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Updated advice on use of high-dose ibuprofen

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

The CMDh[1] has endorsed by consensus updated advice on the use of high-dose ibuprofen. This follows a review carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which confirmed a small increased 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 of 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).

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 include smoking, high blood pressure, diabetes and high blood cholesterol.

The review also looked at data on the interaction between ibuprofen and low-dose aspirin when the latter is taken to reduce the risk of heart attacks and strokes. Laboratory studies have shown that ibuprofen reduces the blood-thinning 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 updated advice on the cardiovascular risk of high-dose ibuprofen will be included in the product information of ibuprofen medicines, along with information 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.

[1] The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

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As the CMDh has now agreed the PRAC advice by consensus, changes to the product information for ibuprofen- and dexibuprofen-containing medicines will be implemented by the Member States where the medicines are authorised, according to an agreed timetable.

Information for patients

- An EU-wide review of ibuprofen has confirmed that there is a small risk of heart attacks and strokes in patients taking high doses of the medicine (at or above 2,400 mg per day). No risk has been seen with ibuprofen at doses up to 1,200 mg per day, which is the highest dose usually taken by the majority of patients.
- 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. For diclofenac, the risk was estimated at about 3 extra cases of heart attack in every 1,000 patients taking diclofenac for a year.
- Use of high-dose ibuprofen is no longer recommended if you have heart or circulatory conditions, such as heart failure, heart disease and circulatory problems or if you have previously had a heart attack or stroke.
- Your doctor will carefully assess you before starting treatment with high-dose ibuprofen to check if you have risk factors such as high blood pressure, high blood cholesterol, diabetes, or if you smoke.
- Prolonged use of ibuprofen may reduce the effect of low-dose aspirin when the latter is taken to reduce the risk of heart attacks and strokes. You should therefore always seek the advice of your doctor or pharmacist before using ibuprofen with 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.
- If you have any questions, speak with your doctor or pharmacist.

Information for healthcare professionals

- Data from meta-analyses and epidemiological studies indicate that there is an increased risk of cardiovascular events (such as myocardial infarction or stroke) associated with the use of high-dose ibuprofen (at or above 2,400 mg per day).[1-4]
- 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. For diclofenac, the risk was estimated at around three additional major vascular events per 1,000 participants per year.
- High doses of ibuprofen should be avoided in patients with cardiovascular conditions (e.g. uncontrolled hypertension, congestive heart failure (NYHA class II-III), established ischaemic heart disease, peripheral arterial disease and cerebrovascular disease).
- Patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should only be treated with high-dose ibuprofen after careful consideration.
- The effect of duration of ibuprofen treatment on cardiovascular risk is uncertain.
- Although no specific data about the cardiovascular risk with dexibuprofen are available, a similar cardiovascular risk to that with high-dose of ibuprofen is expected when dexibuprofen is used at equipotent doses (at or above 1,200 mg per day).

- Experimental data suggest long-term use of ibuprofen/dexibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid (typically 75 mg per day). This is because ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are used concomitantly. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

References

The review looked at data from several studies including:

1. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-79.
2. Salvo F, Fourrier-Reglat A, Bazin F, et al. Cardiovascular and gastrointestinal safety of NSAIDs: a systematic review of meta-analyses of randomized clinical trials. Clinical pharmacology and therapeutics 2011;89:855-66.
3. Olsen AM, Fosbol EL, Lindhardsen J, et al. Long-term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: a nationwide cohort study. Circulation 2012;126:1955-63.
4. Olsen AM, Fosbol EL, Lindhardsen J, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients--a nationwide study. PloS one 2013;8:e54309.

More about the medicine

Ibuprofen is a painkiller and anti-inflammatory medicine that belongs to the class of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It works by blocking an enzyme called cyclo-oxygenase, which produces prostaglandins, substances that are involved in inflammation and pain.

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 review covered formulations for systemic use (intended to act on the whole body, such as use by mouth or by injection); it did 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 latest 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 followed 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 made a set of recommendations. As ibuprofen medicines are all authorised nationally, the PRAC recommendations were forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted 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.

On 20 May 2015 the CMDh adopted its position by consensus, therefore the advice recommended by the PRAC will be implemented by the Member States where the medicines are authorised, according to an agreed timetable.

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