14 June 2013
EMA/353084/2013

PRAC recommends the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that the effects of the painkiller diclofenac on the heart and circulation when given systemically (by means such as capsules, tablets or injections) are similar to those of selective COX-2 inhibitors, another group of painkillers. This applies particularly when diclofenac is used at a high dose (150 mg daily) and for long-term treatment. The PRAC concluded that the benefits of diclofenac still outweigh the risks but recommended that the precautions already in place to minimise the risks of arterial thromboembolic events (blood clots in the arteries) with selective COX-2 inhibitors should also be applied to diclofenac.

Patients who have serious underlying heart or circulatory conditions, such as heart failure, heart disease, circulatory problems or a previous heart attack or stroke, should not use diclofenac. Patients with certain cardiovascular risk factors (such as high blood pressure, raised blood cholesterol, diabetes or smoking) should only use diclofenac after careful consideration. Healthcare professionals will also be advised to periodically re-assess the need for patients to continue taking the medicine.

Diclofenac is a widely used medicine for relieving pain and inflammation, particularly in painful conditions such as arthritis. It belongs to a group of medicines called 'non-steroidal anti-inflammatory drugs' (NSAIDs). The selective COX-2 inhibitors are a subgroup of the NSAIDs.

The safety of NSAIDs has been closely monitored by regulatory authorities in the European Union. Reviews of these medicines carried out in 2005, 2006 and 2012 have confirmed that NSAIDs as a class are associated with a small increased risk of arterial thromboembolic events, which in some cases has led to heart attack or stroke, particularly if used at high dose and for long-term treatment.

The product information for all NSAIDs warns of this risk, and recommends that NSAIDs be used at the lowest effective dose for the shortest period of time necessary to control symptoms.

The PRAC review of diclofenac was started in October 2012 in response to findings from the 2012 review of NSAIDs, which identified a small increased risk of these cardiovascular side effects with diclofenac compared with other NSAIDs - an increase similar to that seen with the COX-2 inhibitors. The absolute cardiovascular risk with any NSAID depends on a person's underlying risk factors, such as high blood pressure and cholesterol levels. For diclofenac, the overall number of heart attacks would be

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

expected to increase by approximately 3 cases per year for every 1,000 people at moderate risk treated (from 8 per 1,000 people per year normally, to 11 per 1,000 people per year taking the medicine)[1].

Generating best evidence to address regulatory research needs

The availability of robust evidence generated by independent academic research has been a central element of the reviews of NSAIDs and diclofenac. This includes an independent research project called 'safety of non-steroidal anti-inflammatory drugs' (SOS)[2], set up and funded by the European Commission's Seventh Framework Programme to address questions identified in the 2006 review of NSAIDs, which provided data reviewed in 2012. Other groups have also been investigating the cardiovascular safety of NSAIDs, notably the Coxib and traditional NSAID Trialists' (CNT) collaborative group[1], who shared their results from a large meta-analysis of more than 600 randomised clinical trials with the Agency.

The PRAC recommendation will be considered by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) at its meeting on 24-26 June 2013. Healthcare professionals will receive a letter with detailed information on the outcome of this review. Patients who have any questions should speak to their doctor or pharmacist.

More about the medicine

Diclofenac is authorised for the relief of pain and inflammation in a wide range of conditions, including arthritic conditions and acute musculoskeletal disorders. It is currently available in the European Union (EU) in a number of different formulations. Most formulations are for systemic use (given as treatment throughout the body, such as oral and injectable medicines), which are covered by the current review. Diclofenac-containing medicines 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.

Diclofenac is an NSAID. Traditional 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. 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. In addition to diclofenac, widely used NSAIDs also include ibuprofen and naproxen. A different group of NSAIDs, called 'selective COX-2 inhibitors' (also known as 'coxibs'), acts by blocking the COX-2 enzyme only.

More about the procedure

The review of systemic diclofenac was initiated on 31 October 2012 at the request of the United Kingdom medicines agency, under Article 31 of Directive 2001/83/EC.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As diclofenac-containing medicines are all authorised nationally, the PRAC recommendations will be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a medicines regulatory body representing the EU Member States.

If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority

[1] See http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60900-9/abstract
[2] See www.sos-nsaids-project.org.

vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.

Contact our press officers

Monika Benstetter or Martin Harvey

Tel. +44 (0)20 7418 8427

E-mail: press@ema.europa.eu