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European Medicines Agency recommends restricting use of cilostazol-containing medicines

The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) has recommended that the use of cilostazol-containing medicines in the treatment of intermittent claudication – a condition where poor blood supply to the leg muscles causes pain and affects the ability to walk – should be restricted with a range of new measures aimed at targeting a patient population in which there are clinical benefits, and at the same time minimising important risks.

The recommendations follow a review of current evidence which indicates that the modest benefits of these medicines, i.e. their ability to increase the distance patients are able to walk, are only greater than their risks, in particular the risks of side effects affecting the heart or serious bleeding, in a limited subgroup of patients.

Cilostazol-containing medicines are available in the EU under the names Pletal and Ekistol.

The Committee recommended that cilostazol should only be used in patients whose symptoms have not improved despite prior lifestyle changes such as exercise, healthy diet and stopping smoking. In addition, cilostazol-containing medicines should not be used in patients who have suffered severe tachyarrhythmia (fast, abnormal heart rhythm), or recent unstable angina, heart attack or bypass surgery, or who take two or more antiplatelet or anticoagulant medicines such as aspirin and clopidogrel.

Doctors should review their patients at their next routine appointment and assess the continued suitability of cilostazol treatment.

Detailed recommendations for patients and healthcare professionals are available below.

The Spanish Agency for Medicines and Health Products (AEMPS) asked the CHMP to carry out a review of these medicines following a number of reports of serious suspected side effects, in particular affecting the heart, as well as cases of serious bleeding.

The CHMP examined available clinical trial data on the benefits and risks of the medicines provided by the companies that market these medicines, as well as data from scientific literature, reports of suspected side effects, post-marketing studies and experimental studies before making its recommendations. More information on the studies and the CHMP's conclusions is available below.

The CHMP recommendation will now be sent to the European Commission for the adoption of a legally-binding decision throughout the European Union (EU).

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Information to patients

- Cilostazol is used to treat intermittent claudication, a condition where walking becomes painful and difficult because of problems with blood circulation in the arteries of the legs. Cilostazol-containing medicines are available in the EU under the names Pletal and Ekistol.
- The Agency has recommended some restrictions on the use of cilostazol. If you are taking cilostazol-containing medicines, you should make a non-urgent appointment with your doctor to review your treatment.
- Your doctor will advise you whether you should continue taking cilostazol, stop taking cilostazol, or change the dose that you are taking. The advice will vary for each patient depending on factors such as lifestyle options that could improve your condition, whether your walking symptoms have improved since you started cilostazol, whether you have had recent heart problems, and which other medicines you are taking.
- If you have any questions, you should contact your doctor or pharmacist.

Information to healthcare professionals

Healthcare professionals should follow these recommendations:

- Cilostazol should only be used for intermittent claudication when lifestyle changes (including smoking cessation and exercise programmes) and other appropriate interventions alone have not produced adequate benefit.
- Treatment should only be started by physicians experienced in the management of intermittent claudication, and should be reviewed after three months. Treatment should be stopped in patients who have not shown clinically relevant benefit.
- Cilostazol should not be given to patients who have unstable angina or who have had myocardial infarction or a coronary intervention (PCI) within the last six months, nor to those with a history of severe tachyarrhythmia.
- Cilostazol should also not be given to patients also receiving both aspirin and clopidogrel, or any other combination of two or more additional antiplatelet or anticoagulant medicines.
- Prescribers should be aware of the risk of interactions with cilostazol; its dose should be reduced in patients also taking strong inhibitors of CYP3A4 or CYP2C19.
- Other healthcare professionals should refer patients to the prescribing physician as appropriate.

For the full changes to information for doctors and patients, see under the ‘All documents’ tab.

More information on the assessment:

The Agency’s recommendations are based on a review by the Committee for Medicinal Products for Human Use (CHMP), which looked at available data on the benefits and risks of cilostazol.

- Cilostazol has been shown to produce modest increases in walking distance compared with placebo; meta-analysis of pooled individual patient data from nine efficacy trials involving 3,122 patients indicated a mean percentage increase from baseline of 59.4% for cilostazol, compared with 24.3% for placebo. This corresponded to an absolute increase in walking distance of 87.4 metres and 43.7 metres respectively (from a baseline of about 133 metres). CHMP concluded that

the magnitude of benefit was clinically important in a subgroup of patients, and that response can be adequately assessed after three months of treatment.

- Safety data from nearly 14,000 suspected adverse drug reaction reports (in the context of over 6 million patient years' exposure worldwide) and 4,000 events in non-interventional studies confirmed the known adverse effect profile of cilostazol from clinical trials. Cases of haemorrhage represented about 8% of the spontaneous reports. The most common cardiovascular events reported were palpitations and tachycardia (each about 5% of total spontaneous reports).
- Long-term cardiovascular safety of cilostazol was examined post-marketing in the CASTLE study[1], a randomised double-blind placebo controlled study involving 1,439 patients given cilostazol 100 mg twice daily (reduced to 50 mg twice daily if necessary) or placebo. The trial, which examined all-cause mortality as a primary endpoint, was terminated early (after about 3 years) because of a high drop-out rate in both groups (397 out of 721 cilostazol patients and 391 out of 718 patients taking placebo) and because of a much lower mortality rate than expected. There were 49 deaths in the cilostazol group, of which 12 were due to cardiac disorders, and 52 in the placebo group (13 cardiac). When a composite endpoint of cardiac morbidity (coronary and cerebrovascular events) and mortality was considered, there were 135 events with cilostazol and 153 with placebo. Although the design and early termination of the study limit the conclusions that can be drawn, these results provide some reassurance with regard to cardiovascular safety of cilostazol.
- Analysis of available data suggests an increased risk of haemorrhage when cilostazol is given to patients also taking both aspirin and clopidogrel. However the evidence suggests that cilostazol alone, or in combination with one other antiplatelet drug, does not increase the risk of bleeding.

In conclusion, the CHMP considered that although on average the efficacy of cilostazol is modest, there is a small group of patients in whom it is of clinical relevance, not least in helping them to begin exercise programmes. Although suspected adverse drug reaction reports have raised some safety concerns, these have not been substantiated in the clinical trial data (including the CASTLE study), and it remains possible to exclude high-risk patients in clinical practice. CHMP therefore recommended a number of measures aimed at targeting use of cilostazol to the population most likely to benefit, and in whom the risk of side effects is low.

References.

1. Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: A Study in Long-term Effects). J Vasc Surg. 2008;47:330-336.

More about the medicine

Cilostazol is a medicine that is used to improve walking distance in patients who have intermittent claudication due to peripheral arterial obstructive disease (obstruction and narrowing of the arteries of the limbs, leading to reduced blood flow).

Medicines containing cilostazol have been approved in the EU through national procedures since 2000 and are available in France, Germany, Italy, Spain, Sweden and the United Kingdom under the invented names Pletal and Ekistol.

Cilostazol works by blocking an enzyme called phosphodiesterase type 3, which is found in the walls of arteries and is involved in various processes affecting circulation, including aggregation (clumping together) of blood platelets and narrowing of the arteries. Blocking the enzyme reduces these actions and blood flow is improved, allowing patients to walk further without disabling pain.

More about the procedure

The review of cilostazol was initiated at the request of Spain, under Article 31 of Directive 2001/83/EC.

The Spanish Agency for Medicines and Health Products (AEMPS) asked the CHMP to carry out a full assessment of the benefit-risk balance of cilostazol and to issue an opinion on whether the marketing authorisations for products containing cilostazol should be maintained, varied, suspended or withdrawn across the EU.

The request followed reports to the Spanish agency of serious adverse effects affecting the heart including fatal heart attacks, angina and arrhythmias (irregular heartbeat) as well as cases of serious bleeding including bleeding in the brain. Many of the patients who were prescribed the medicine were much older, and taking more medicines, than those in whom it was originally tested before marketing, which may explain the increased risk of side effects. There was evidence that many of these patients had to stop taking the medicine. In addition, the benefits of treatment were modest.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final decision in due course.