



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

18 October 2012  
EMA/653433/2012  
EMA/H/ A-5(3)/1319

## Questions and answers on the review of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular risk

Outcome of a procedure under Article 5(3) of Regulation (EC) No 726/2004<sup>1</sup>

On 18 October 2012, the European Medicines Agency completed a review of the latest scientific data on the cardiovascular risk of non-selective non-steroidal anti-inflammatory drugs (NSAIDs). The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the latest study results are in line with previous evidence. The data consistently indicate a higher cardiovascular risk with diclofenac than with other non-selective NSAIDs.

Diclofenac will now be assessed by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC), to determine the need to update the existing treatment advice for patients and prescribers with regard to cardiovascular risk.

### What are non-selective NSAIDs?

NSAIDs are medicines used to relieve pain and inflammation. They are indicated in a wide range of conditions such as such arthritis and many other painful conditions, including headache, back pain, fever and minor ailments.

'Non-selective' NSAIDs act by blocking the effects of the two cyclo-oxygenase (COX) enzymes, known as COX-1 and COX-2, resulting in a reduced production of substances called prostaglandins. A different class of NSAIDs, called 'selective COX-2 inhibitors' (also known as 'coxibs'), acts by blocking the COX-2 enzyme only. Since some prostaglandins are involved in causing pain and inflammation at sites of injury or damage in the body, a reduced production of prostaglandins reduces pain and inflammation.

There are many medicines in the non-selective NSAID class, including diclofenac, ibuprofen, naproxen and several other medicines. They have been authorised by national approval procedures in the EU Member States and have been available for many years under a wide range of trade names. They are mainly available with a prescription, but some non-selective NSAIDs used for short-term treatment are available without a prescription.

---

<sup>1</sup> Article 5(3) of Regulation (EC) 726/2004, opinion on any scientific matter concerning the evaluation of medicinal products for human use.



## Why were non-selective NSAIDs reviewed?

NSAIDs have been the subject of European reviews in the past, due to concerns about cardiovascular risks, gastrointestinal side effects (affecting the stomach and gut) and serious skin reactions. The CHMP has continuously monitored the safety of NSAIDs, and the current review was triggered by the availability of new data since the CHMP's last recommendations were made in 2006.

In 2005, the CHMP reviewed the safety of COX-2 inhibitors. In terms of cardiovascular safety, it identified an increased risk of thrombotic events, such as heart attack and stroke with these medicines<sup>2</sup>. In 2006, the CHMP carried out a similar review of non-selective NSAIDs, which concluded that a small increased risk of thrombotic events could not be excluded, particularly when these medicines are used at high doses for long-term treatment<sup>3</sup>. It found that the level of risk may vary between medicines, but there was not enough evidence to confirm these differences. Following these reviews, the prescribing information for each medicine concerned was updated based on the available evidence; however, the selective COX-2 inhibitors were given stronger contraindications and warnings than non-selective NSAIDs, to reflect their higher cardiovascular risk. The CHMP advised that, although the benefits of NSAIDs outweighed the risks, these medicines should be used at the lowest effective dose for the shortest possible treatment duration.

Further study data were needed on the safety of non-selective NSAIDs, and the CHMP recommended that the European Commission fund independent epidemiological research (population-based studies of the causes and distribution of disease) on the safety these medicines. An independent research project was subsequently set up called 'safety of non-steroidal anti-inflammatory drugs' (SOS)<sup>4</sup>. The findings of the SOS project, together with a number of other studies, have provided more evidence on the risk of stroke, heart attack, heart failure and other cardiovascular complications with the use of non-selective NSAIDs since 2006.

Therefore, the CHMP started a new review in October 2011 at the request of the UK medicines regulatory agency, to assess all the newly available evidence since its previous conclusions and to provide an updated opinion on the evidence of cardiovascular risk with non-selective NSAIDs.

## Which data has the CHMP reviewed?

The CHMP reviewed all the data that has become available since 2006. These come from new epidemiological studies or meta-analyses of earlier clinical trials and epidemiological studies (where data from several studies are pooled and analysed together).

Most of the data related to the three most widely used non-selective NSAIDs – diclofenac, ibuprofen and naproxen. However, the studies also provided data on several other medicines such as etodolac, indomethacin, ketoprofen, ketorolac, meloxicam, nabumetone, nimesulide and piroxicam.

## What are the conclusions of the CHMP?

The CHMP considered that there were important limitations in all the recently available study data, due to the methodologies used and the populations studied. Most data came from epidemiological studies, where people already using the medicine were compared with people not taking the medicine, while

---

<sup>2</sup> See

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2010/01/news\\_detail\\_000969.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/01/news_detail_000969.jsp&mid=WC0b01ac058004d5c1).

<sup>3</sup> See

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2009/12/news\\_detail\\_000752.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/12/news_detail_000752.jsp&mid=WC0b01ac058004d5c1).

<sup>4</sup> A project funded by the European Commission under the 7th EU Framework Programme. See [www.sos-nsaids-project.org/](http://www.sos-nsaids-project.org/).

there were limited new data from clinical trials comparing NSAIDs with a comparator treatment in a more scientifically controlled setting. There were also only limited data on the effects of different doses or durations of treatment for any of the non-selective NSAIDs.

For naproxen and ibuprofen, the Committee concluded that the latest available evidence on cardiovascular risk was in line with the CHMP's previous conclusions. The possibility of a small increased risk of thrombotic events cannot be excluded, particularly when these medicines are used at high doses and for long-term treatment. Therefore, it decided that the existing prescribing information accurately reflects the known level of cardiovascular risk for these medicines.

For diclofenac, the Committee also concluded that the latest study results were in line with previous evidence of an increased risk of heart attack, stroke or other thrombotic events. However, the currently available data consistently indicated that this risk is higher for diclofenac than other widely used non-selective NSAIDs, and is comparable to the risk seen with selective COX-2 inhibitors. Although the risk seen with diclofenac is only slightly higher than with other non-selective NSAIDs, the CHMP considered that it may be appropriate to assess the matter further, to determine whether the existing recommendations and warnings on cardiovascular risk for diclofenac-containing medicines are appropriate.

For other non-selective NSAIDs, there was not enough data for the CHMP to reach firm conclusions on cardiovascular risk. The Committee therefore concluded that, in line with current recommendations, the possibility of an increased risk with these medicines cannot be excluded.

### **What will happen next?**

Diclofenac will now be assessed by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC), as formally requested by the United Kingdom on 17 October 2012. The review will begin at the PRAC meeting of 29-31 October 2012. In addition to the published study data assessed by the CHMP, the PRAC will require companies that market diclofenac-containing medicines to submit relevant data for the review. The PRAC will make recommendations on the need for regulatory action, such as updating the existing recommendations and warnings on cardiovascular risk for diclofenac-containing medicines.

### **What are the recommendations for patients and prescribers?**

- Non-selective NSAIDs should continue to be used according to the existing product information for each medicine. There is no change to the current treatment advice following the CHMP review.
- All non-selective NSAIDs should be used at the lowest effective dose for the shortest possible treatment duration, in line with existing treatment advice.
- Prescribers should note the information on cardiovascular safety and other risks in the product information for non-selective NSAIDs. They should follow the relevant precautions and take account of the known level of risk with each medicine when selecting a suitable treatment for individual patients.
- Patients who have any questions should speak to their doctor or pharmacist.