports will be promptly provided to the appropriate global regulatory agencies.

In addition, we will continue distribution to healthcare professionals of the white paper containing guidance regarding prevention, diagnosis, and treatment of ONJ.

An agreement in principle has been reached by the advisory panel members on the final content and conclusions of a draft manuscript intended to discuss the topic of ONJ in greater detail and to be made available to a wider audience through publication in journals that are widely read by health care professionals in both the dental and medical communities. Preliminary discussions have already taken place with journal editors in both disciplines to seek guidance on the most expeditious means of publishing these guidelines.

Novartis has also reached out to additional individuals and organizations for the purpose of receiving input on the design of a prospective study for further investigations in specific patient groups, e.g., those with multiple myeloma, to define the clinical course of ONJ in such patients following bisphosphonate therapy, and to identify imaging features and other clinical correlates of ONJ. Novartis is actively reviewing and evaluating these proposals.

In addition, Novartis will include additional steps in protocols involving cancer patients that will be initiated in the near future for the purpose of specifying screening dental exams and ONJ monitoring.

Novartis will follow to completion the retrospective study begun last year at the MD Anderson Cancer Center to gather additional data on the frequency of ONJ in cancer patients receiving bisphosphonate therapy and factors that may place patients at risk for developing ONJ as well as the frequency of ONJ in cancer patients not receiving bisphosphonates but may have some of the risk factors previously identified.

In an effort to reach out to patients, at a meeting held in late May 2004, Novartis briefed representatives from many of the major patient advocacy groups in the oncology community on the reports received on ONJ in patients with advanced cancer treated with bisphosphonates and other therapies. Representatives of CancerCare, the National Coalition for Cancer Survivorship, Susan G. Komen Breast Cancer Foundation, Y-ME, Multiple Myeloma Research Foundation, National Prostate Cancer Coalition, Us TOO, Alliance for Lung Cancer Advocacy, Support and Education and the Kidney Cancer Association were all in attendance. To assist these and other patient organizations in responding to patient questions, Novartis has prepared and disseminated patient education materials. In addition, some of the these same groups mentioned above were contacted again during the time of the annual meeting of the American Society of Hematology (ASH) in San Diego, CA, December 2004 in order to provide an update on the topic of ONJ.

Novartis is committed to working with outside experts and health regulatory agencies to help ensure that patients with ONJ are evaluated appropriately and that information continues to be provided to clinicians and patients.

8 Novartis assessment and recommendations

8.1 Overall assessment of ONJ

Evaluation of data

ONJ in cancer patients was only sporadically reported in the literature prior to 2003, with the exception of osteoradionecrosis of the jaw in head and neck cancer patients receiving radiotherapy. In late 2002, Novartis first received spontaneous reports of ONJ in patients who were receiving bisphosphonate therapy. Subsequently, there has been an increase in the reports of ONJ, with more than 600 reported cases reported to Novartis as of December 2004. In an effort to better understand this clinical entity, we have evaluated clinical trial data, post marketing spontaneous reports, preliminary data from the MD Anderson retrospective chart review, and literature. All of these datasets have limitations which prevent firm conclusions

from being drawn, which will be discussed later. As a consequence, a causal relationship between bisphosphonate use and ONJ cannot be established.

A recent review of the clinical trial database for Zometa and Aredia, involving over 5,200 patients in pivotal trials, utilizing 18 MedDRA search terms that could identify cases of ONJ, led to the identification of six potential cases of ONJ, and 2 cases of osteonecrosis that did not have location specified. While we cannot rule out underreporting, these data from controlled clinical trials indicate that ONJ is an uncommon adverse event.

More than 2.8 million patients are estimated to have received treatment with Aredia or Zometa, or both worldwide since the products launched. As of December 7, 2004, 610 spontaneous report of ONJ in patients treated with these medications have been received by Novartis. A detailed evaluation of these cases is presented in Appendix 3 and summarized in Section 4.2.

A retrospective chart review was undertaken at MD Anderson Cancer Center to try to better understand the natural history of ONJ, the frequency, and clinical information (risk factors, outcomes) related to this condition. It was felt that this retrospective study, at a large institution with comprehensive medical, pharmacy, and dental records, could provide detailed information about ONJ, which would lead to hypotheses that could be tested in other studies. This study provides a clear denominator: patients within the institution that have received bisphosphonates. Preliminary observations from this study as of January 2005, identified 18 cases of ONJ among approximately 1,000 charts reviewed so far. Due to limitations and biases described in Section 4.4, it is premature to draw conclusions about the frequency of ONJ in these patients treated with bisphosphonates.

The literature on ONJ in bisphosphonate treated patients consists primarily of case reports and case series, which are described in Section 4.1 In addition, Durie et al (2004) recently presented observations from data collected via a web-based anonymous respondent survey. Durie observed that among the respondents to the survey, duration of bisphosphonate use is associated with increased risk of ONJ, that 36 month estimates of ONJ are higher for Zometa versus Aredia, that other therapies analyzed were not associated with increased risk of ONJ, and that prior dental problems increase the risk of ONJ.

This web-based survey has a number of limitations. The information was supplied anonymously by the respondents and therefore cannot be validated against medical records. The bias associated with this survey methodology may be significant and has the potential to substantially affect the study conclusions.

All the datasets (summarized in Table 8-1), with the exception of the clinical trial database, have limitations in terms of the information available or are subject to selection bias. The clinical database for Aredia and Zometa was established at a time when awareness of the condition was not as great as it is today.

Table 8-1 Summary of ONJ for datasets

Source		N*	# of Cases	By Tumor Type†	By Drug	Duration/ Latency (Months)
Clinical	Pivotal (11)	Z = 2647	6	4 MM	2 A	<1 - 28

Studies (# of trials)		A = 1334 P = 1234		1 PC 1 H&N	4 Z 0 P	
	Other (20)	3067	0			NA
	Ongoing (>100)	~ 8000	4	1 MM 1 PC 2 BC	4 mg Z	4-9
Spontaneous Reports	Post-marketing & Literature	2.8 million**	610	218 MM 125 BC 267 Others	119 A 248 Z 243 both	<1 – 156 Avr – 28 Z = 18‡ A = 44‡ A+Z = 29
MD Anderson Cancer Center	Retrospective Chart Review	963 (631 BC, 148 MM)	18	11 BC 6 MM 1 Thyroid 1 unknown	3 A 5 Z 9 Both 1 unknown	4-57 Median 33 A 4-33 Z 7-25 A+Z 24-57
Durie	Web-based Survey	904 Respondents (804 had BP)	62***	MM	17 A 40 Z	NA
		299 Respondents	13	BC	NA	NA

*A = Aredia, Z = Zometa, P = Placebo

† MM = Multiple Myeloma, BC = Breast Cancer, PC = Prostate Cancer, H&N = Head and Neck

‡See Appendix 3 for limitations on the estimated average duration of latency for Z and A

**Estimated based on active substance sold

***62 cases of ONJ among all 904 patients, but only 804 patients had BP. 57 ONJ in 804 patients with BP, so 5 ONJ appear to be in the 100 MM patients without BP treatment

Data show a higher reporting frequency of ONJ cases in multiple myeloma compared to other cancers. Data also indicate a wide range (<1-156 months) between treatment initiation with bisphosphonates and the onset of ONJ with an average reported latency shorter for Zometa and than for Aredia. This estimate is confounded by the recent increase in awareness of ONJ, the longer period that Aredia has been available to patients (about 14 years) compared to Zometa (40 months), and the greater current use of Zometa versus Aredia (70% versus 3%), as well as the bias inherent in the data collection as previously described.

There are a number of additional issues which confound and limit the analysis of the datasets above.

- The lack of a clear case definition for ONJ. The series and reports above include a variety of conditions, which make interpretation of results difficult.
- A lack of data on the incidence rate of ONJ in cancer patients not treated with a bisphosphonate. Data from the Durie study indicated that some respondents in the survey who did not receive bisphosphonate reported ONJ suggesting that factors other than BP use may contribute significantly to the disease.

- Recent increase in awareness: the total number of reported ONJ cases has increased within the last year, correlating with the increased awareness from publications and Novartis actions.
- Patterns of health care practice may lead to a lack of shared information between the dentist or oral surgeon who sees these cases, and the oncologist who is caring for the patient medically.
- The period of time that Aredia and Zometa have been on the market differs.. Aredia was approved in the US for hypercalcemia of malignancy (HCM) in October 1991 for osteolytic bone lesions of multiple myeloma in September 1995 and for osteolytic bone metastases of breast cancer in July 1996. Zometa was approved in the US for HCM in August 2001 and for the treatment of bone metastases in February 2002. Thus there are patients who are long-lived, who have had much greater exposure to Aredia than have occurred for Zometa.. Also, most patients who were treated with Aredia were treated in the period before information on ONJ became widely available. These factors may have significant effects on the reported difference in the latency of ONJ for Aredia and Zometa.
- Cancer patients have many risk factors that could lead to osteonecrosis, including their cancer treatment. Evolution of management of myeloma therapy over time, for example, has included the introduction of a number of modalities (thalidomide, velcade, transplant) that could potentially be risk factors for ONJ and have been introduced in the same period of time that cases have been reported.. In addition, the longer the survival becomes the more likely that the patients received more cycles of anticancer treatment and / or more treatment modalities.

With all these caveats, we have evaluated these datasets to better understand this condition and to identify hypotheses for future study. Taken together, these data indicate the presence of significant risk factors for ONJ in many patients, including smoking, trauma, radiation, concomitant medications such as chemotherapy and corticosteroids and prior dental conditions. Notably, prior dental problems appears to be one of the common characteristics of the majority of the cases, tooth extraction served as a triggering event in more than half of the patients, and mandibular tori were noted in several ONJ patients from the MD Anderson chart review. These are important findings that may help us to develop strategies to identity patients at risk and develop prevention strategies to decrease the incidence of ONJ.

8.2 Benefit risk assessment

The high prevalence of bone metastases in patients with advanced metastatic diseases contributes significantly to the burden of disease. Bone metastasis are associated with considerable skeletal morbidity which substantially reduced the quality of life, and in some cases lead to an increase in mortality.

The clinical benefit of Zometa and pamidronate were clearly demonstrated in randomized clinical trials. Prior to introduction of bisphosphonate, >70% of patients with myeloma and bone metastases from breast cancer suffered from skeletal related events (SRE) which can cause considerable morbidity and negatively impact patient's quality of life. Bisphosphonates have now become a standard of care in patients with multiple myeloma and breast cancer, and are recommended in the ASCO guidelines. More recent studies have shown that Zometa is

superior to placebo in the treatment of metastases due to prostate cancer and lung cancer. Treatment with bisphosphonate cannot only keep a significant number of patients free of any SREs, it also reduces the overall risk of developing SREs, i.e, a reduction in the total number of events as well as an increase in time to each event.

The very strong benefit of Zometa and pamidronate to patients in reducing, delaying or preventing skeletal complications of their cancer is undisputed. The condition of ONJ can be a significant medical condition for some patients. Based on current information and the experience that the incidence of ORN has also decreased due to preventive oral hygiene measures and careful dental evaluations, it is likely that this condition can be managed, if dealt with in accordance with the guidance put forth by the oral surgeons. We believe that with these and additional efforts to further elucidate the issue and further drive knowledge of the management guidelines, the positive risk benefit of these compounds can be maintained.

Novartis is committed to investigating these reports, and communicating the findings to physicians and patients. Areas that need further research include better understanding of the natural history of ONJ, identification of risk factors that predict for the development of ONJ, identification of strategies (such as dental care guidelines) which can prevent the development of ONJ, and guidelines for the optimal management of ONJ.

8.3 Novartis recommendation

8.3.1 Additional studies

Based on the discussion above, Novartis recognizes that there is a need to further investigate and understand ONJ. In that light, Novartis will be continuing with the ongoing MD Anderson chart review to better characterize risk factors that might play a role. In addition, Novartis is considering additional studies to obtain more information about ONJ. Studies that are being considered (among others):

1. Data collection on ONJ in ongoing clinical studies
    - Additional data to be collected in ongoing studies on ONJ
    - Additional safety monitoring for ONJ added to a planned postmarketing study recently proposed to the FDA assessing treatment duration & frequency of dosing post 12 months of Zometa therapy. This is a randomized study to determine efficacy and safety in >3000 multiple myeloma and breast cancer patients who have received 10 or more infusions of Zometa, who will be randomized to receive monthly Zometa vs.q 3 month Zometa vs placebo for 12 additional months. This study will be initiated in 2005.
2. Retrospective study in multiple myeloma patients: additional retrospective chart review in center that treats myeloma patients. We are also exploring additional retrospective studies to look at other tumor types. It is critical to identify centers where complete medical, dental, and pharmacy records for patients are available.
3. Prospective study in cancer patients newly treated with bisphosphonates assessing natural history of ONJ.
4. Mechanistic studies to explore potential role of BP use, pending further consultation with experts in the field.

8.3.2 Continue to promote awareness

Novartis will proactively disseminate available information and guidance to healthcare providers and the patients they care for, to increase the awareness of ONJ, and to provide management guidelines. It is important that medical professionals, dentists, and oral surgeons, are aware of ONJ, and work together to coordinate care. Planned actions include:

- Distribute the scientific publication derived from the "white paper" advisory panel through the field sales force and medical services to physicians and nurses and to patient advocacy groups to drive health care professional and patient awareness of management guidelines
- Further support Continuing Medical education activities on ONJ
- Reconvene the Novartis Advisory Board as necessary to update the guidelines

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