13 June 2014
EMA/PRAC/332909/2014

PRAC List of questions

To be addressed by the marketing authorisation holders for medicinal products containing ibuprofen and dexibuprofen (systemic formulations)

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1401

INN/active substance: ibuprofen, dexibuprofen

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1. Background information

The Pharmacovigilance Risk Assessment Committee (PRAC) is currently considering the arterial thrombotic risks of ibuprofen and dexibuprofen (systemic formulations) under Article 31 of Directive 2001/83/EC, resulting from pharmacovigilance data.

As part of its review the PRAC will consider new data on cardiovascular effects of non-steroidal anti-inflammatory drugs (NSAIDs) from a large meta-analysis of more than 600 randomised clinical trials conducted by the UK Coxib and traditional NSAID Triallists' (CNT) collaborative group[1]. The results indicate that the arterial thrombotic risk with high dose ibuprofen (2400mg/day) may be similar to COX-2 inhibitors. This new data will be reviewed alongside previously available clinical trial and epidemiological data considered by the Committee for Medicinal Products for Human Use (CHMP) in 2011/2012 under Art. 5(3) of Regulation (EC) 726/2004[2]. This includes data from:

- The EU Commission funded SOS Project
- Trelle *et al* (2011)[3]
- Varas-Lorenzo *et al* (2011)[4]
- Mc Gettigan and Henry (2011)[5]

The PRAC will make a recommendation based on these data as to the adequacy of the current contraindications, precautions and warnings relating to arterial thrombotic risk of high dose ibuprofen (doses at or above 2400mg/day) and dexibuprofen-containing medicinal products, and whether any updates to the product information or any other regulatory measure is needed.

In addition, there is accumulating clinical data[6,7,8] that ibuprofen may inhibit the antiplatelet action of low-dose aspirin for cardiovascular prophylaxis. The current product information includes a warning about this possible interaction but is based on non-clinical data and the clinical significance is unknown. Therefore the PRAC will also review the cumulative up to date data on this interaction and its clinical relevance and provide a recommendation on whether the current SmPC advice on the interaction with aspirin is sufficient to minimise the risk of failure of its cardiovascular prophylactic action, and whether any updates to the product information or any other regulatory measure is needed.

[1] Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Coxib and traditional NSAID Trialists' (CNT) Collaboration. The Lancet - 30 May 2013
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf
[3] Trelle S, et al (2011); BMJ; 342:c7086.
[4] Varas-Lorezo C, et al (2011); Drug Safety. 12:1225-36
[5] Mc Gettigan P, Henry D (2011); PLoS Med; 8(9):e1001098.
[6] Hohlfeld T (2013); Thrombosis and Haemostasis; 109: 825–833
[7] MacDonald TM, Wei L. Lancet 2003;361:573-4
[8] Meek et al Eur J Clin Pharmacol 2013 ; 69(3) : 365-71

2. List of Questions

The marketing authorisation holders (MAHs) for ibuprofen- and dexibuprofen-containing medicinal products (systemic formulations) are requested to address the following questions:

Question 1

Please provide any further new clinical trial and epidemiological data not already under consideration by PRAC, on the arterial thrombotic risks (heart attack, stroke, and other relevant events) associated with ibuprofen and dexibuprofen.

This should include new clinical trial and epidemiological data on:

- the thrombotic risks associated with ibuprofen/dexibuprofen compared with those of other non-selective NSAIDs and COX-2 inhibitors, or placebo.
- the absolute risk (i.e. additional serious cardiovascular events per 1000 patient years exposure, relevant to no treatment or comparator).
- the thrombotic risks associated with ibuprofen/dexibuprofen at different licensed doses (in particular for doses ≤1200mg and those > 1200mg) and with different durations of treatment.

In light of the available data please comment on the adequacy of the current PI wording relating to thrombotic risks, including contraindications and warnings and precautions for use, and make proposals for updates as appropriate.

Question 2

Please provide all non-clinical and clinical data from unpublished MAH conducted studies in relation to the potential interaction between ibuprofen/dexibuprofen and aspirin. This should include:

- any data on whether the interaction is dose related (to ibuprofen/dexibuprofen and/or aspirin dose).

In light of the available data please comment on the adequacy of the current PI wording relating to this potential interaction, including warnings and precautions for use and interactions, and make proposals for updates as appropriate.