

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

Non-steroidal anti-inflammatory drugs (NSAIDs) are valuable therapeutic agents in the treatment of pain and inflammation and the risk-benefit profile of these medicines has been closely monitored nationally and at EU level. Previous EU reviews have confirmed that NSAIDs, as a class, are associated with a small increased risk of arterial thromboembolic events (such as myocardial infarction and stroke) particularly if used at high dose and for long-term treatment. The product information for all NSAIDs warns of the risks and class labelling recommends that NSAIDs be used at the lowest effective dose for the shortest period of time necessary to control symptoms.

Ibuprofen is an NSAID commonly used for the reduction of pain, inflammation and fever. The most recent EU review completed by the Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed a small increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke) in patients taking high doses of ibuprofen ($\geq 2,400\text{mg/day}$). The review clarified that the risk with high dose ibuprofen ($\geq 2,400\text{mg/day}$) is similar to the risk seen with COX-2 inhibitors and diclofenac. There are no or limited data on the arterial thrombotic risk of ibuprofen at doses between 1,200mg and 2,400mg/day which makes it difficult to determine exactly how the risk changes over this dosage range. However the PRAC considered that it is likely that there is a dose-dependent increase in risk with increasing doses between 1,200mg and 2,400mg/day. The review did not suggest an increase in cardiovascular risk with ibuprofen at doses up to 1,200mg/day i.e. at the maximum daily doses typically used in the case of products available as over the counter medicines.

The PRAC also reviewed data on the interaction between ibuprofen and low-dose aspirin when the latter is taken to reduce the risk of myocardial infarction and stroke. The PRAC noted that ibuprofen

has been shown in non-clinical studies to reduce the anti-platelet effects of aspirin. However, the epidemiological data available to date does not support a clinically significant interaction but the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose aspirin cannot be excluded. The review concluded that occasional use of ibuprofen should not affect the benefits of low-dose aspirin.

Advice for Healthcare Professionals

- Ibuprofen (and all NSAIDs) should be prescribed at the lowest dose for the shortest duration possible to minimise the risk of undesirable effects.
- Cardiovascular risk may be higher in patients with cardiovascular disease (e.g. severe heart failure NYHA Class IV), and high doses of ibuprofen should be avoided in this population.
- Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses ($\geq 2,400\text{mg/day}$) should be avoided.
- Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking), particularly if high doses of ibuprofen ($\geq 2,400\text{mg/day}$) are required.
- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for all systemic ibuprofen-containing products will be updated as soon as possible to reflect this updated advice.
- Further information about this review is available on the HPRA and EMA websites.

**Further details on ibuprofen-containing products are available at www.hpra.ie*

Key message

- The PRAC considered that there is a small increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke) in patients taking high doses of ibuprofen ($\geq 2,400\text{mg/day}$).
- There is no evidence to suggest an increase in cardiovascular risk with ibuprofen at doses up to 1,200mg/day (which is the maximum daily OTC dose).
- Ibuprofen should be avoided in patients with existing cardiovascular disease and used in caution in patients with certain cardiac conditions (e.g. uncontrolled hypertension, congestive heart failure, established ischaemic heart disease etc.).
- There is no evidence to suggest that occasional use of ibuprofen affects the benefits of low-dose aspirin.
- Ibuprofen should be prescribed at the lowest dose for the shortest duration possible.

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