European Medicines Agency finalises review of recently published data on cardiovascular safety of NSAIDs

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Information on Medicinal Product

Non Steroidal Anti Inflammatory Drugs (NSAIDs) are medicines used to relieve pain and inflammation. They are indicated in a wide range of conditions such as arthritis, headache, back pain, fever and minor ailments.

NSAIDs can be selective or non selective. The 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.

NSAIDs have been available for many years under a wide range of trade names via national marketing authorisations. They are mainly available with a prescription, but some non-selective NSAIDs used for short-term treatment are available without a prescription.

A list of authorised presentations of NSAIDs in Malta can be extracted using the Malta Medicines List at www.maltamedicineslist.com by searching M01 in the ATC search function and then using the export button.

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Information from European Medicines Agency (EMA) about the safety concern

In summary:

- A review of available data on NSAIDs confirms that the benefit risk of these medicines remains positive but also raises concerns that an increased risk of heart attack, stroke or other thrombotic events 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.
- There is no change to treatment advice following this review and all non-selective NSAIDs should be used at the lowest effective dose for the shortest possible treatment duration, in line with existing treatment advice

In 2005, the EMAs Committee on Human Medicinal Products (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[1] (see Medicines Authority Circular No P19/2005).

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)[2].

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.

[1] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/01/news_detail_000969.jsp&mid=WC0b01ac058004d5c1.

[2] A project funded by the European Commission under the 7th EU Framework Programme. See www.sos-nsaids-project.org/.

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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.

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.

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 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.

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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.

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.

In Malta

For Healthcare Professionals

- 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.

For more information please see the **press release** and **question-and-answer** document issued by the European Medicines Agency

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Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on NSAIDs. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/pub/adr.doc** or to the marketing authorisation holder or their local representatives.>

{Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.}

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