European Medicines Agency

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CHMP ASSESSMENT REPORT

ON

BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW

Procedure under Article 5(3) of Regulation (EC) No 726/2004

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1 BACKGROUND INFORMATION ON THE PROCEDURE

On 19 February 2009, Denmark (DK) presented to the EMEA a request for a CHMP opinion under Article 5(3) of Regulation (EC) No 726/2004 to review issues related to the adverse event osteonecrosis of the jaw (ONJ) following the use of bisphosphonates.

Currently, medicinal products authorised in the European Union containing bisphosphonates are manufactured using alendronic acid, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, tiludronic acid, and zoledronic acid as active substance.

Centrally authorised bisphosphonate-containing medicinal products include Aclasta and Zometa (zoledronic acid), Bondenza, Bonviva, Bondronat (ibandronic acid) and Adrovance and Fosavance (alendronic acid).

A first informal class review performed by the Pharmacovigilance Working Party (PhVWP) in 2005 resulted in revised labelling aiming at minimising the risk for developing ONJ. During 2007 increasing concern emerged that these risk minimisation measures did not suffice, as the numbers of spontaneously reported cases did not decline substantially.

A second class review was therefore initiated in December 2007. Information was requested from the Marketing Authorisation Holders (MAHs) of bisphosphonate-containing medicinal products with Lists of Questions issued in December 2007 and April 2008.

The overall conclusions of the assessment of the MAH responses at PhVWP was that sufficient progress had not been achieved and that lack of knowledge hindered appropriate prospective risk management. Since the 2005 class review the complexity of the safety issues has increased considerably, as mirrored by the extensive amount of experimental, preclinical, clinical and pharmaco-epidemiological studies published in the scientific literature, as well as by the fact that the occurrence of cases of ONJ has developed further across the class, across different indications and routes of administration. Therefore it is considered necessary to apply other measures to ensure a satisfactory outcome in the interest of patient safety.

The CHMP has been formally asked by DK to draw up an opinion on the suspected association between the use of bisphosphonates and osteonecrosis of the jaw (ONJ). Denmark was appointed overall Rapporteur and was supported in their work by Austria, France and the United Kingdom as Co-Rapporteurs.

The CHMP opinion was sought on the following:

(1) the criteria for the diagnosis or definition of ONJ,

(2) the underlying pathophysiological mechanism(s)

(3) a risk stratification between products and patient populations;

(4) the appropriate/necessary risk minimisation measures.

To further aid the CHMP in reaching its opinion an *ad hoc* expert meeting was convened on 19 March at the EMEA. This assessment report considers the views of this expert meeting alongside the available data from the published literature including clinical guidelines produced by learned societies.

1.1 Steps taken for the procedure

- During the March 2009 CHMP meeting the following was agreed:
  - Dr. Thirstrup (DK) CHMP Member, was appointed Rapporteur for the review procedure under Article 5 (3) for bisphosphonates and osteonecrosis of the jaw.

- Prof. Andrea Laslop (AT) CHMP Member, was appointed Co-Rapporteur for the review procedure under Article 5 (3) for bisphosphonates and osteonecrosis of the jaw.
- Prof. Philippe Lechat (FR), alternate CHMP Member, was appointed Co-Rapporteur for the review procedure under Article 5 (3) for bisphosphonates and osteonecrosis of the jaw.
- Dr. Rafe Suvarna (UK) alternate CHMP Member, was appointed Co-Rapporteur for the review procedure under Article 5 (3) for bisphosphonates and osteonecrosis of the jaw.
- The procedure started on 23 March 2009.

- An ad-hoc expert meeting took place on 19 March 2009. A meeting report dated 16 April 2009 was circulated to all CHMP members during the April 2009 CHMP plenary meeting.
- The Rapporteurs' Joint Assessment Report was circulated to all CHMP members on 3 July 2009
- The Rapporteurs' updated Joint Assessment Report was circulated to all CHMP members on 15 July 2009.
- A revised Rapporteurs' Joint Assessment Report was circulated to all CHMP members on 22 July 2009
- A further revised Rapporteurs' Joint Assessment Report was circulated to all CHMP members on 16 September 2009
- On 24 September 2009, the CHMP adopted an opinion.

2. SCIENTIFIC DISCUSSION

2.1 Background

In 2005 a class review resulted in revised labelling for all bisphosphonates aiming at minimising the risk for developing ONJ in patients treated with bisphosphonates for a variety of malignant and benign diseases.
Since then the complexity of the safety issue has increased considerably, as is mirrored by the extensive amount of experimental, preclinical, clinical and pharmaco-epidemiological studies published in the scientific literature, as well as by the fact that the occurrence of cases of ONJ has developed further across the class, across different indications and administration forms.

During 2007 increasing concern emerged that these risk minimisation measures did not suffice. Therefore it was considered necessary to apply other measures to ensure a satisfying outcome in the interest of patient safety.

Consequently the PhVWP initiated a second class review and the CHMP agreed to request information from the MAHs, in the form of two sets of questions issued in December 2007 and April 2008 respectively.

Main findings and conclusions of the 2008 class review

Osteonecrosis of the jaw in association with bisphosphonates is a rare but serious and most often irreversible event. A total of 5300 cases of ONJ have been identified in the Eudravigilance database (as per October 2008), and a signal of disproportionate reporting has been confirmed across the class. The evaluation was hampered by the lack of a common definition of ONJ and by the scarce information in many of the case reports. The majority of cases of ONJ occured in association with the most potent bisphosphonates and in patients who had malignant disease and were treated with intravenous bisphosphonates. The reporting trend is presumably decreasing for the majority of the products. Patient exposure is extensive and the risk/benefit balance is in general not questioned.

The underlying pathophysiological mechanism is still unknown. Several hypotheses have been proposed and some research is ongoing. It is clear though that future research areas need to be further explored. Multiple risk factors have been identified, but treatment and prevention are still largely empirically based.

Following discussions at the level of the PhVWP in February 2009 it was considered necessary to obtain a better understanding of the underlying pathophysiological mechanism(s), to reach agreement on a definition of ONJ, to be able to rate the risk in-between products and patient populations and to be able to implement evidence-based preventive measures. Denmark initiated this procedure in March 2009.

For this purpose it was agreed to convene an expert meeting in March 2009 within the frame of this procedure (Meeting Report see annex 6). A List of Questions to be addressed to the experts was agreed (see annex 5).

2.1 Definition of ONJ

Currently, different definitions of ONJ are being used by the marketing authorisation holders of registered bisphosphonate products. Reporting of ONJ is further hampered by the fact that while "Osteonecrosis of jaw" exists as a low-level term (LLT) in the MedDRA terminology, there is currently no specific ICD-10 code for ONJ.

A common, widely accepted definition of ONJ is regarded as a first step towards gaining more knowledge of this rare adverse event in relation to bisphosphonate treatment. It is also seen as a prerequisite for assessing the effectiveness of preventive measures.

Jaw bone necroses with a similar presentation were already known in the "pre-bisphosphonate era" and were historically associated with actinomyces infections. Triggers of ONJ other than bisphosphonates, such as corticoid treatment, have been described. Hence, it is proposed that the name of the event should primarily focus on the clinical presentation and then indicate the possible cause. This results in a hierarchical naming convention, as follows:

Osteonecrosis of the Jaw → Drug related → Bisphosphonate related

After consultation with experts and considering definitions proposed by different scientific societies, the CHMP recommended to use a case definition based on the Position Paper on Bisphosphonate-related Osteonecrosis of the Jaw published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2007 and its 2009 update. To further describe the severity and stages of the condition, a staging system largely in accordance with the AAOMS 2007 position paper is recommended**.**

Compared with the AAOMS position paper the CHMP proposed minor changes: To be consistent with the above proposed hierarchical naming convention, the order of the characteristics of ONJ given by AAOMS is changed; the definition as adopted by the CHMP describes first the event and then the possible cause. Secondly, it is currently being discussed whether to include the term "necrotic" in addition to "exposed bone" in the definition of ONJ. In the 2009 update of the position paper on bisphosphonate-related ONJ, the AAOMS removed the term "necrotic" from the definition of ONJ and defined an early stage of ONJ ("stage 0"). "Stage 0" describes patients with no clinical evidence of necrotic bone, but presence of non-specific symptoms or clinical and radiographic findings, such as odontalgia, bone pain, etc. The value of defining a "stage 0" that can only be diagnosed retrospectively seems rather limited, and the likelihood of a patient with "stage 0" advancing to a higher disease stage is not known at present. It seems therefore preferable not to include this stage in the proposed definition. Early findings that could raise suspicion of ONJ as well as proposed diagnostic steps will be described in an addendum to the staging system.

The CHMP further noted that there is no difference in the clinical presentation between spontaneously occurring cases of ONJ and cases of ONJ occurring following dental invasive procedures. Therefore, this differentiation should not be part of a case definition. According to expert opinion, it may well be that first changes of the jaw bone in relation to bisphosphonates may have already developed before dental surgery is performed, and surgery can therefore be considered as a co-factor precipitating the

clinical picture of ONJ (mainly due to the risk of infection). It should be noted that any other event that exposes the jaw bone could theoretically have this effect. This may possibly include trauma following the use of toothpicks or periodontal treatment, which could expose bone to bacteria. In this context, a dental extraction could also be seen as a consequence of already existing bone changes preceding clinically overt ONJ, with the subsequent exposure of the bone potentially worsening the situation.

In conclusion, the CHMP considered that "Osteonecrosis of the jaw related to bisphosphonates" can be defined as follows:

"A patient may be considered to have ONJ related to bisphosphonates if all of the following 3 characteristics are present:

1) Exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks

2) No history of irradiation of the jaw

3) Current or previous treatment with a bisphosphonate"

The following staging system for ONJ should be used describing 3 stages* of the condition:

Stage 1: Exposed or necrotic bone in patients who are asymptomatic, no evidence of infection

Stage 2: Exposed or necrotic bone in patients with pain and clinical evidence of infection

Stage 3: Exposed or necrotic bone in patients with pain, infection and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor

**Addendum*
It should be noted that at an early stage of the condition, patients can have non-specific symptoms such as odontalgia, bone pain, etc. without exposed bone ("stage 0"). An X-ray might be helpful in identifying such early ONJ, although X-ray alone is probably not sufficient to make the definitive diagnosis. However, findings at this stage could raise suspicion in patients at risk to develop ONJ. Additionally, it has been suggested that a scintigram or a PET image could help identifying ONJ at this stage; however the value of these methods is not sufficiently proven. In case of non-specific findings, dentists should ask about the patient's history concerning bisphosphonates, and patients should be closely followed.

2.2 Pathophysiology

Bisphosphonates have a high affinity for bone mineral and bind strongly to hydroxyapatite resulting in selective uptake to the target organ and high local concentration in bone, particularly at sites of active bone remodelling. Bisphosphonates act by inhibiting osteoclast cell function resulting in reduced bone resorption. Bisphosphonates may also reduce osteoblast and osteocyte apoptosis (Drake et al., 2008).

There are 2 main types of bisphosphonates: non-nitrogen containing bisphosphonates and nitrogen containing bisphosphonates (Russell et al., 2008). Non-nitrogen containing bisphosphonates (etidronate, clodronate and tiludronate) act by interacting with ATP in osteoclasts forming ATP analogues that induce osteoclast apoptosis. Nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonic acid pathway, in osteoclasts which prevents the production of proteins essential for their function and survival. Inhibition of this enzyme also leads to an accumulation of isopentenyl diphosphate (IPP) which is incorporated into an analogue of ATP that can induce osteoclast apoptosis. Nitrogen-containing bisphosphonates can be further divided into 2 groups: alkyl-amino bisphosphonates (pamidronate, alendronate, and ibandronate) and heterocyclic bisphosphonates (risedronate and zoledronate). In addition to inhibiting FPPS, the

heterocyclic bisphosphonates form a more stable enzyme-bisphosphonate complex which increases the inhibitory potency of these drugs.

Significant differences have been found in studies of mineral binding affinity and FPPS enzyme inhibition between individual bisphosphonates and may account for the differences in clinical effects between individual members of this drug class (Russell et al., 2008). Zoledronate has been found to have the highest affinity to bone mineral and the following rank order for mineral affinity has been established: clodronate < etidronate < risedronate < ibandronate < alendronate < pamidronate < zoledronate). FPPS enzyme inhibition also varies between individual bisphosphonates with zoledronate having the greatest inhibitory effect (rank order: etidronate = clodronate (extremely weak inhibitors) <<<< pamidronate < alendronate < ibandronate < risedronate < zoledronate). The effect of bisphosphonate binding to bone on surface charge (zeta potential) has also been studied and is thought to influence the further binding of the bisphosphonate to bone and impact on drug accumulation. The following rank order has been reported with alendronate reported to have the greatest effect on binding capacity: risedronate < clodronate < etidronate < zoledronate < ibandronate < alendronate. Zoledronate is the most clinically potent bisphosphonate with both potent biochemical actions and a high level of affinity to bone mineral.

2.2.1 Restriction of bisphosphonate-induced osteonecrosis to the jaw

The restriction of bisphosphonate-induced osteonecrosis to the jaw is thought to be related to the unique nature of the blood supply, structure, function and microbiology of the jaw bones (Adamo et al., 2008, Marx et al., 2005). The jaw bones have a high blood supply which may result in an increased concentration of bisphosphonates in this area. Bone turnover is also thought to be high in the jaw due to forces related to chewing and the presence of teeth. Dental procedures and dental diseases may also increase bone turnover. The jaw bones may be more vulnerable to trauma and infection as there is only a fragile barrier of a thin mucosa and the periosteum between the jaw bones and the external environment. Furthermore, teeth are only separated from bone by thin connective tissue which may allow easy access for bacteria. There may also be differences within the jaw and between the mandible and maxilla.

2.2.2 Possible pathophysiological mechanisms of osteonecrosis of the jaw

A number of possible mechanisms of ONJ have been proposed (Novince et al., 2009, Reid et al., 2009, Silverman et al., 2009).

Immunomodulation
Immunomodulation, including impairment of local immunity of the jaw bone and changes in immune and inflammatory responses (Wimalawansa 2008), may play an important role in the pathogenesis of ONJ. Local bisphosphonate concentrations or the resulting increase of IPP in the case of nitrogen-containing bisphosphonates may be possible factors responsible for immunosuppressive effects which allow the development of infections at ONJ sites. As bisphosphonates bind calcium, a release of bisphosphonates from the jaw bone, e.g. due to trauma or necrosis, could also lead to localised immunosuppression as some immunological reactions, such as the recruitment of T-lymphocytes and the expression of specific functional signals of dendritic cells, are calcium-dependent.

Infection
The presence of bacteria is an almost universal finding in histological samples of ONJ (*Actinomyces*). Yeast has also been identified in some patients. Biofilms, which are resistant to natural immunity and antibiotics, have also been found at ONJ sites. Bacteria may increase bone resorption and some bacteria may also inhibit bone formation. Bone coated with bisphosphonate may also increase bacterial adhesion through electrostatic interactions (Kos & Luczak, 2008). A role for infection is further supported as the jaw is prone to trauma and bacterial contamination and there are reports of ONJ healing after antibiotic treatment. There is little evidence in the literature *against* a role of bacteria although some authors caution that bacteria in oral lesions would be expected in the micro-organism rich environment of the mouth. Infections may be a secondary complication that worsens the situation due to the reduced local immune response rather than the primary cause of ONJ.

Excessive reduction of bone turnover

Excessive reduction of bone turnover that may impair bone remodelling and repair has been proposed as a mechanism for ONJ. Bisphosphonates are known to reduce bone turnover and remodelling through inhibition of osteoclasts. This is supported by evidence from genetic conditions which affect osteoclast activity and thereby provide means of studying the effects of remodelling suppression. The requirement for remodelling may also be increased in the jaw following infection or dental procedures which are risk factors for ONJ. However osteonecrosis is rarely seen at sites other than the jaw (although this may be due to conditions unique to the jaw) and ONJ does not appear to occur in other conditions associated with reduced bone turnover such as hypoparathyroidism. There is also evidence that bone turnover may not be reduced in ONJ lesions as osteoclasts have been observed in ONJ lesions indicating active bone resorption at these sites.

Impaired angiogenesis

The anti-angiogenic effect of bisphosphonates has been proposed as a possible mechanism for ONJ either as an initiating factor or secondary to reduced bone turnover. Reduced blood supply may be of particular importance in wound healing following dental procedures. Bisphosphonates are known to inhibit vascular endothelial growth factor and formation of capillaries. In cases of ONJ, bisphosphonates may inhibit the building of new capillaries that lead into the bone however this anti-angiogenic effect is not seen in the soft tissue. However, ONJ occurs in both the maxilla which is well supplied with blood vessels as well as the mandible which has a more restricted vascular supply. Furthermore, ONJ has not been identified as a possible drug safety signal in association with other anti-angiogenic drugs although combination treatment of bisphosphonates with other anti-angiogenic drugs (e.g. glucocorticoids, chemotherapy) may have a synergistic effect in the pathogenesis of ONJ.

Bisphosphonate toxicity to soft tissue

Bisphosphonate toxicity to the soft tissue may result in suppression of cell proliferation, mucosal thinning and reduced healing in the oral mucosa which spreads into adjacent bone. Sites with elevated bone turnover are expected to have increased bisphosphonate concentrations which may lead to the release of bisphosphonate from bone into the surrounding oral mucosa. Bisphosphonates are known to be toxic to epithelial cells and oesophageal erosions and ulcers are recognised side-effects. In addition, zoledronate has been demonstrated to induce apoptosis in oral fibroblasts and epithelial cells and there is evidence from *in vitro* studies that the presence of osteoclasts may increase the release of bisphosphonates from bone (Scheper et al., 2008). However some authors have suggested that in cases of ONJ bone damage may be present before soft tissue damage occurs.

Direct bisphosphonate toxicity to bone

At high concentrations in bone bisphosphonates may be toxic to other bone cells as well as osteoclasts. Bisphosphonate concentration may be higher in the jaw and inhibition of the FPPS enzyme affected by nitrogen-containing bisphosphonates can cause apoptosis in any cell. However generalised bone toxicity is not seen with bisphosphonates. The effects of bisphosphonates in the microenvironment may be dependent on the local concentration of bisphosphonate. For IV bisphosphonates the high concentration of bisphosphonate in the blood achieved during the infusion may enable bisphosphonates to enter other cells in addition to osteoclasts and the duration of IV infusion may have important clinical effects.

Other proposed mechanisms

Other mechanisms for bisphosphonate-induced ONJ have been proposed including hypocalcaemia and secondary hyperparathyroidism (Ardine et al., 2009), uncoupling of the osteoblast-osteoclast equilibrium (Sarin et al., 2008), metastasis (Novince at al., 2008) and synergistic effects with other drugs such as chemotherapy and corticosteroids and concurrent diseases. Genetic factors have also been implicated and Matrix Metalloproteinase 2 (MMP) and Rs1934951 polymorphism on CYP2C8 have been proposed as possible candidate genes (Lehrer et al., 2009, Sarasquete et al., 2008).

Proposed models of the mechanism of osteonecrosis of the jaw

Models of possible interacting factors contributing to the pathogenesis of ONJ are discussed in the literature. Adamo et al., 2008 proposed that both the inhibitory effects of bisphosphonates on bone

resorption and their antiangiogenic effects in bone may impair bone remodelling and reduce blood flow. Chemotherapy and antiangiogenic drugs may contribute to this effect together with a greater need for bone remodelling following tooth extraction or infection. The overall effect is lack of bone healing and development of ONJ. Reid, 2009 suggests an alternative model of a vicious cycle in which soft tissue and bone damage following tooth extraction can not heal because of persistent infection which leads to sustained bone resorption and the release of bisphosphonates which may be toxic to epithelial, mesenchymal, vascular and immune cells.

2.3 Risk Stratification

2.3.1 Incidence of ONJ

Patients receiving IV bisphosphonates for cancer indications are considered to be at the highest risk of developing ONJ (Malden et al., 2009, Silverman, 2009). The incidence of ONJ in patients receiving IV bisphosphonates for cancer indications is reported as ranging from 0.8% to 12 % in different studies (AAOMS position paper, 2009).

Patients receiving oral bisphosphonates for osteoporosis or Paget's disease are considered to be at much lower risk of developing ONJ (Malden et al., 2009, Silverman, 2009). In the majority of published studies the incidence of ONJ in patients receiving oral bisphosphonates for osteoporosis or Paget's disease is reported to be low ranging from 0.0004% to 0.06% (AAOMS position paper, 2009). However, one recent study reported that ONJ occurred after invasive dental procedures in 4% of patients receiving alendronate treated in their dental school (Sedghizadeh et al., 2009). So far this is an isolated study and with important selection bias (in that the patients were all at high risk of ONJ), and the result should be interpreted with caution. The reporting rates of post-marketing spontaneous reports of ONJ are much higher for IV bisphosphonates for cancer indications than for oral bisphosphonates approved for non- cancer indications.
The risk of ONJ with IV bisphosphonates used for osteoporosis is not yet known but appears to be lower than in cancer indications. In a double-blind, placebo-controlled trial of once-yearly zoledronate for the treatment of postmenopausal osteoporosis, 2 potential cases of ONJ were identified, one case in the zoledronate and one case in the placebo group (Black et al., 2007). In this trial, 3889 patients received a zoledronate infusion and 3876 patients received placebo. No data are available beyond three years of treatment. Cases reported post-marketing with zoledronate in the treatment of osteoporosis are discussed in the section 2.3.2 below.

2.3.2 Risk factors for ONJ

Bisphosphonate exposure
The most significant risk factor for the development of ONJ in association with bisphosphonates is considered to be bisphosphonate exposure, in particular, individual bisphosphonate potency, the route of administration and cumulative dose.

Zoledronate is the most potent bisphosphonate (both in terms of degree of mineral binding affinity and FPPS enzyme inhibition) and patients receiving iv zoledronate for cancer indications are at the highest risk of developing ONJ (Dimopoulos et al., 2006, Durie et al., 2005, Woo et al., 2006). Pamidronate is less potent than zoledronate and patients taking pamidronate appear to be at a lower risk of developing ONJ compared to zoledronate (Corso et al., 2007). For example, a web-based survey of ONJ in 2004 found that ONJ developed in 10% of patients receiving zoledronate compared to 4% of patients receiving pamidronate (Durie et al., 2005). The nitrogen-containing oral bisphosphonates, alendronate, ibandronate and risedronate are more potent than the non-nitrogen containing oral bisphosphonates, etidronate, clodronate and tiludronate. Most cases of ONJ in association with oral bisphosphonates have been reported in association with alendronic acid which is also the most widely used bisphosphonate world-wide (Hess et al., 2008). Cases of ONJ have also been reported in association with other oral bisphosphonates (both nitrogen-containing and non-nitrogen-containing bisphosphonates): risedronate, ibandronate, clodronate and etidronate (Wimalawansa 2008).

The route of administration is considered to be an important factor in the development of ONJ. A review of 481 cases of ONJ in association with bisphosphonates published in the literature up to 30 June 2007 found that ONJ occurred more frequently in patients treated with iv bisphosphonates (94.2 % of cases) than in patients treated with oral bisphosphonates (5.8 % of cases) (King et al., 2008). The IV route of bisphosphonate administration results in a higher bioavailability of bisphosphonate compared to the oral route and results in greater exposure to the drug (Sarin et al., 2008). It has also been suggested by the experts that the speed of IV administration could play a role.

The cumulative dose of bisphosphonate is also considered to be an important factor in the development of ONJ and is determined by the dose, frequency of administration, duration of therapy and half-life of the drug. The risk of developing ONJ increases with the dose and duration of iv bisphosphonate exposure for cancer indications (Badros et al., 2006, Bamias et al., 2005, Dimopoulos et al., 2006, Durie et al., 2005, Hoff et al., 2008, Jadu et al., 2007, Woo et al., 2006) and may be related to the number of bisphosphonate infusions (Zervas et al., 2006). The time to onset of ONJ for IV bisphosphonates for cancer indications reported in the literature ranges from 4 to 120 months (Abu-Id et al., 2008, Dimopoulos et al., 2006, Hoff et al., 2008, Woo et al., 2006). A longer mean time to onset of ONJ has been reported in patients receiving pamidronate therapy compared to patients receiving zoledronate (Durie et al., 2005, Marx et al., 2005, Woo et al., 2006). For example, the web-based survey of ONJ found that the mean time to onset of ONJ was earlier with zoledronate (18 months) than pamidronate (6 years) (Durie et al., 2005). In the vast majority of cases of ONJ reported in association with bisphosphonates given for non–cancer indications the onset of ONJ occurred after one year or more of bisphosphonate treatment (Hess et al., 2008).

The individual bisphosphonate potency, route of administration and cumulative dose appear to be of greater importance than the indication for treatment with regard to the risk of developing ONJ. The increased risk of ONJ in patients with cancer is thought to be related to higher cumulative doses of bisphosphonates used for cancer indications compared to the doses used in non-cancer indications. Patients receiving IV bisphosphonates for osteoporosis receive lower doses and less frequent drug administrations than for cancer indications. The most potent bisphosphonate, zoledronate, is now available as a yearly IV formulation for the treatment of osteoporosis. To date, only one single case of possible ONJ has been reported with IV zoledronate given for osteoporosis in clinical trials (in study H2301, in which also one case of ONJ was identified in the placebo group). To date (data from PSUR no. 6 with data lock point (DLP) of 30 April 2009) 21 reports of ONJ have been reported post marketing. Only 6 of these cases were reported with diagnostic evidence of ONJ (e.g. exposed or necrotic bone). Further data are needed to state if this may reflect a lower risk of ONJ in this patient population due the reduced dose and frequency of administration of zoledronate in the osteoporosis indication compared to zoledronate in cancer indications.

The CHMP considered that the use of IV bisphosphonate formulations in non-cancer settings should be kept under close review, particularly with regard to any change in the risk in developing ONJ following increased duration of IV bisphosphonate exposure in this indication. In addition, although currently the risk of ONJ with oral bisphosphonates is considered to be low, more cases of ONJ may be observed in the future as the risk of developing ONJ may increase with increasing long term use of bisphosphonates in an aging female population. Therefore, the risk of developing ONJ with the long term use of oral bisphosphonates should also be kept under close review.

History of dental disease

A history of dental disease, including invasive dental procedures, dental trauma and periodontal disease, may also be an important risk factor for the development of ONJ in association with bisphosphonates.

The recent review of published literature cases of ONJ found that in the majority of cases (68.8%) the diagnosis of ONJ was preceded by a tooth extraction or other dentoalveolar surgery (King et al., 2008). A number of studies have identified dental extractions as a significant risk factor for developing ONJ in patients receiving bisphosphonate for cancer indications (Badros et al., 2006, Durie at al., 2005, Hoff et al., 2008, Jadu et al., 2007, Kyrgidis et al., 2008). Other dental procedures have also been implicated in the development of ONJ including bone exostosis, intubation-induced trauma and

dental implants (Marx et al., 2005, Hoff et al., 2008). Invasive dental procedures have also been identified as a possible risk factor ONJ for bisphosphonates given for non-cancer indications (Hess et al., 2008). It is possible, in at least some of these cases, that the invasive dental procedure may have been a consequence of pre-existing ONJ rather than a precipitating factor and subsequent exposure of bone and increased risk of infection following the procedure may have worsened the situation.

The use of dentures and the presence of inflammatory dental disease such as periodontal disease, dental abscesses and poor dental hygiene have also been identified as risks factor for ONJ (Durie et al., 2005, Hoff et al., 2008, Kyrgidis et al., 2008).

Other possible risk factors

A number of other possible risk factors for the development of ONJ following bisphosphonate treatment have been proposed.

i) Jaw anatomy

ONJ occurs approximately two times more frequently in the mandible than in the maxilla and areas with thin mucosa, such as the torus mandibularis, torus palatinus and mylohyoid ridge appear to be more susceptible to ONJ (Jadu et al., 2007, Marx et al., 2005, Woo et al., 2006).

ii) Malignant disease

Duration of malignant disease and duration of bone metastases may be associated with an increased risk of ONJ development (Hoff et al., 2008). A possible explanation may be the concomitant use of anti-angiogenic drugs such as glucocorticoids and thalidomide, but the literature is conflicting. The type of cancer may also play a role in the development of ONJ. ONJ predominantly occurs in breast cancer, multiple myeloma and prostate cancer (Abu-Id et al., 2008). Metastasis has also been associated with an increased risk of ONJ (Wessel et al., 2008). These findings may be related to the dose and duration of bisphosphonate treatment in these patients (Hoff et al., 2008).

iii) Concomitant treatment

The first PhVWP class review of bisphosphonates and ONJ in 2006 identified chemotherapy and corticosteroids as possible risk factors for ONJ and the use of these drugs is a common finding in patients with this condition. Significant associations between ONJ and cyclophosphamide, prednisone, erythropoietin and thalidomide have been found in some studies of ONJ with bisphosphonates for cancer indications (Jadu et al., 2007 and Zervas et al., 2006). However other studies have not found any increased risk of ONJ with anthracyclines, melphalan, glucocorticoids or thalidomide (Badros et al., 2006, Bamias et al., 2005, Durie et al., 2005 and Hoff et al., 2008). The systematic review of cases of ONJ reported in the literature in association with bisphosphonates for non–cancer indications found that many of the patients were taking steroids and/or other drugs that affect bone turnover and may potentially be a risk factor for ONJ (Hess et al., 2008). Radiotherapy treatment to the head and neck has also been proposed as a risk factor for ONJ (Mehta et al., 2008).

iv) Age, sex and race

Advanced age has been identified as a possible risk factor for the development of ONJ in patients taking bisphosphonates (Badros et al., 2006, Jadu et al, 2007) although not all studies have found significant differences in age of patients with and without ONJ (Bamias et al., 2005, Hoff et al., 2008). A review of literature cases of ONJ in association with bisphosphonates found that ONJ more commonly occurred in females than males (3:2 ratio) (Woo et al., 2006) however other studies indicate that gender does not appear to be significantly associated with ONJ (Bamias et al., 2005, Hoff et al., 2008, Zervas et al., 2006). Caucasian patients may be at higher risk of developing ONJ (Badros et al., 2006).

v) Genetic factors

Single nucleotide polymorphisms of the cytochrome P450 CYP2C8 gene have been identified as a possible risk factor for the development of ONJ in multiple myeloma patients receiving zoledronate or pamidronate treatment (Sarasquete et al., 2008). Four Single nucleotide polymorphisms were associated with ONJ: rs1934951, rs1934980, rs1341162 and rs17110453. Matrix metalloproteinase 2 (MMP2) has also been hypothesised as a candidate gene for an increased risk of bisphosphonate-

induced ONJ (Lehrer et al., 2009). It has been proposed that genetic differences in the risk of developing ONJ may contribute to the findings of different incidences of ONJ across different geographical regions (Hoff et al., 2008).

vi) Smoking
Smoking was identified as a possible risk factor for ONJ from spontaneous suspected adverse reaction reports of ONJ received in association with alendronate in which 25% of patients were smokers. A recent case control study also found an association between smoking and ONJ in patients receiving bisphosphonates (Wessel et al., 2008). However another study did not identify a significant association between smoking and ONJ (Hoff et al., 2008).

vii) Co-morbid conditions
Co-morbid conditions reported as possible risk factors for ONJ in cancer patients include low haemoglobin levels (Jadu et al, 2007), low serum calcium and secondary hyperparathyroidism (Ardine et al., 2006), renal dialysis (Jadu et al, 2007), diabetes (Khamaisi et al., 2007) and obesity (Wessel et al., 2008). A history of osteoporosis has also been identified as a possible significant risk factor for the development of ONJ in patients with multiple myeloma receiving iv bisphosphonates (Hoff et al., 2008). Co-morbid conditions (e.g. hypertension, hyperlipidaemia, hypercholesterolaemia, rheumatoid arthritis and diabetes) may possibly contribute to the risk of developing factors ONJ in patients receiving bisphosphonates for non-cancer indications (Hess et al., 2008).

2.4 Risk Minimisation

Dental measures
There is some evidence from retrospective studies that preventive and conservative dental measures may reduce the risk of ONJ.

Dimopoulos et al (2008) reported reduced (but not eliminated) risk of ONJ after implementation of preventive dental measures in patients with multiple myeloma.

Ripamonti et al (2008) reported reduced risk of ONJ in solid tumour patients following a dental exam +/- ortho-pantomography prior to initiation of bisphosphonate therapy. Two patient populations were enrolled in the study: 154 consecutive patients receiving a dental exam prior to initiation of bisphosphonate therapy (from April 2005 and onwards) and 812 patients treated with bisphosphonates from 1999 until 2005, without receiving any preventive measure. When comparing the "pre- and post-implementation of preventive measures programme" a reduction in the incidence of ONJ from 3.2% to 1.3% was observed. The enrolled patients had various malignant diseases, but the majority, 73%, suffered from breast cancer. The majority of patients received pamidronate (62%); the remaining received zoledronate (25%), pamidronate followed by zoledronate (8%) and clodronate (5%) respectively.

Mehrotra et al (2008) reported the clinical outcome of osteonecrotic lesions following thorough staging succeeded by stage-specific dental preventive measures in a retrospective analysis of 207 patient records. Ninety four patients were serially followed for clinical outcome data regarding clinical course following cessation of bisphosphonate therapy. The authors concluded that…"With early detection at a lower stage, and careful conservative management, the large majority (74-92%) of patients presenting with ONJ will have stabilisation or improvement in their clinical presentation after discontinuation of bisphosphonate therapy". Furthermore the importance of managing these patients by coordinated action by a multidisciplinary team was emphasised.

Optimising the treatment regimen for iv bisphosphonates
The most significant risk factor for the development of ONJ in association with bisphosphonates is considered to be bisphosphonate exposure (potency, the route of administration and cumulative dose). The risk of developing ONJ increases with the dose, longer duration and frequency of administration of iv bisphosphonate exposure for cancer indications (Badros et al., 2006, Bamias et al., 2005, Dimopoulos et al., 2006, Durie et al., 2005, Hoff et al., 2008, Jadu et al., 2007, Woo et al., 2006, Zervas et al., 2006). It has therefore been considered whether changes in the treatment regimen for iv

bisphosphonates, such as reducing the bisphosphonate dose, duration of therapy and frequency of administration, may reduce the risk of ONJ while maintaining the therapeutic benefits of these drugs.

A retrospective study of a different dose schedule in 106 patients with multiple myeloma found that the risk of developing ONJ was eight-fold lower in patients receiving iv bisphosphonates (zoledronate and/or pamidronate) at a reduced frequency (monthly administration during the first year and then every 3 months) compared to patients receiving iv bisphosphonates according to the monthly administrations (Corso et al., 2007). Further studies are required to optimise the treatment regimen (dose, frequency and duration of therapy) for iv bisphosphonates in order to reduce the risk of ONJ while maintaining clinical efficacy. It has also been proposed that longer infusion times for iv bisphosphonates may reduce peak plasma concentrations of bisphosphonates and subsequently lower the risk of ONJ. However, this hypothesis has not yet been tested.

The risk of ONJ may increase with the duration of oral bisphosphonate therapy although there is no evidence to suggest whether different dose schedules for oral bisphosphonates have any impact on the risk of ONJ. Further studies are required regarding the long-term safety and efficacy of oral bisphosphonates.

Discontinuing bisphosphonate therapy
Dental extractions and other invasive dental procedures have been identified as a significant risk factor for developing ONJ. The possibility has been raised that discontinuation of bisphosphonate therapy 3 months before and after elective invasive dental surgery may reduce the risk of ONJ however as highlighted in the literature review by Khosla et al there is no evidence base for this approach at present. Although there is some evidence of ONJ healing after stopping bisphosphonate therapy the long half-life of bisphosphonates may mean that stopping bisphosphonates for a short period of time prior to and following dental surgery may not have any effect on the risk of developing ONJ (King et al., 2008, Woo et al., 2006). Further studies are needed to determine the value of interrupting bisphosphonate therapy in order to carry out dental procedures.

Best practice for risk minimisation measures
There appears to be general consensus in the literature and from expert opinion that preventive and conservative dental measures play an important role in minimising the risk of ONJ in association with bisphosphonates. The extent of dental measures recommended is different according to the level of the risk of developing ONJ. Patients receiving bisphosphonates intravenously for cancer indications are considered to be at the highest risk of developing ONJ and the most stringent dental measures are recommended for this group of patients. Based on the available evidence the risk appears to be much lower for the non-cancer indications and less stringent dental measures are generally recommended in these groups of patients.

Both patient and health professional education about the risk of developing ONJ while receiving bisphosphonate therapy is also considered to be an important measure in minimising the risk of ONJ. In particular, it is important to raise awareness of the risk of ONJ and bisphosphonates with dentists and GPs and how this risk differs between bisphosphonates for cancer and bisphosphonates for non-cancer indications, and to educate patient on the need to maintain good oral hygiene and receive regular dental examinations while taking bisphosphonates.

At the present time, there are no data to suggest whether stopping or interrupting bisphosphonate therapy in order to carry out dental procedures reduces the risk of ONJ. Therefore any decisions concerning any change in bisphosphonate treatment should be based on the assessment of the balance of risks and benefits for individual patients.

3 CONCLUSIONS

Diagnosis/Definition
The CHMP considered that a common, widely accepted definition of ONJ should be a first step towards gaining more knowledge on this rare adverse event in relation to bisphosphonate treatment. It

is also seen as a prerequisite for assessing the effectiveness of preventive measures. There appears to be consensus in the scientific literature and from experts over a hierarchical naming convention, a definition and a staging system. It is reflected in the agreed definition that there is no difference in clinical presentation between spontaneously occurring cases of ONJ and cases of ONJ occurring following dental invasive procedures. The recommended definition of ONJ is provided below.

With regards to the diagnosis/definition, it is considered that the following definition reflects current scientific knowledge and consensus reached after discussion with experts in a meeting at the EMEA in March 2009:

"A patient may be considered to have ONJ related to bisphosphonates if all of the following 3 characteristics are present:

1) Exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks

2) No history of irradiation of the jaw

3) Current or previous treatment with a bisphosphonate"

The related staging system as outlined above should be applied.

Pathophysiology

The underlying pathophysiological mechanism of ONJ following the use of bisphosphonates is likely to be multifactorial (involving factors such as immunomodulation, infection, excessive reduction of bone turnover, impaired angiogenesis and bisphosphonate toxicity to soft tissue and bone). Involvement of only the jaw is thought to be related to the unique nature of the blood supply, structure, function and microbiology of jaw bones. Additional studies are needed to further elucidate the underlying pathophysiological mechanism.

Whilst according to literature findings it is clear that the occurrence of ONJ is positively associated with the potency of the bisphosphonates and strongly related to the malignant indications and intravenous administration form, it is less clear why this is the case, and further understanding of the pathogenesis of ONJ is required.

Animal studies are likely to provide the most informative data in determining the pathophysiological mechanisms of ONJ, and a suitable model should ideally be developed to allow the study of the unique nature of the blood supply, structure, function and microbiology of the jaw bones. Molecular and biochemical studies may also provide further information. Pre-clinical studies to investigate the half-life of bisphosphonates in the bone may provide evidence in deciding clinical factors regarding bisphosphonate treatment e.g. dose and duration of treatment, the duration of treatment interruptions prior to dental surgery, or on the classification of the individual risk of ONJ for a patient during and after stopping bisphosphonate therapy.

Risk stratification

The CHMP considered that the risk of ONJ is significantly greater for patients receiving iv bisphosphonates for cancer indications than in patients receiving oral bisphosphonates for osteoporosis/Paget's disease. The risk of developing ONJ in association with oral bisphosphonates appears to be low. The full extent of the risk of ONJ with iv bisphosphonates used in non-cancer indications is not yet known but appears to be much lower than in cancer indications. However, there is still concern with respect to the patient population treated for osteoporosis, as it is expected that cases of ONJ will appear in the years to come.

Whilst it is recognised that risk factors for ONJ are multiple and currently not fully elucidated, the most significant risk factors for the development of ONJ in association with bisphosphonates are considered to be bisphosphonate potency, route of administration and cumulative dose of

bisphosphonate exposure. The impact of these parameters appears to be greater than the indication for treatment per se.

The history of dental disease and the nature of preceding dental procedures also seem to be of importance, with the majority of patients having had invasive dental procedures prior to the occurrence of ONJ. It should be highlighted though, that it is debatable whether invasive dental procedure is a consequence of pre-existing ONJ rather than a precipitating factor.

For the remaining risk factors the CHMP found that the literature findings were conflicting and the documentation less solid.

The CHMP highlighted the need for clinical and epidemiological studies in order to facilitate the prospective risk management of ONJ. There is a need for further research to help obtain information regarding the risk stratification between individual bisphosphonates and patient populations. The CHMP supported the view of the experts that a pan-European database capturing all ONJ cases would help obtain information. A registry or database could expectedly provide valuable information regarding risk factors. A registry could also provide data on ONJ background incidence (stratified according to individual bisphosphonates, indications and route of administration), time to onset, effect of drug holidays and of alternative bisphosphonate dosing schedules, impact of dental procedures and preventive and therapeutic measures. An ONJ-register is already planned in some Member States, e.g. in the UK.

In addition retrospective studies (e.g. case-control studies) could add to the knowledge concerning risk factors. Pharmacogenetic studies should be considered as well.
Identification of screening tools and diagnostic tests to identify patients at increased risk of developing ONJ would also be valuable. Currently available metabolic markers of overall bone turnover (e.g. CTX, NTX) are not helpful, as these are not specific for local bone metabolism.

Risk Minimisation

Given the gaps in knowledge that exist in relation to risk stratification and potential risk factors it is very difficult to propose clear evidence-based risk minimisation measures, and most of the available advice is empirically based. Further research is clearly needed. At present, decisions concerning treatment regimen including the value of a temporary discontinuation need to be determined on an individual patient basis, taking into account the risks and benefits of bisphosphonate therapy for the individual patient.

Much of the current focus in clinical guidelines with regards to management strategies is around the need to maintain good dental hygiene in order to prevent dental disease and also to ensure that any dental interventions that are considered necessary are as conservative and preservative as possible. Some retrospective reviews indicate beneficial effects of dental preventive measures, but additional prospective and controlled studies are needed. Further clinical research is also required to optimise the treatment regimen (dose, frequency and duration of therapy) for iv bisphosphonates, to determine the value of interrupting bisphosphonate therapy and to assess the long-term safety and efficacy of oral bisphosphonates. The use of iv bisphosphonate formulations in non-cancer settings and the risk of developing ONJ with the long term use of oral bisphosphonates should be kept under close review.

Further research

Further experimental and pre-clinical studies are required in order to provide more information regarding the possible pathophysiological mechanisms of ONJ and bisphosphonates. Further clinical and epidemiological studies should also be performed aimed at obtaining further information regarding risk stratification and risk minimisation. Areas identified for future research, together with recommendations as how these proposals can be taken forward, are outlined below.

The following recommendations are made regarding further research:

- Areas identified for future research, including experimental, pre-clinical, clinical and epidemiologic studies are as follows:

  Experimental and preclinical studies

  Highest priority
  - Development of a suitable animal model to allow examination of local vascularisation, anatomy, bone turnover, microtrauma, immunological mechanisms and bisphosphonates in the jaw.

  Lower priority
  - Studies investigating toxic concentrations and accumulation of bisphosphonates in keratinocytes, macrophages, dendritic cells, osteocytes and osteoclasts may be helpful in determining whether a reduction in clinical dose might be necessary to avoid toxic effects on the jaw.
  - Pre-clinical pharmacokinetic studies investigating the accumulation and half-life of bisphosphonates in the jaw bone compared to other bones and whether (and how) different injection rates might have an impact in the accumulation of these substances in the jaw bone.
  - Examination of whether increased accumulation of IPP affects local immune responses.

  Clinical and epidemiological studies

  Highest priority
  - A need for a unified pan-European database capturing all ONJ cases and allowing detailed analysis could help obtain further information on ONJ including: the background incidence of ONJ, the incidence of ONJ for individual drugs and indications, the time to onset, risk factors, possible genetic factors, the effects of drug holidays and alternative bisphosphonate dosing schedules, the effects of dental procedures and the prevention and treatment of ONJ.
  - Prospective controlled randomised studies to examine alternative dosing schedules
  - Retrospective case control studies to identify risk factors for ONJ, which ideally would include field-based studies.
  - Consideration of genetic factors in pharmacogenetics and pharmacoepidemiology investigations and routine collection of saliva samples during ongoing studies would greatly aid the conduct of such studies.

  Lower priority
  - Further clinical information regarding the dose, half life and pharmacokinetics of treatment with bisphosphonates in order to determine a clinically efficacious dose while minimising ONJ. It may be advisable that consideration is given to whether ongoing/proposed studies could be employed to provide this sort of valuable information
  - Investigation of whether there is any connection between the observed cytokine release (responsible for flu-like symptoms) after infusion of bisphosphonates and the subsequent occurrences of ONJ. If evidence is found for an association between the development of flu-like symptoms post infusion and the development of ONJ, the infusion times of IV bisphosphonates should be re-considered.

- Research areas particularly suitable for MAHs to take forward should be identified and discussions with MAHs on appropriate studies should be initiated.

- Learned societies should be informed of the areas identified for future research and made aware of the possibility of applying for research funding via the European Commission's 7th Framework programme (FP7), under the Health Theme. A proposed letter to learned societies can be found in Annex 4.

- Institutions who are part of the European Network of Centres of Pharmacoepidemiology (ENCEPP) should be approached as some of these might be interested in doing research in the field.

- It should be considered if the EMEA initiative aiming at creating a list of contractors able at performing a wide range of safety studies, thereby facilitating the regulatory decision-making process, may be a relevant tool in relation to bisphosphonates and ONJ. (Reference is made to the recently published EMEA "Notice of Call for Expressions of Interest for Urgent Drug Safety Studies" http://www.emea.europa.eu/htms/general/admin/tenders/list.htm).

Risk Communication

Whilst it is recognised that further research is needed to more clearly define the most appropriate risk minimisation measures, key messages should be communicated to health care professionals as well as to patients and patient organisations. The key messages for health care professionals, patients and patients organisations identified from this review are outlined in section 3 below (Recommendations).

The following key messages should be communicated to health care professionals, patients and patients' organisations:

- The risk of ONJ is significantly greater for patients receiving iv bisphosphonates for cancer indications than in patients receiving oral bisphosphonates for osteoporosis/Paget's disease. The risk of developing ONJ in association with oral bisphosphonates appears to be low.

- There appears to be clearer evidence for significant impact of bisphosphonate-specific and indication-specific risk factors such as potency, route of administration and cumulative dose. The evidence base appears to be less robust for other proposed risk factors, e.g. duration and type of malignant disease, concomitant treatment, gender, genetic factors, smoking and co-morbid conditions. However, these risk factors should be considered by prescribers and patients when evaluating an individual's potential risk of developing ONJ.

- A history of dental disease, including invasive dental procedures, dental trauma, periodontal disease and poorly fitting dentures are associated with an increased risk of ONJ.

- Recommended preventive dental measures before starting and during bisphosphonate therapy should be proportionate to the risk of developing ONJ. In particular dental check ups prior to treatment in all patients for cancer indications and dental examinations only if the dental status of the patient is poor for non-cancer indications.

- The need for patients to maintain good oral hygiene, to receive routine dental check ups and to report any oral symptoms such as dental mobility, pain or swelling.

- The risk of ONJ with bisphosphonates will be kept under close review within Europe. Further research is needed in order to increase the knowledge relating to the underlying mechanisms and risk factors for ONJ, and how best to minimise these risks. The EU regulatory authorities will explore strategies to promote this research. The CHMP has adopted a definition of ONJ related to bisphosphonates, in order to facilitate future case reporting and research.

The CHMP recommended that the distribution of the key messages should be coordinated nationally by individual MSs. The choice of suitable communication tools should be decided on MS basis.

In addition, the EMEA will inform learned societies and European patient organisations on the above key messages.

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