



**OPINION OF THE COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
PURSUANT TO ARTICLE 5(3) OF REGULATION (EC) No 726/2004, ON
BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW**

Basis for opinion

On 30 January 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.

Specifically, the Committee was requested to draw up an opinion on the suspected association between bisphosphonates and ONJ, including advice on the following issues:

1. The criteria for the diagnosis or definition of ONJ,
2. The underlying pathophysiological mechanism,
3. The risk stratification between products and patient populations,
4. To reach an agreement on appropriate/necessary risk minimisation measures.

On the basis of the request made by Denmark, the CHMP considered that there were sufficient grounds to start the procedure.

The procedure started on 19 February 2009.

Opinion

The CHMP, having considered the matter as set out in the appended assessment report (Appendix 1), reviewed the available evidence and came to the conclusion that

- 1) The criteria for the diagnosis or definition of ONJ should be as follows:

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

- Exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks
- No history of irradiation of the jaw
- Current or previous treatment with a bisphosphonate”

The related staging system should be applied.

2) The underlying pathophysiological mechanism of ONJ following the use of bisphosphonates is likely to be multifactorial. 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.

3) In view of the risk stratification between products and patient populations, the CHMP considered that the risk of ONJ is significantly greater for patients receiving intravenous (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 might be foreseen 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 under debate whether invasive dental procedure is a consequence of pre-existing ONJ rather than a precipitating factor.

For the remaining risk factors the literature findings are conflicting and the documentation less solid.

Clinical and epidemiologic studies are required 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. 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. 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.

4) Given the gaps in knowledge that exist in relation to risk stratification and potential risk factors it is 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.

Therefore, 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. The following recommendations are made regarding further research, including experimental, pre-clinical, clinical and epidemiologic studies:

Experimental and preclinical studies

First priority

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

Second 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

First 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.

Second 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 be 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 (see the related EMEA press release: <http://www.emea.europa.eu/pdfs/human/phv/49762409en.pdf>).

Institutions being 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>).

The CHMP further recommended that Member States should communicate key messages to health care professionals as well as to patients. The EMEA will liaise with learned societies to communicate the areas identified for future research and patient organisations at EU level to communicate the key messages. Furthermore the role of the treating physician as well as of the patients in terms of reporting their observations should be emphasised. A range of options for further communication with healthcare professionals and in particular patient organisations should be explored.

The following key messages should be included in a communication targeted for health care professionals and patients:

- 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 Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.

This opinion is forwarded to Denmark, all other Member States, Iceland, Norway and to the European Commission together with its appendix.

The opinion will be published on the EMEA website with its appendix.

London, 24 September 2009

On behalf of the CHMP
Dr Eric Abadie, Chairman

Appendix 1

**CHMP Assessment Report on bisphosphonates and osteonecrosis of the jaw dated
24 September 2009**