Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used for the reduction of inflammation, pain and fever. It is commonly used and is widely available without prescription, typically at doses ≤1200mg daily, to treat a range of conditions including pain, fever, rheumatic conditions and minor ailments. Ibuprofen is also prescribed for the chronic management of rheumatic conditions such as osteoarthritis (typically doses higher than 1200mg daily).

Ibuprofen contains equal quantities of R(-)-ibuprofen and S(+)-ibuprofen. As it is the S(+)-enantiomer which confers the anti-inflammatory and analgesic activity and not the R(-)-enantiomer, dexibuprofen which contains only S(+)-ibuprofen is also available as a medicinal product. The approved indications for dexibuprofen are similar to those for ibuprofen.

The cardiovascular (CV) risk of NSAIDs, including ibuprofen, has been kept under close review over the past years. A previous review conducted in 2006 concluded that NSAIDs as a class were associated with an increased risk of arterial thrombotic events, although the risk was considered to be higher for selective cyclooxygenase-2 (COX-2) inhibitors (also known as coxibs). Clinical trial data at that time suggested that ibuprofen at a high dose (2400 mg daily) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies did not suggest that ibuprofen at low doses (≤1200 mg daily) is associated with an increased risk of arterial thrombotic events, in particular myocardial infarction (MI)[1].

Another evaluation, conducted by the CHMP in 2012, considered all available published evidence to date from epidemiological studies and also meta-analyses of clinical trials and observational studies as well as the results of the 'safety of non-steroidal anti-inflammatory drugs' (SOS) research project funded by the European Commission under the Seventh Framework Programme. Based on the available evidence, the review concluded, in line with previous conclusions, that ibuprofen at a high dose may be associated with an increased risk of arterial thrombotic events, and that ibuprofen at low doses is not consistently associated with an increased risk of arterial thrombotic events[2].

Since the 2012 review, the Coxib and traditional NSAID Triallists' (CNT) collaborative group published results from a large meta-analysis of more than 600 randomised clinical trials. The results suggested that the cardiovascular risk with high dose ibuprofen (2400mg) may also be similar to COX-2 inhibitors[3].

In light of the above, and given the widespread use of ibuprofen, UK considered that it is in the interest of the Union to refer ibuprofen and dexibuprofen containing products for systemic use to the PRAC and request, that it gives its recommendation under Article 31 of Directive 2001/83/EC, on whether the new evidence on the risk of thrombotic events when used at high doses, doses at or above 2400mg per day, in adults and new evidence on interaction with low-dose acetylsalicylic acid require any updates to the advice to healthcare professionals and patients including warnings or contraindications as expressed in the current ibuprofen product information, or whether any other regulatory measure would be needed.

[1] Information on the review conducted in 2006 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf
[2] Information on the review conducted in 2012 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf
[3] 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

The scope of the procedure included medicinal products containing (racemic) ibuprofen and dexibuprofen (S(+)-ibuprofen). Although there is very little data available regarding the arterial thrombotic risks of dexibuprofen or regarding a possible interaction between dexibuprofen and low-dose acetylsalicylic acid, it is reasonable to assume that dexibuprofen shares similar risks with (racemic) ibuprofen, hence its inclusion in the scope of this referral procedure.

The scope of the referral procedure included only systemic formulations (e.g. oral formulations, rectal preparations) but did not include products authorised for use solely in children or topical preparations intended for local effects with low systemic absorption (e.g. creams, gels, sprays, vaginal and ophthalmic preparations).

In the results of the CNT Collaboration's network meta-analysis which partly triggered this review, high doses of ibuprofen (2400mg/day) significantly increased major coronary events (MCE) (MI or coronary heart disease (CHD) death) but not major vascular events (MVE) (non-fatal MI, coronary death, MI or CHD death, non-fatal stroke, stroke death, any stroke, and other vascular death). The adjusted rate ratio for ibuprofen vs placebo for MCE and MVE were 2.22 (1.10-4.48) and 1.44 (0.89-2.33), respectively. In the coxib vs ibuprofen comparisons the rate ratios favoured coxibs for both MCE and MVE (i.e. slightly increased risk with ibuprofen vs coxibs group) but these were not statistically significant.

In the initial PRAC consideration of the CNT collaboration network meta-analyses, a number of important questions regarding statistical methodology were raised which were considered to limit the interpretation of the results in particular for the traditional NSAIDs (tNSAIDs), including ibuprofen. Consequently, further clarifications from the CNT Collaboration were requested around the use of indirect comparisons for tNSAIDs, the handling of zero event trials and shorter than average follow-up for ibuprofen trials that could bias the results upwards for ibuprofen.

The CNT Collaboration's responses to the PRAC questions confirmed that zero event trials and possible unequal randomisation are unlikely to have introduced any significant bias to the results of the network meta-analysis for ibuprofen. The responses also confirmed that there is very little randomised evidence directly comparing ibuprofen to placebo and that the results of the network meta-analysis are primarily derived from studies that directly compared coxibs with ibuprofen. The PRAC was of the view that this makes it difficult to judge the size of any biases which may have been introduced by any differences in study population and study duration.

The CNT Collaboration's responses also confirmed that the trials that compared ibuprofen with placebo were shorter in duration than the trials that compared ibuprofen with coxibs and thus there is the possibility that including the trials that compared ibuprofen with placebo in the network meta-analysis could inflate the treatment effect. The data provided by ibuprofen vs placebo trials are too limited to draw any conclusions on the risk.

Given the outstanding uncertainties regarding the size of potential biases in the network meta-analysis and the paucity of information available directly comparing ibuprofen with placebo, the PRAC was of the view that any conclusions on the magnitude of the CV risk of ibuprofen drawn from this meta-analysis should be based on the results of studies that compared ibuprofen with coxibs and not the indirect comparisons derived from the network meta-analysis.

Overall, the PRAC was of the opinion that the data from the coxib vs ibuprofen trials indicate that the CV risks of high dose ibuprofen may be similar to that for coxibs.

Several other data sources informed the recommendation of the PRAC, including available data from previous reviews, clinical studies, published literature as well as data submitted by marketing authorisation holders (MAHs) of medicinal products containing ibuprofen or dexibuprofen.

The PRAC was of the opinion that clinical trial data suggest that high daily doses of ibuprofen (2400mg/day) are associated with an increased risk of cardiovascular events (MI, stroke), which may be similar to that observed with coxibs or diclofenac. The review of the updated epidemiological data confirms the findings of previous EU reviews and does not suggest that ibuprofen at low doses (≤1200mg/day) is associated with an increased risk of cardiovascular events.

The PRAC noted that there are no or limited data on the arterial thrombotic risk of ibuprofen at doses between 1200mg and 2400mg/day and so it cannot be determined exactly how the risk changes over this dosage range. However the PRAC considered that it is likely that there is a dose-dependent increase in risk with increasing doses between 1200mg and 2400mg/day.

The effect of ibuprofen treatment duration on cardiovascular risk has not been extensively studied and is therefore uncertain.

Cardiovascular risk may be higher in patients with cardiovascular disease, and high ibuprofen doses should be avoided in this population. Similarly, high daily doses should not be recommended to patients with risk factors for cardiovascular disease.

The PRAC considered that, in general terms, the current product information of ibuprofen-containing products already contains meaningful information regarding cardiovascular risks. However, the information about the use of high ibuprofen doses in certain populations with pre-existing cardiovascular disease and/or risk factors for arterial thrombotic events merits further clarification and thus updates should be made to section 4.4 and 4.8.

Although no specific data about cardiovascular risk of dexibuprofen are available, a similar cardiovascular risk to that of high-dose of ibuprofen is expected when dexibuprofen is used at equipotent doses. The data submitted by the MAHs widely supported the definition of dexibuprofen high dose as 50% of the high dose of ibuprofen. The PRAC concluded that dexibuprofen product information should be amended in the same way as ibuprofen product information.

Regarding the interaction between ibuprofen and acetylsalicylic acid, the PRAC was of the opinion that new pharmacodynamic and epidemiological data investigating a possible interaction between ibuprofen and acetylsalicylic acid are consistent with the conclusions of the previous EU-wide review of this issue – that whilst pharmacodynamic studies show that ibuprofen inhibits the antiplatelet effect of acetylsalicylic acid when it is administered concurrently, the clinical implications of such an interaction are still uncertain. The PRAC further concluded that the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded.

The PRAC was of the view that updates should be made to section 4.5 and 5.1 to reflect current data on the potential clinical effect of the pharmacodynamic interaction when ibuprofen is taken with acetylsalicylic acid.

There are limited available data on a potential interaction between dexibuprofen and acetylsalicylic acid. However, the results of a single pharmacodynamic study submitted by one of the MAHs in response to the PRAC questions suggest that dexibuprofen also reduces the antiplatelet effect of acetylsalicylic acid *ex vivo*. The PRAC was of the view that any update to the ibuprofen product information should also be applied to the product information for dexibuprofen, taking into consideration any dexibuprofen specific details, e.g. equipotent dose.

The recommendation for update of the product information should be applicable to all medicinal products containing ibuprofen and dexibuprofen, regardless of maximum recommended daily dose.

Having noted all of the above, the PRAC concluded that the benefit-risk balance for ibuprofen and dexibuprofen containing medicinal products (systemic formulations) remains favourable subject to the agreed changes to the product information.

Overall conclusion and grounds for the variation to the terms of the marketing authorisations

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for ibuprofen- and dexibuprofen-containing medicinal products (systemic formulations).
- The PRAC considered the totality of the data available in relation to the cardiovascular risk of ibuprofen- and dexibuprofen-containing medicinal products and in relation to the potential interaction between ibuprofen/dexibuprofen and acetylsalicylic acid, acknowledging the conclusions from previous reviews, the submissions by marketing authorisation holders, and additional data from independent researchers.
- The PRAC considered that with regard to the arterial thrombotic risks of ibuprofen, the data available to date from randomised clinical trials, observational studies and individual epidemiological studies, including meta-analysis thereof, supports that ibuprofen at high doses (2400mg or above per day) is associated with an increased risk of arterial thrombotic events. It was observed that this risk may be similar to that of selective COX-2 inhibitors. The available data do not suggest that ibuprofen at low doses (equal to or below 1200mg per day) is associated with an increased risk of arterial thrombotic events.
- The PRAC considered that although no specific data about the cardiovascular risk of dexibuprofen are available, a similar cardiovascular risk to that of high-dose of ibuprofen is expected when dexibuprofen is used at equipotent doses.
- The PRAC considered that with regard to the interaction between ibuprofen/dexibuprofen and acetylsalicylic acid the pharmacodynamic studies available to date show that ibuprofen/dexibuprofen inhibit the antiplatelet effect of acetylsalicylic acid when it is administered concurrently. The epidemiological data available to date, however, do not demonstrate a clinically significant interaction but the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded.
- The PRAC considered that in general terms, the current product information of ibuprofen- and dexibuprofen-containing products already contains meaningful information regarding cardiovascular risks and pharmacodynamic interaction with acetylsalicylic acid. However, the PRAC concluded that information about the risks associated with the use of high doses of ibuprofen/dexibuprofen in certain populations with pre-existing cardiovascular disease and/or risk factors for arterial thrombotic events merits further clarification, as well as some additional information on the potential clinical effect of the pharmacodynamic interaction when taken with acetylsalicylic acid.

The PRAC concluded that the benefit-risk balance for ibuprofen- and dexibuprofen-containing medicinal products (systemic formulations) remains favourable subject to the agreed changes to the product information.

Therefore, the PRAC recommended the variation to the terms of the marketing authorisation for all medicinal products referred to in Annex I and for which the amendments of the relevant sections of the

summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation.

CMDh agreement

The CMDh, having considered the PRAC recommendation dated 10 April 2015 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC agrees with the overall scientific conclusions by the PRAC and to the variation to the terms of the marketing authorisations of medicinal products containing ibuprofen or dexibuprofen (systemic formulations) as set out in Annex III.

The timetable for the implementation of the agreement is set out in Annex IV.