AWTORITÀ DWAR IL-MEDIĊINI

New safety advice for diclofenac to minimise cardiovascular risk

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Information on Medicinal Product

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 Malta in a number of different formulations. Most formulations are for systemic use (given as treatment throughout the body, such as oral, suppository 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.

Information from European Medicines Agency about the safety concern

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. 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.

A recent review by the European Medicines Agency (EMA) of new data has now concluded that the effects of systemic diclofenac on the heart and circulation are similar to those of selective COX-2 inhibitors. This applies particularly when diclofenac is used at a high dose and for long-term treatment. The EMA therefore recommended that although the benefits of systemic diclofenac still outweigh the risks, the same precautions already in place to minimise the risks with selective COX-2 inhibitors should be applied to diclofenac.

The EMA's recommendation has now been sent to the European Commission and a final binding decision will be issued in due course

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In Malta
For Healthcare Professionals

In Summary:

- **Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events 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 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.**
- **In the light of the above, all patients receiving regular diclofenac therapy should be reviewed at the next scheduled appointment.**
- **All doctors and pharmacists should expect to receive a Direct Healthcare Professional Communication by local marketing authorization holders with information on the new amendments to the Summary of Product Characteristics.**

Further Information

The effectiveness of diclofenac is well established. However, data from previous EU regulatory 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 Pharmacovigilance Risk Assessment Committee (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

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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.

The product information will be amended and healthcare professionals prescribing or dispensing systemic diclofenac will receive Direct Healthcare Professional Communications by local marketing authorisation holders with information on the new amendments to the Summary of Product Characteristics of diclofenac.

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.

Advice for 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.

For more information please visit the European Medicines Agency website at www.ema.europa.eu

Reporting Adverse Drug Reactions

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

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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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