Annex II

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

Scientific conclusions

The CMDh, having considered the PRAC recommendation dated 13 June 2013 with regards to diclofenac containing medicinal products (systemic formulations), agrees with the recommendation therein as stated below:

Overall summary of the scientific evaluation of diclofenac containing medicinal products (systemic formulations) (see Annex I)

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs, such as diclofenac, are indicated in the relief of all grades of pain and inflammation associated with a wide range of conditions, including arthritic conditions, acute musculo-skeletal disorders and other painful conditions resulting from trauma. Diclofenac containing medicinal products (systemic formulations) are available as tablets, capsules for oral administration, suppositories for rectal administration and solutions for intravenous or intramuscular injection.

Epidemiological and clinical trial data on the cardiovascular risks of NSAIDs, including diclofenac, were previously reviewed by the Committee for Medicinal Products for Human Use (CHMP).
In 2006 it was concluded that a small increase in the absolute risk of thrombotic events could not be excluded for NSAIDs as a class, especially when used at high-doses and long-term therapy, although the risk was considered to be higher for the selective cyclooxygenase-2 (Cox-2) inhibitors (also known as coxibs) compared to NSAIDs. Risk minimisation measures (in the form of contraindications and warnings in the product information) were implemented at the time for Cox-2 inhibitors. The data available (in particular data from the MEDAL[1] programme) suggested that the risk of arterial thrombotic events with diclofenac was similar to that for coxibs, but firm conclusions could not be drawn and further epidemiological studies were needed to obtain additional data.
Another evaluation conducted by the CHMP in 2012[2] considered all available published evidence to date from meta-analysis of clinical trials and observational studies, and also epidemiological studies. Results of the 'safety of non-steroidal anti-inflammatory drugs' (SOS) research project funded by the European Commission under the Seventh Framework Programme were considered in the review that concluded that available evidence regarding diclofenac seemed to consistently point towards a less favourable cardiovascular risk profile compared to other NSAIDs, and similar risks as those of Cox-2 inhibitors.
A new review was considered necessary and was initiated to address the cardiovascular safety concerns for diclofenac and their impact on the benefit-risk balance of diclofenac containing medicinal products (systemic formulations). This review was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC).

The PRAC acknowledged the conclusions of previous reviews with regards to the cardiovascular safety of diclofenac. Data provided by the MAHs in writing and at an oral explanation and relevant data made available by independent researchers were also considered.

The PRAC concluded that diclofenac is effective in reducing inflammation and pain. Recognised risks associated with NSAID treatment in general, and with diclofenac treatment in particular, include serious gastrointestinal effects including PUB (perforation, ulcer, bleeding), cardio-renal effects, hepatic effects and skin reactions (including Stevens Johnson syndrome and toxic epidermal necrolysis). These are appropriately reflected in the product information.

With regards to cardiovascular risks, the PRAC noted that the initial signal from the MEDAL programme was confirmed by the meta-analyses of randomised clinical trials conducted by *Trelle et al* (2011) and *Chen and Ashcroft* (2007). Meta-analyses of observational data and individual observational studies also consistently indicated that diclofenac is associated with a similar level of risk as Cox-2 inhibitors. An increased risk with diclofenac was also observed in the SOS nested-cases control studies across all databases and for both myocardial infarction and ischaemic stroke. *Schjerning Olsen et al* (2011) provided data on risks in relation to duration of exposure and found that the risks associated with diclofenac were very similar to those of coxibs at all time points.

The new evidence provided by marketing authorisation holders including evidence from new case-control studies and retrospective studies add to the evidence of an increased risk with diclofenac

[1] For more details on the MEDAL programme, including its components, please refer to the assessment report for the review conducted in 2006 at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf.
[2] For more information on the review conducted in 2012, please refer to the assessment report for the procedure at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf

compared to other NSAIDs and that the risk with diclofenac is similar to that of coxibs. The study by *Krum et al* 2012, a post hoc analysis of the MEDAL trial, showed that there was no significant differential effect between etoricoxib and diclofenac in relation to cardiovascular events, except for confirmed congestive heart failure.
Evidence available from a new meta-analysis of randomised clinical trials conducted by an independent research group was included in the review. The study, which looked at more than 600 randomised clinical trials, concluded that the vascular risks of high dose diclofenac are comparable to Cox-2 inhibitors. Major vascular events were increased by about one third by a coxib (rate ratio [RR] 1.37, 95% confidence interval [CI] 1.14-1.66; p=0.0009) or diclofenac (1.41, 1.12-1.78; p=0.0036), mainly due to an increase in major coronary events (coxibs: 1.76, 1.31-2.37; p=0.0001; diclofenac: 1.70, 1.19-2.41; p=0.0032).

The data available today do not allow conclusion on the specific mechanisms underlying the cardiovascular thrombotic risks of diclofenac, although several studies have explored different options and it can be noted that is unlikely that one single mechanism would explain the risk.

Considering that an increased cardiovascular risk with diclofenac is observed, and this appears similar to that of selective Cox-2 inhibitors, it therefore follows that any risk minimisation in place for Cox-2 inhibitors with respect to cardiovascular risk should also apply to diclofenac. The PRAC therefore recommended an amendment to the product information for diclofenac to include an updated contraindication in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. In addition, patients with certain cardiovascular risk factors (such as hypertension, hyperlipidaemia, diabetes mellitus or smoking) should only use diclofenac after careful consideration and therefore the warnings should also be updated to reflect this. Moreover, the general rule that NSAIDs should be used at the lowest dose for the shortest duration possible should be consistently implemented in the posology section of the product information. Furthermore, a proactive communication of these new measures through a direct healthcare professional communication (DHPC) was recommended.

The PRAC considered that the recommendation for update of the product information should be applicable to all medicinal products containing diclofenac (systemic formulations), regardless of dose. The available information on the dose effect of diclofenac is limited. Although the data point towards a dose dependent effect on thrombotic risk associated with the use of diclofenac, particularly at high dose, it is difficult to establish a clear cut-off dose above which the risks become significantly increased. Some studies also report an association with lower doses. Based on the available data to date, the PRAC therefore concluded that the cardiovascular thrombotic risk cannot be excluded across all doses of diclofenac, especially in patients with pre-existing co-morbidities.

Benefit / risk balance

Having noted all of the above, the PRAC concluded that the benefit-risk balance for diclofenac containing medicinal products (systemic formulations) remains favourable subject to the agreed restrictions, warnings, other changes to the product information and additional risk minimisation measures, in the form of a DHPC letter.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for diclofenac containing medicinal products (systemic formulations).

- The PRAC considered the totality of the data available in relation to the cardiovascular safety of diclofenac containing medicinal products, acknowledging the conclusions from previous reviews by the CHMP, the submissions by marketing authorisation holders in writing and at an oral explanation, and emerging data from independent researchers.

- The PRAC considered that with regards to the arterial thrombotic risks of diclofenac, the data available to date from randomised clinical trials, observational studies and individual epidemiological studies, including meta-analysis thereof, allow the conclusion that diclofenac is associated with increased cardiovascular risks. It was observed that these are similar to those of selective Cox-2 inhibitors.

- The PRAC considered that diclofenac containing medicinal products are effective in their approved indications.

- The PRAC concluded that in view of the currently available safety data in order to maintain a favourable benefit/risk, diclofenac containing medicinal products should be contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. In addition, patients with certain cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only use diclofenac after careful consideration and therefore the warnings should be updated to reflect this. Moreover, the general rule that NSAIDs should be used at the lowest dose for the shortest duration possible should be consistently implemented in the posology section of the product information.

- The PRAC also concluded that there was need for further risk minimisation measures such as information to healthcare professionals. Key elements for a direct healthcare professional communication were agreed, together with the timelines for distribution.

The PRAC concluded that the benefit-risk balance for diclofenac containing medicinal products (systemic formulations) remains favourable subject to the agreed restrictions, warnings, other changes to the product information and additional risk minimisation measures, in the form of a communication letter.

Therefore in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the variation of the marketing authorisations for all medicinal products referred to in Annex I and for which the amendments to the product information are set out in annex III of the recommendation.

CMDh position

The CMDh, having considered the PRAC recommendation dated 13 June 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached a position on the variation of the marketing authorisations of diclofenac containing medicinal products for which the amendments to the product information are set out in annex III.