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Questions and answers on the review of the marketing authorisations for topical formulations of ketoprofen

Outcome of a procedure under Article 107 of Directive 2001/83/EC

The European Medicines Agency has completed a review of the safety and effectiveness of ketoprofen-containing medicines used topically (on the skin). The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of topical ketoprofen continue to outweigh its risks, but that further measures should be put in place to minimise the risk of adverse skin reactions.

What is ketoprofen?

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs work by blocking an enzyme called cyclo-oxygenase, which is involved in the production of prostaglandins. Prostaglandins are messengers in the development of inflammation. Blocking their production helps to reduce the signs of inflammation.

Topical formulations of ketoprofen are used to treat the symptoms of pain and inflammation in conditions such as minor trauma (sprains, bruising), tendonitis (inflammation of a tendon), small-joint osteoarthritis (swelling and pain in the small joints), acute low-back pain and phlebitis (inflammation of a vein).

Topical ketoprofen-containing medicines have been available in all Member States except for the Netherlands since 1978. They may be available as creams, gels, solutions, sprays and plasters under various trade names and as generics. They may be obtained with or without a prescription.

Why was topical ketoprofen reviewed?

Since their marketing authorisation, the French medicines regulatory agency (Afssaps) has reviewed the safety of topical ketoprofen-containing medicines several times because of reports of photoallergy (allergic reactions to a medicine following exposure to sunlight) in patients using these medicines. As a result, measures to reduce harm were implemented in France, such as the inclusion of warnings and precautions in the French product information, a pictogram on the packaging and dissemination of letters to healthcare professionals. In spite of these measures, new cases of photoallergy have been reported, which occurred even in cases of exposure to dim sunlight. In addition, new skin reactions

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have been reported following use of products containing octocrylene. Octocrylene is a chemical sunscreen found in several cosmetics and care products such as shampoo, skin creams, anti-ageing creams, make-up removers and hair sprays.

In December 2009, after re-assessing these medicines, the French agency considered that their benefit-risk balance was no longer positive and decided to suspend the marketing authorisations of all topical medicines containing ketoprofen in France.

As required by Article 107, the French agency informed the CHMP of its actions so that the Committee could prepare an opinion on whether the marketing authorisations for topical products containing ketoprofen should be maintained, changed, suspended or revoked across the EU.

Which data has the CHMP reviewed?

The CHMP looked into all the available safety data, including data from member states' databases and data provided by the companies marketing topical ketoprofen in the EU. In particular, the Committee considered the responses given by the companies to a list of questions on photosensitivity reactions, including photoallergy, in patients using these medicines.

What are the conclusions of the CHMP?

The CHMP noted that the number of reports of adverse skin reactions including photoallergy is low throughout the EU and that the risk of these side effects could potentially be reduced using appropriate minimisation measures. The Committee also noted that, although alternative topical NSAIDs are available in the EU, ketoprofen is the only topical NSAID authorised for the treatment of acute low-back pain.

The CHMP concluded that the benefits of topical ketoprofen-containing medicines continue to outweigh their risks but recommended the following risk minimisation measures:

- these medicines should no longer be available over the counter but should only be obtained with a prescription from a doctor;
- strengthened warnings on sun exposure should be included in the product information, as well as advice to stop using topical ketoprofen if any skin reactions develop, including when using ketoprofen together with octocrylene;
- the risks of photoallergy with topical ketoprofen and the way to prevent it should be clearly communicated to healthcare professionals and to patients.

Finally, the CHMP agreed to review the effectiveness of these risk minimization measures in three years time.

What are the recommendations for patients and healthcare professionals?

- Doctors, pharmacists and patients should be aware of the risk of photoallergy with topical ketoprofen.
- Doctors should tell their patients how to use topical ketoprofen-containing medicines appropriately.
- Patients should make sure that the treated areas are protected from sunlight during the whole period of ketoprofen treatment and the two weeks after stopping the treatment. They should also wash their hands carefully after each application of ketoprofen.

- Patients should discontinue treatment immediately if they develop any skin reaction after application of these medicines, and seek their doctor's advice.
- Patients who have any questions should speak to their doctor or pharmacist.

The European Commission issued a decision on this opinion on 29 November 2010.

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