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Appendix 3:
Comprehensive Medical Safety Evaluation Osteonecrosis of the
Maxillofacial Area December 2004 Overview

Zometa® (zoledronic acid) Injection

and

Aredia® (pamidronate disodium) Injection

Submitted: February 1, 2005

Oncologic Drugs Advisory Committee Meeting

March 4, 2005

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1   Introduction and background

Aredia (pamidronate disodium for injection), is an inhibitor of bone-resorption belonging to a class of compounds known as bisphosphonates, developed for use in various diseases of bone and calcium metabolism. It is approved in the treatment of conditions associated with increased osteoclastic activity, specifically of hypercalcemia of malignancy, of Paget's disease of bone, and of predominantly lytic bone metastases and multiple myeloma. The international birth date (date of first approval in any country) of this drug is May 2, 1989, and it is currently marketed in 94 countries. On the basis of worldwide sales data (942 kg active substance sold), and assuming a defined total average dose of 500 mg per patient treated, the exposure from the market introduction until 30 November 2004 was estimated to be approximately 1,880,000 patients treated. Aredia has been widely prescribed in cancer patients. For example, in the USA, it is estimated that, during the period January 1999 to January 2001, 72-82% of multiple myeloma patients and 55-73% of metastatic breast cancer patients received this drug [Internal Novartis data October 2003].

Zometa® (zoledronic acid) appears to be the most potent bisphosphonate identified to date.

Zometa® has been approved and marketed for two indications: hypercalcemia of malignancy (HCM) and for prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone. Zometa was first registered in Canada on 21 August 2000, followed by Latvia (Baltic States) and Brazil for the indication treatment of hypercalcemia of malignancy (HCM). The EU authorization via the Centralized Procedure for this indication was received on 20 March 2001 and the US authorization was received on 20 August 2001.

The second indication was first registered in Malta on 13 August 2001, followed by Ecuador and Dominican Republic. The US authorization for this indication was received on 22 February 2002 and the European approval was received on 19 July 2002. Zometa is currently approved in 89 countries worldwide.

The estimate of patient exposure was calculated based on worldwide sales volume in kilogram (22.298 kg) of active substance sold since market introduction until 30 November 2004, divided by the overall average dosage of 24 mg per patient (consisting of 6 treatment cycles at a dose of 4 mg per cycle). Based on this calculation, approximately 929,000 patients received zoledronic acid in the indication HCM and treatment of bone metastases world-wide in the above period.

Based on market research data (Intrinsiq, March 2004), an estimated >85% of breast cancer and multiple myeloma patients in the U.S. with bone metastases receive an I.V. bisphosphonate, of which approximately 65% of receive Zometa and 35% pamidronate.

> **Comment:** To be updated by Marketing if more recent data available

In January 2003 Novartis (the sponsor) was informed that an oral surgeon, Dr. Sal Ruggiero in Long Island, New York (USA), was in the process of collecting a case series of cancer patients with osteonecrosis (ON) of the maxillofacial area (ONJ), having in common a concomitant treatment with Aredia® or Zometa®. After repeated follow up contacts, the sponsor obtained the available case details. Subsequently, the sponsor was informed that

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another oral surgeon, Dr. R. Marx in Miami, Florida (USA), was collecting a similar case series. Because of these reports, Novartis immediately initiated a comprehensive medical assessment of ON in cancer patients treated with the company's bisphosphonates. Previously, overviews and updates on this issue have been submitted to FDA with the due US Periodic Reports [Maladorno D, Breitz B. Zometa Periodic Safety Report. Novartis, March 2003], [Maladorno D, Breitz B. Zometa Periodic Safety Report. Novartis, June 2003], [Maladorno D, Eaton K. Zometa Periodic Safety Report. Novartis, June 2003], [Maladorno D, Eaton K. Zometa Periodic Safety Report. Novartis, September 2003], [Maladorno D, Breitz B. Zometa Periodic Safety Report. Novartis, September 2003], [Maladorno D, Breitz B. Zometa Periodic Safety Report. Novartis, December 2003], [Maladorno D, Eaton K. Zometa Periodic Safety Report. Novartis, March 2004], [Maladorno D, Curtis C. Aredia Periodic Safety Report. Novartis, December 2003], [Maladorno D, Breitz, B. Zometa Periodic Safety Report Novartis, June 2004], [Maladorno D, Eaton, K. Zometa Periodic Safety Report Novartis, September 2004], [Maladorno D, Curtis C. Aredia Periodic Safety Report. Novartis, December 2004]. This document updates the findings for both Aredia and Zometa.

2   Preclinical data

2.1   Preclinical pharmacology

It has long been recognized that there is an intimate relationship between endothelial cells, chondrocytes and osteoclasts, both in the formation of new bone and during the remodelling of old bone. Vascular invasion is an essential component of endochondral bone formation, a process in which bone replaces cartilage through the simultaneous invasion of osteoclasts and endothelial cells. As chondrocytes differentiate, they secrete into the matrix factors, such as vascular endothelial growth factor and transferrin, which induce vascular invasion. This concept of coupling between the differentiation of chondrocytes and angiogenesis in the growth plate is supported by animal studies showing that inhibition of cartilage differentiation disrupts vascular invasion (Schyipani 1997, Komori 1997). Similarly, inactivation of VEGF with a specific antibody in young mice suppresses angiogenesis in the epiphyseal growth plate and impairs trabecular bone formation, thus indicating that VEGF-mediated capillary invasion is essential for growth plate morphogenesis and cartilage remodelling (Parfitt 2000). However, endochondral bone formation and angiogenesis do not appear to require osteoclast activity. In osteoclast deficient animals endochondral bone formation and vascular invasion proceed normally in the absence of any osteoclastic (or chondroclastic) resorption (Deckers et al, 2002). Angiogenesis also appears to be important for the renewal of old bone (bone remodelling). In the cortical cutting cone the actively resorbing osteoclasts are usually located at the tip of sprouting capillaries, and in trabecular bone osteoclasts are in close contact with endothelial cells (Gerber, et al 1999).

Against this background of a close association between osteoclasts and endothelial cells, it is pertinent to consider the potential effects that inhibitors of osteoclast activity, such as bisphosphonates, might exert on angiogenesis. Recently several nitrogen-containing bisphosphonates (pamidronate, ibandronate, risedronate, zoledronate) have been shown to inhibit angiogenesis in non-mineralized tissue in various rodent models (Wood 2002, Fournier 2002, Fournier 2003). The mechanism of this soft tissue effect of bisphosphonates has yet to

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be elucidated. Bisphosphonates rapidly bind to bone and have a short plasma half-life, as a result there is only a low, transient exposure of non-mineralized tissues to drug. Despite the fact that bisphosphonates accumulate in bone, there are no data to suggest that that these compounds inhibit angiogenesis of normal vessels or induce osteonecrosis in vivo when given at pharmacologically relevant doses. However, there is a report -- yet to be independently confirmed -- that pamidronate treatment can induce a modest blood flow reduction in the tibia and distal femur of young female rats (Kapitola and Zak 1998). By contrast, both short- and long-term studies in rats and monkeys, have produced no evidence that administration of pamidronate or zoledronate at doses which markedly suppressed bone resorption exerted any deleterious effect on bone (Pataki 1997, Hornby 2003, Azuma 1998, Binkley 1998, Bouquot 2000, External Study Report MIN 955041). On the contrary, recent data indicate that zoledronate exerts a beneficial effect in 2 rat models of osteonecrosis by preserving femoral head structure while revascularization occurs (Little 2003a, Little 2003b). Moreover, preliminary data from a rat fracture repair model indicate that zoledronate treatment does not delay endochrondral ossification, a process that requires revascularization (McDonald, Zulai and Little 2004).

In contrast to the above findings obtained in animal models of benign bone disease, zoledronate has been shown to reduce micro vessel density in the bone lesions of mice bearing the 5T2 myeloma cell line (Croucher, et al 2003). However, the dose schedule used in this study, 120 µg/kg SC twice a week, corresponds to more than ten-fold the human 4 mg dose and the vessels investigated were predominantly tumor vessels.

Although bisphosphonates have primarily been developed for the treatment of osteoporosis and bone metastases, they have also been investigated as a potential therapy for periodontitis. Several preclinical studies have indicated that bisphosphonates (risedronate, pamidronate, alendronate, neridronate) can inhibit the elevated alveolar bone loss associated with experimental periodontitis in a variety of animal models (Shoji 1995, Shibutani 2001, Reddy 1995, O'uchi 1998, Weinreb 1994, Brunsvold 1992). In these studies there was no evidence of osteonecrosis of the jaw bones despite bisphosphonate treatment lasting for up to 6 months at doses of up to an order of magnitude greater than those approved for clinical use.

Apart from the specific dental studies, there is very little preclinical literature on the effects of bisphosphonates on bone metabolism in the jaw. In a histomorphometric study comparing bone turnover in the humerus and mandible of aged ovariectomized rats, risedronate (dosed SC for 10 weeks at approximately twice the equivalent oral human weekly dose for osteoporosis treatment) markedly reduced bone formation rates on the endocortical surface of the humerus and the endosteal surface of the mandible. By contrast, there was little effect on bone turnover at the periosteal surface of either the mandible or mid-shaft humerus (Hunziker, Wronski and Miller 2000).

These data suggest a differential sensitivity of bone turnover to bisphosphonate inhibition at different sites within a particular bone, but do not indicate that the overall response pattern of the mandible is any different from that of the humerus.

In conclusion, there is no evidence from the preclinical studies that either pamidronate or zoledronate affects angiogenesis during bone formation or bone remodelling in normal or estrogen-deficient animals. The observation that bisphosphonates inhibit angiogenesis in soft

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tissues and in myelomatous bone lesions implies a tissue-specific response to bisphosphonates, and this observation does not appear to be generalizable to the jaw bone. Moreover, there has been no published report of osteonecrosis in animal models, in the axial or appendicular skeleton or in the jaw bones, associated with either pamidronate or zoledronate or indeed any other bisphosphonate. On the contrary, pamidronate and zoledronate are now being used in pilot clinical trials for the prevention and treatment of osteonecrosis. Finally, it is interesting to note that, in the absence of bisphosphonate treatment, marked changes in blood flow and vascularization of the mandible have been noted in a monkey model of experimental inflammation of the mandible, as well as in chronic osteomyelitis of the jaw in humans (Wannfors 1989, Wannfors 1991).

2.2   Toxicological studies

A comprehensive pre-clinical safety assessment has been performed for pamidronate and zoledronate that includes a wide range of oral and parenteral toxicology studies in multiple species at doses comparable to and at many mulitples of those typically administered to the oncology patient (90 mg pamidronate, 4 mg zoledronate). These studies included acute studies in three species; repeat-dose subchronic and chronic studies in two species, including extensive IV infusion studies in the dog; reproductive studies in two species; 2-year carcinogenicity studies in two species; in vivo/in vivo mutagenicity studies; and additional special studies including local irritation, dermal, etc.

Nonproliferative hyperostosis of the metaphyseal junction in growing animals is a change produced by all bisphosphonates, including pamidronate and zoledronate. It was observed in virtually all treated animals in the pre-clinical safety studies and involved a lengthening of the growth plates as a consequence of a reduction in osteoclastic bone resorption, clearly a pharmacological effect. Degenerative bone findings similar to those described for osteonecrosis in humans have not been observed following pamidronate administration. The only osseous changes of a degenerative nature seen with zoledronate occurred in a pilot study in dog wherein exposure at the level of bone was estimated to be very high (30 - 80x therapeutic human dose, daily for up to one week) (Longo 2002). In this study bone focal lesions were observed at the metaphyseal junction (growth plates) of rib and femur, the two bones evaluated histologically. They were characterized by osteoclast karyorrhexis and increased mitotic activity, hemorrhage, edema, necrosis, inflammation and two instances of an accompanying periosteitis. The etiology was attributed to concomitant gastrointestinal ulceration produced by the zoledronate oral formulation being tested resulting in direct, unimpeded systemic exposure affecting the growth plates of these developing animals. It is known that bone is the recipient of up to 60% of the administered dose of zoledronate. Moreover there is a propensity for zoledronate to further concentrate in those areas of bone where growth and remodeling is greatest such that these osseous changes were not unexpected.

Based upon microanatomy and anatomic location, the bone finding described as osteonecrosis of the jaw in the human (Marx and Stern 2002) bears no morphological resemblance to those bone changes described in the latter animal study. Moreover a careful search of the literature did not reveal any known association between bisphosphonate administration and the phenomenon of osteonecrosis in animals. Animal experiments to study the possible role of

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bisphosphonates (including pamidronate and zoledronate) in the etiology and pathogenesis of ONJ were considered. However, it was concluded that the design and conduct of such studies would be extraordinarily complex taking into account this condition's multifactorial etiology and traumatic (e.g. tooth evulsion studies in the canine) yielding what could at best be considered equivocal results.

3   Review of the drug safety database

3.1   Methodology

The Novartis worldwide spontaneous reports drug safety database for Aredia and Zometa was searched for the following MedDRA Version 6.1 preferred terms:

'osteomyelitis', 'osteomyelitis acute', 'osteomyelitis chronic', 'osteomyelitis drainage', 'aseptic necrosis bone, 'osteonecrosis', 'bone infarction', 'necrosis', 'sequestrectomy', 'primary sequestrum', 'secondary sequestrum', 'tertiary sequestrum', 'maxillofacial operation', 'jaw operation', 'mandibulectomy', 'oral surgery', 'jaw lesion excision', 'bone debridment'.

The primary reporters of osteonecrosis of the jaws have been using interchangeably terms suggestive of osteonecrosis and terms suggestive of osteomyelitis and other jawbone infections. In fact the assumption has been made that, cases presenting with signs and symptoms of maxillofacial bone infection previously experienced an otherwise non-documentable primary vascular event. The drug safety database indeed appears to be made up of reports with a combination of various terms associated with these etiologically different conditions. Therefore, the search was designed to capture both.

The cut-off date of the search was from introduction until December 7, 2004 (date of case creation in the drug safety database). The selected cases were printed in detailed line listing format and medically reviewed in order to eliminate cases proven not to be or unlikely to refer to osteonecrosis of the maxillofacial area.

3.2   Results

The drug safety spontaneous reports database search screening identified 610 reports of patients experiencing signs and symptoms suggestive of osteonecrosis and/or osteomyelitis of the maxillofacial area:

- 120 reports noted Aredia as the only suspect drug (including one case with Zometa in the medical history),
- in 116 reports both Aredia and Zometa were reported as suspected (the two drugs were given most frequently sequentially, but in a few cases the treatments were switched, sometimes more than once)
- 374 reports noted Zometa as the suspect drug. Of these 374 reports, 126 reported Aredia in the treatment history

In 8 cases out of the 610, the patients also received oral bisphosphonates concomitantly or prior to the IV bisphosphonate treatment.

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Two reports (PHEH2003US02597 with Aredia and PHEH2003US02566 with Zometa) refer to the same patient. In one case it is unknown if the patient received Aredia or Zometa (PHEH2003US04611: for the purpose of the analyses done, this case was handled as if both drugs were administered).

The first report of osteonecrosis of the jaws was received by the sponsor in December 2002, while reports from sources outside the US have been received only since February 2004.

The country of origin of the reports is displayed below:

Table 3-1   Distribution of spontaneous reports by country

Country	Number of reports
Australia	7
Belgium	25
Brazil	18
Canada	7
Chile	2
France	2
Germany	55
Greece	1
Israel	11
Italy	14
Mexico	1
Norway	4
Singapore	1
S.Africa	1
Spain	12
Sweden	1
UK	1
USA	440
Switzerland	7
TOTAL	610

Of the 610 reports, the majority (557) reported the adverse event term of osteonecrosis, in association with a variety of other maxillofacial abnormalities, particularly osteomyelitis, which frequently was the presenting clinical picture of the patient at time of diagnosis. "Impaired healing" following dental extractions was often the first abnormality which led to a subsequent diagnosis of osteomyelitis or osteonecrosis. Twenty seven reports had a documented actinomycotic infection of the maxillofacial lesion.

The most common osteonecrosis or osteomyelitis location was the mandible (222/610 reports), followed by the maxilla (69/610). The remaining cases had other or unspecified maxillofacial localization, including a generic localization to the "jaw". Some reports did not specifically mention a maxillofacial localization of the lesion, but based on the contest of the

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information (e.g. when received from maxillofacial surgeons), they have been interpreted as having such location.

The current tally of the type of reports is as follows: 531 spontaneous reports and 79 literature cases. Most reports were initially received as spontaneous reports by the sponsor. However, the two primary reporters, Drs. Marx and Ruggiero, have also collected information on a large number of cases seen by others, and included them in their publications (Marx 2003, Ruggiero 2004). Several cases were consequently re-classified as literature cases. It is also possible that some of the patients mentioned with few details in Dr. Ruggiero's paper (Ruggiero, et al 2004), were actually already included in Novartis' safety database. Several reporters have in fact contacted both Novartis and Dr. Ruggiero providing information on their cases. However, for lack of details available in Dr. Ruggiero's database, an exact match with existing cases was not always possible.

Most of the reports occurred in females (340/610, 56%) while 231/610 (39%) occurred in males. In 39 cases the gender was not reported.

Age was not reported in 142 reports. Among the remaining 468, the mean age was 64 years (range 27-93). When stratified by gender, the mean age was 62.6 for females (n=281, range 27-93), and 66.4 for males (n= 182, range 41-89).

Aredia and Zometa were prescribed for the following indications: multiple myeloma (218) breast cancer (125), bone metastases (110), prostate cancer (37), osteoporosis (13, of which nine reported concomitant cancer), hypercalcemia (6), oral neoplasm (2), lung cancer (3), uterine cancer (1), CML (1), renal cell carcinoma (2), breast and ovarian cancer (2), lymphoma (4), Paget's disease (1), unspecified cancer (6) and unknown diagnosis (79).

It should be noted that this type of information is often quite vague, and that typically both the oral surgeons and the sponsor experienced difficulties in integrating the case information pertinent to the oral events with the information available to the family dentists and to the prescribers of the bisphosphonate therapy, which often did not respond to the requests for additional clarifications. Consequently, the information on parameters such as indication, dosage and duration of treatment is often vague or incomplete or sometimes contradictory, despite the sponsor's efforts to collect it.

In 251/610 (41%) of the reports there is an unknown duration of bisphosphonate treatment and/or the date of the event diagnosis is not available, therefore information on the temporal relationship can not be confirmed.

However, in 359/610 (59%) of the reports the information regarding the treatment and the event dates was available, and a calculation of the time from bisphosphonate treatment start to onset of osteonecrosis (reported diagnosis or first symptoms) was possible.

In cases where the patient switched from one drug to the other, including cases reported only with one suspect drug, we calculated the total time from the treatment start (Aredia or Zometa) until the establishment of the diagnosis or until the first symptoms indicative of osteonecrosis (eg impaired healing after tooth extraction, bone exposure, etc.).

The time interval between initiation of the bisphosphonate treatment (Aredia or Zometa) to AE onset, for these 359 reports , ranged from <1 week to 626 weeks (<1 to 156 months), and

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averaged 28 months. When stratified by treatment group (without adjusting for biases such as different time of drugs on the market), the time interval between initiation of the bisphosphonate treatment to AE onset, averaged 44 months for the assessable patients who received only Aredia (64/359, 18%), 29 months for the patients who received both Aredia and Zometa (177/359, 49%), and 18 months for the patients who received only Zometa (118/359, 33%).

In 303 (50%) of the cases potential triggering events like dental surgery, local trauma, tooth extraction or dental infection were reported, preceding the diagnosis of ONJ.

In 450 (74%) of the reports the patients had at least one of the below listed risk factors. It should be noted that several reports were initially provided to the sponsor lacking information on risk factors, which were subsequently found after follow-up. Similarly, it can be assumed that cases without apparent relevant risk factors, particularly the ones received more recently, may have been incompletely documented. For example, with respect to the patient population with metastatic cancer, it is expected that the vaste majority of the patients have received chemotherapy (and additional corticosteroids in the multiple myeloma subset).

Table 3-2   Risk factors

Reported Risk Factors	Number of Reports (%)
Corticosteroids(concomitant or in medical history)*	230 (38%)
Chemotherapy (concomitant or in medical history)*	315 (52%)
Hormonal therapy	63 (10%)
Radiotherapy to the head and neck area	28 (5%)
Anemia	89 (15%)
Thalidomide	89 (15%)
Transplant	57 (9%)
Other**	263 (43%)
*in 188 (31%) reports the patients had both corticosteroids and chemotherapy	
** broad criteria used including all conditions and medications with potential impact on bone metabolism. See reference 1.	

Among the 263 reports with "Other" risk factors included in the table above, three had a prior Herpes infection of the maxillofacial area.

The case narratives were reviewed for information pertaining to bioptic procedures, with the following results:

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Table 3-3   Cases with reported biopsy procedures (n=171/610)

	Osteonecrosis	Osteomyelitis without osteonecrosis	Other		Total
Aredia	19	12	21		52
Aredia and Zometa	17	15	6		38
Zometa	36	24	21		81
Total	72	51	48		171

Of the cases with reported biopsy results, only one was found to possibly have metastatic disease (PHEH2004US03342).

3.3   Discussion

Age is a significant factor associated with ON of the maxillofacial area. It has been published that in a case series of 35 consecutive cadaver jawbones of elderly humans, almost a third had microscopic and macroscopic evidence of ischemic damage of the bone (Bouquot and McMahon 2000). The risk related to age is also associated with risk dependent on gender: in the general population, it is estimated that women 65 years and older have a rate of ON of the jaws more than twice higher than women 25 to 65 of age (Bouquot and McMahon 2000).

The mean age of two maxillofacial ON case series reported in the literature was around 50 years of age (Shankland 2002), with a predominance of females. When the demographic characteristics of the published case series of maxillofacial ON is compared with the demographics of the cases reported to Novartis, it can be noted that the gender distribution of the latter is within the expected limits (56% females), while the mean age is substantially higher (61.7 years old versus the published average in the early 50s). The gender distribution in the reported cases may however be confounded by the use of the drug in gender-specific cancers such as breast or prostate.

Bisphosphonate recipients are primarily cancer patients. From the above considerations it can be inferred that, in addition to factors such as chemotherapy, steroids, anemia, and increased risk of oral infections, the cancer population is at risk of developing ON also because it is typically comprised of patients of relatively advanced age. 218/610 (36%) of the reported cases had multiple myeloma, which can be associated with serum hyperviscosity (Longo 2001), and it may represent a risk factor for ON. Many of the cases reported to Novartis have received corticosteroids therapy. While this has been specifically reported only for some patients, in many other cases it can also be inferred from the underlying cancer diagnosis. Consistently with the published literature, in an epidemiological study conducted by Novartis (Sablinska 2003), the risk of osteonecrosis in systemic corticosteroid users was almost 4 times higher than in non users.

The analysis of time from initiation of bisphosphonate treatment to onset of ONJ provided different average estimates for the patients who only received Aredia, and the patients who only received Zometa. It should be noted however that the data may be confounded by known factors such as cancer history and stage, prior or concurrent corticosteroid and chemotherapy.

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Chemotherapy regimens have been changing over time, and may differ by geographical location. In addition, it is likely that the different time on the market of the two drugs, and the recent increased awareness on osteonecrosis consequent to the Novartis initiatives and published reports, may have biased the data.

It should be noted that in the patients who received both drugs sequentially, the average time from drug initiation until event onset for the individual bisphosphonate drug did not differ significantly from the subgroups who received only one of the IV bisphosphonates.

4   Conclusions

The majority of the cases of maxillofacial osteonecrosis reported to Novartis were identified by reporters who suspect Aredia® or Zometa® as the primary cause of this event. The following evidence should however be weighted against this hypothesis:

- The clinical case information available to a large proportion of the reporters appears to be affected by selection bias, and to be extremely 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. Overall, it appears that most the 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 in order to obtain the maximum level of information available.

- Cases of osteonecrosis of the maxillofacial area have to be expected in the cancer population, because of the simultaneous effects of multiple and significant risk factors: corticosteroids, chemotherapy, transplant, radiotherapy, dental infections and procedures, relatively advanced age.

- Since cancer patients with bone involvement are routinely treated with bisphosphonates, the concurrence of bisphosphonate use and ONJ is not surprising, and it does not establish a causal relationship.. In the USA, it is estimated that, during the period January 1999 to January 2001, 72-82% of multiple myeloma patients and 55-73% of metastatic breast cancer patients received Aredia. Since its market introduction, Zometa became the most frequently used bisphosphonate for the treatment of bone metastases, with a >65% unit share of the bisphosphonate market [Internal Novartis data October 2003]. It is, therefore not unexpected that an increasing number of the recently reported cases of osteonecrosis have been seen in patients treated with Zometa, in line with current medical practice.

- Aredia has been used extensively for years, since it was first introduced in the worldwide market since 1989. As of the end of November 2004, it is estimated that approximately than 2.8 million patients have been treated with Aredia or Zometa. No spontaneous reports associating ON with these drugs have been provided to the sponsor prior to December 2002. After the introduction of Zometa, Aredia sales have been declining: it is to be expected that in the future the number of adverse event reports associated with this drug will be declining as well.

- The preclinical and toxicological studies do not suggest that inhibition of osteoclastic activity is associated with the onset of a significant deficit in bone vascularization. The

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specific effects on angiogenesis seen in some specific experimental conditions do not appear to be applicable to the clinical use of bisphosphonates.

- The recently observed increase in reporting and probable earlier diagnosis (in some cases over- diagnosis) could be explained by the increased awareness, presentations at scientific meetings and Advisory Board meetings including the primary reporters and representatives of other disciplines. Osteonecrosis of the jaws has an unknown latency period, and may remain asymptomatic for many weeks or months and may only be recognized by the presence of exposed bone in the oral cavity. These lesions typically become symptomatic when sites become secondarily infected or there is trauma to adjacent and/or opposing soft tissues via the sharp or rough surfaces of the exposed bone.

- Given also the different reporting sources (including publications, oral surgeons, clinical oncologists, consumers and Health Authorities), there is a high likelihood that the Novartis safety database includes duplicates.

Based on the above, Novartis does not believe that there is sufficient evidence of a causal association between Aredia or Zometa and osteonecrosis. However, in the interest of patient safety and physician awareness, the USPI has been amended for both drugs to reflect that reports of osteonecrosis have been received by the sponsor. The issue will require continuous monitoring, and additional follow-up efforts for the cases already reported.

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