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Our ref: Henrik G. Jensen

Re.: Request for a scientific opinion.

Referring to article 5(3) of regulation 726/2004[1] the Danish Medicines Agency hereby formally ask the Committee for Medicinal Products for Human Use (CHMP) to draw up an opinion on the suspected association between the use of bisphosphonates and osteonecrosis of the jaw (ONJ). There is a great need for a thorough scientific evaluation of the suspected association between bisphosphonates and the serious condition ONJ. We hope that CHMP would take account to our formal request and draw up an opinion on this important safety issue. The opinion of the CHMP would be of great importance for patient safety and supporting to the competent authorities and the marketing authorisation holders evaluation of the product safety profiles.

Background:
On the initiative of the CHMP Pharmacovigilance Working Party a class review is currently ongoing comprising all bisphosphonates and the suspected association with the serious condition ONJ.

This safety issue has been intensively monitored throughout several years. The course of events can be briefly summarised as follows:

A class view was performed in 2005, resulting in revised labelling aiming at minimizing the risk for developing ONJ.

[1] Regulation No 726/2004 of the European Parliament and of the Council of 31 March 2004
laying down Community procedures for the authorisation and supervision of medicinal products
for human and veterinary use and establishing a European Medicines Agency.

During 2007 increasing concern emerged however, that these risk minimization measures were in fact not effective and appropriate.

A second class review was initiated in December 2007. Information was requested from the holders of marketing authorisations in the form of 2 set of LoQs, issued in December 2007 and April 2008 respectively.

The Danish Medicines Agency has as lead rapporteur provided joint assessment reports for discussion in April and December 2008. The overall outcome and conclusions were that sufficient progress had not been achieved, and that lack of knowledge hindered appropriate prospective risk management.

At the level of the CHMP it was therefore agreed to convene an ad hoc expert meeting at the premises of the EMEA, in the margins of the March CHMP / PHVWP meeting.

A detailed LoQs to be dealt with at the expert meeting is currently being drafted. However the main issues have been identified and concern in particular the scientific evidence base for factors such as the underlying pathophysiological mechanism, the criteria for the diagnosis or definition of ONJ, the risk stratification in between products and patient populations and future risk minimization measures.

The 2005-class review resulted in revised labelling through an informal procedure. 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.

Whilst it was possible to reach agreement and implementation of revised labelling through an informal procedure following the 2005-class review, it is the opinion of the Danish Medicines Agency, that the likelihood for informal agreement - based on the current overall experience - is considerably less.

Therefore it is deemed necessary to consider which measures could be taken to ensure a satisfying outcome in the interest of the patient safety. To that end an article 5(3) procedure, leading to a formal and publicly available CHMP-opinion, is considered to be the best solution. It follows from article 5 (3) that the CHMP shall take due account of any requests by Member States for an opinion on any scientific matter concerning the evaluation of medicinal products for human use.

The Danish Medicines Agency is available for clarification of any questions and further information if necessary.

Kind regards,

[redacted]

Henrik G. Jensen
Director of Consumer Safety Division

[redacted]

Doris I. Stenver
Chief Medical Officer
PHVWP Delegate