



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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PRAC recommends updating advice on use of high-dose ibuprofen

Review confirms small increased cardiovascular risk with daily doses at or above 2,400 mg

European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review confirming a small increase in the risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2,400 mg per day). The review clarifies that the risk with high-dose ibuprofen is similar to the risk seen with some other non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors and diclofenac.

No increase in cardiovascular risk is seen with ibuprofen at doses up to 1,200 mg per day, which is the highest dose generally used for over-the-counter (OTC) preparations taken by mouth in the European Union (EU).

The PRAC concluded that the benefits of ibuprofen outweigh the risks but recommended updating advice on the use of high-dose ibuprofen to minimise the cardiovascular risk. High doses of ibuprofen (2,400 mg per day or higher) should be avoided in patients with serious underlying heart or circulatory conditions, such as heart failure, heart disease and circulatory problems or in those who have previously had a heart attack or stroke.

In addition, doctors should carefully assess a patient's risk factors for heart or circulatory conditions, before initiating long-term treatment with ibuprofen, particularly if high doses are required. Risk factors for these conditions include smoking, high blood pressure, diabetes and high blood cholesterol.

These recommendations follow PRAC's review of data on ibuprofen from several publications, including combined analyses of numerous clinical trials (known as meta-analyses) and data from population-based studies.

The PRAC also reviewed data on the interaction between ibuprofen and low-dose aspirin when the latter is taken to reduce the risk of heart attacks and strokes. The PRAC noted that ibuprofen has been shown in laboratory studies to reduce the anti-clotting effects of aspirin. However it remains uncertain whether long-term use of ibuprofen in clinical practice reduces the benefits of low-dose aspirin in preventing heart attacks and strokes. Occasional use of ibuprofen should not affect the benefits of low-dose aspirin.



The PRAC recommended that updated advice on the cardiovascular risk of high-dose ibuprofen be included in the product information of ibuprofen medicines, along with information on the available evidence on the interaction between ibuprofen and aspirin.

The recommendations for ibuprofen also apply to dexibuprofen, a medicine similar to ibuprofen. A high dose of dexibuprofen is a dose at or above 1,200 mg per day.

The PRAC recommendations for ibuprofen and dexibuprofen will now be sent the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a body representing EU Member States and Iceland, Liechtenstein and Norway.

More about the medicine

Ibuprofen is a painkiller and anti-inflammatory medicine. It works by blocking an enzyme called cyclo-oxygenase, which produces prostaglandins, substances that are involved in inflammation and pain. Ibuprofen is found in medicines used to treat pain, inflammation and fever.

The usual dose for adults and children over 12 years of age is 200 to 400 mg, 3 or 4 times a day as needed.

Ibuprofen is present in medicines as a mixture of two molecules that are enantiomers (mirror images of each other). Dexibuprofen, the active enantiomer, is sometimes available on its own and is therefore included in this review. A dose of 2,400 mg per day of ibuprofen is equivalent to 1,200 mg per day of dexibuprofen.

Ibuprofen and dexibuprofen are currently available in the European Union (EU) in a number of different formulations. The current review covers formulations for systemic use (intended to act on the whole body, such as use by mouth or by injection); it does not cover formulations such as gels or sprays applied to the skin of the affected area. Ibuprofen and dexibuprofen medicines have been authorised in the EU through national approval procedures and have been available for many years under a wide range of trade names. They are available on prescription and over the counter.

More about the safety of NSAIDs

The safety of NSAIDs, including ibuprofen, has been reviewed regularly by authorities in the EU over the past few years. Reviews carried out in [2005](#), [2006](#), and [2012](#) confirmed that NSAIDs as a class are associated with a small increase in the 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, and particularly if used at high doses.

A class warning of this risk is already in place and the product information for all NSAIDs, including ibuprofen, recommends that these medicines be used at the lowest effective dose and for the shortest period of time necessary to control symptoms.

This current review considered accumulated evidence which clarifies the cardiovascular risk related to ibuprofen taken at high doses and the interaction between ibuprofen at any dose and aspirin.

More about the procedure

The review of ibuprofen was initiated on 9 June 2014 at the request of the UK's medicines agency (MHRA), under Article 31 of Directive 2001/83/EC. It follows concerns that high doses of ibuprofen could have a similar cardiovascular risk to that of COX-2 inhibitors and diclofenac.

The review was conducted 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 ibuprofen medicines are all authorised nationally, the PRAC recommendations will now be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

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

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