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New safety advice for diclofenac

New measures aim to minimise cardiovascular risks

On 28 June 2013, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed by majority new safety advice for diclofenac-containing medicines that are given by means such as capsules, tablets, suppositories or injections, intended to have an effect on the whole body (known as a systemic effect). The new advice aims to minimise the risks of effects on the heart and circulation from these medicines.

This followed a review by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) which found that the effects of systemic diclofenac on the heart and circulation are similar to those of selective COX-2 inhibitors, another group of painkillers. This applies particularly when diclofenac is used at a high dose and for long-term treatment. The PRAC therefore recommended that the same precautions already in place to minimise the risks of blood clots in the arteries with selective COX-2 inhibitors should be applied to diclofenac.

The CMDh agreed with the PRAC conclusion that although the benefits of systemic diclofenac still outweigh the risks, those risks were similar to the risks with COX-2 inhibitors, and it endorsed the recommendation that similar precautions should be applied.

The CMDh position was sent to the European Commission, which confirmed it and took a final legally binding decision throughout the EU on 25 September 2013.

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 safety of NSAIDs has been closely monitored by regulatory authorities in the EU. 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 (blood clots in the arteries) especially in patients with underlying heart or circulatory conditions or with certain cardiovascular risk factors, which in some cases has led to heart attack or stroke, particularly if used at high dose and for long periods.

A class warning of this risk is in place and the product information for all NSAIDs recommends that these medicines be used at the lowest effective dose for the shortest period of time necessary to control symptoms. As the risk is known to be somewhat higher with the subgroup of NSAIDs known as selective COX-2 inhibitors, increased measures to minimise risk are recommended in their product information.

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The PRAC review of diclofenac was started at the request of the UK medicines regulatory agency, the MHRA, in October 2012 in response to findings from the 2012 review of NSAIDs. The latter 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 cardiovascular risk with any NSAID depends on a person's underlying risk factors, such as high blood pressure and cholesterol levels and also any underlying heart or circulatory conditions. About 8 people in 1,000 at moderate risk of heart disease are likely to have a heart attack over one year. The overall number of heart attacks in people at moderate risk would be expected to increase by around 3 cases per year for every 1,000 people treated with diclofenac (to 11 per 1,000 people per year).

Information to patients

- Overall, the benefits of this medicine are greater than its risks, but there is a small risk of heart attack or stroke in patients taking systemic diclofenac regularly, especially at high doses (150 mg daily) and for long periods. If 1,000 patients at moderate risk took diclofenac for a year, there would be about 3 extra cases of heart attack among them, compared with patients not taking diclofenac.
- The risk with diclofenac is increased more if you are already at higher risk, so use is no longer recommended if you have already had a heart attack or stroke, or have heart failure, blockages to blood vessels to the heart or brain or an operation to clear or bypass such blockages, or circulatory problems that restrict blood flow to your limbs.
- If you have other risk factors such as high blood pressure, high blood cholesterol, diabetes, or if you smoke, your doctor will need to assess if you should use diclofenac and the best way to take it.
- If you are on long-term diclofenac treatment you will need to have your treatment reviewed to ensure that it is still right for you. Speak to your prescriber at your next scheduled appointment.
- You should not stop taking your treatment without talking to your doctor.
- If you have any questions, speak with your doctor or pharmacist.

Information to healthcare professionals

- Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment.
- Use of diclofenac is contra-indicated in patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.
- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
- As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
- In the light of the above, all patients receiving regular diclofenac therapy should be reviewed at the next scheduled appointment.

Further information about the EU-wide safety review:

- The effectiveness of diclofenac is well established. However, data from previous reviews carried out in 2005, 2006 and 2012 suggested an increased relative risk of arterial thromboembolic events which was sometimes greater than for other commonly prescribed NSAIDs and in some cases as great or greater than that seen with certain COX-2 inhibitors. Limitations in the data had made it hard to quantify the risk initially, but a consistent picture was emerging by the time of the 2012 review. The latest review by the PRAC was therefore initiated specifically to assess the benefit-risk of systemic diclofenac.
- The PRAC has further reviewed available data including several new case-control and cohort studies, a post-hoc analysis of data from the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) programme,[1] and a meta-analysis[2] by the Coxib and traditional NSAID Trialists Collaboration which involved over 600 clinical trials. The latter found that, compared with placebo, the risk of major vascular events was increased by about one third by a COX-2 inhibitor (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). Overall, compared with placebo, allocation to diclofenac or a coxib caused around three additional major vascular events per 1,000 participants per year, with one such event causing death; in high-risk individuals, about seven or eight more would have a major vascular event, of which two would be fatal. Although the risk is likely to be dose-dependent, the PRAC considered that cardiovascular thrombotic risk cannot be excluded across all doses of diclofenac, especially in patients with pre-existing co-morbidities.

Diclofenac is effective in reducing inflammation and pain. However, considering that the cardiovascular risk with systemic diclofenac appears similar to that of selective COX-2 inhibitors, it was considered that any risk minimisation in place for COX-2 inhibitors with respect to cardiovascular risk should also apply to diclofenac. The product information will be amended and healthcare professionals prescribing or dispensing systemic diclofenac will receive further appropriate communication at a national level.

References

1. Krum H, Swergold G, Gammaitoni A, et al. Blood pressure and cardiovascular outcomes in patients taking nonsteroidal antiinflammatory drugs. Cardiovasc Ther. 2012;30(6):342-50.

2. Coxib and traditional NSAIDs Trialists Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013. doi:10.1016/S0140-6736(13)60900-9.

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 subgroup of NSAIDs, called 'selective COX-2 inhibitors' (also known as 'coxibs'), acts by blocking the COX-2 enzyme rather than both.

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.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). As diclofenac-containing medicines are all authorised nationally, the PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by majority it was sent to the European Commission, which confirmed it and took a final legally binding decision valid throughout the EU.

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