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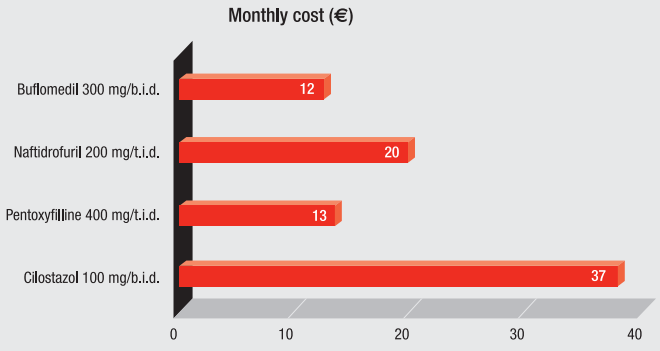
Cilostazol▲ (Ekistol®, Pletal®)

Too many risks



- Cilostazol is an antiplatelet agent indicated in patients with intermitent claudication to improve maximum and pain-free walking distance and time in peripheral arterial disease.
- It has not been shown to be more effective than pentoxifylline in the increment in walking distance without pain.
- In trials, the incidence and withdrawal of patients from treatment due to adverse effects was high. The most frequent adverse effects were headache and diarrhoea. In addition, cardiovascular disorders included: vertigo, oedema, palpitations, tachycardia and arrhythmias.
- Numerous potentially severe interactions can occur with other drugs: antihypertensives, anticoagulant and antiaggregant agents or proton pump inhibitors.

Treatment indications[1]

It is indicated for the improvement of the maximal and pain free walking distance in patients with intermitent claudication in peripheral arterial disease Fontaine stage II (with no rest pain or evidence of peripheral tissue necrosis).

Mechanism of action and pharmacokinetics[1]

Cilostazol is a reversible inhibitor of cellular phosphodiestarase III with platelet antiaggregation and vasodilatory effects.

It is rapidly absorbed, is 95-98% protein bound and is metabolized by the P-450 cytochrome (CYP3A4, and to a lesser degree, CYP2C19 and CYP1A2).

Important risks and low tolerance for only a modest benefit.

Cilostazol and its active metabolites are eliminated predominantly through the kidney. Its elimination half-life is 10.5 hours.

Dosage and administration[1]

The recommended dosage of cilostazol is 100 mg twice a day. It should be taken 30 minutes before or 2 hours after breakfast and the evening meal. It should not be administered with food.

Clinical efficacy

There is one long-term[8,10] and 6 short-term clinical trials[2-7] (12 to 24 weeks) published that have evaluated the efficacy and safety of cilostazol in the treatment of intermitent claudication (range from 81 to 698 patients).

The short-term trials included patients of 40 years or more with moderate to severe stable intermitent claudication of at least 6 months duration and secondary to peripheral arteriopathy. The primary endpoint of efficacy was the maximum distance upon treadmill testing. In the majority of the trials, patients under antiaggregant

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

therapy were excluded, which does not adjust to the profile of the patients the drug is produced for.

Cilostazol *vs* placebo: there is a meta-analysis[9] evaluating 7 clinical trials that included more than 1,500 patients, where cilostazol was compared to placebo for a maximum treatment period of 24 weeks. Cilostazol 100 mg twice daily significantly increased the maximum pain-free distance walked with respect to the baseline average by 50 metres when compared to placebo and the distance upto the onset of pain was increased by 31 metres. This effect was lower in diabetes patients[1].

Cilostazol *vs* pentoxifylline: in 3 short clinical trials (24 weeks) 100 mg cilostazol twice a day was compared to 400 mg pentoxifyllin three times a day and placebo in 689, 370 and 785 patients respectively[7,8]. In the only study published[7] it was observed that cilostazol presented significant improvement in the maximum pain-free distance walked (105 m) compared to 64 m with pentoxifylline and 65 m in the placebo group. In the two unpublished trials[8] there were no differences between cilostazol and pentoxifylline. Neither were there differences between either cilostazol or pentoxifylline and placebo in the maximum walking distance reached without pain. In the three trials the percentage of withdrawals, despite the short period, was over 20%.

The long-term trial[8,10] included 1,435 patients with intermitent claudication. The primary endpoint was total mortality while secondary endpoints were cardiovascular morbimortality, and disease progression. The median follow up period was 18 months. At the end of the study period, the number of deaths was similar in both groups, 49 with cilostazol and 52 with placebo. Neither were there any differences with regard to the secondary endpoints. The trial ended prematurely, given that the number of deaths was lower than expected in the trials protocol and due to the high rate of withdrawals.

Safety and precautions for use

In the only long-term trial, there was an important number of patient withdrawals (60%) which raises serious doubts about the drugs long-term tolerance[8,10].

Adverse reactions[1]

Very common: headache (> 30%) and diarrhoea (> 15%).

Common (≥1% to < 10%): Ecchymosis, oedema (peripheral, face), dizziness, palpitation, tachycardia, angina, arrhythmia, ventricular extrasystoles, rhinitis, pharyngitis, nausea and vomiting, dyspepsia, flatulence, abdominal pain, rash, pruritus, chest pain, asthenia.

Contraindications

Cilostazol is contraindicated in patients with any known predisposition to bleeding, (e.g. active peptic ulcer, recent hemorrhage stroke, proliferative diabetic retinopathy, poorly controlled hypertension); with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, a prolonged QTc interval; congestive heart failure, severe renal impairment, moderate or severe hepatic impairment, and hypersensitivity to cilostazol or any of the excipients.

Precautions[1]

Patients should be warned to report any bleeding or easy bruising whilst on therapy. Cilostazol should be stopped 5 days before any surgical intervention.

A full blood count should be carried out when any infection is suspected or in cases of any other sign of blood dyscrasia.

Precaution should be taken when concomittant use of any hypotensive agent is employed, given the additional hypotensive effect with a reflex tachycardia.

Precaution with those patients suffering from atrial or ventricular ectopy and patients with atrial fibrillation or flutter.

Interactions[1]

Given the increased risk of bleeding, caution is recommended when cilostazol is employed with any anticoagulant or antiaggregant agent. In patients treated with clopidogrel and acetylsalicylic acid, a considerable increase in the risk of bleeding was observed[8].

Drugs inhibiting CYP3A4 isoenzyme (such as some macrolides, azole antifungal agents, protease inhibitors, diltiazem) or CYP2C19 (for example, proton pump inhibitors) increase the concentration of cilostazol and can enhance the undesirable effects. The summary of product characteristics recommends a reduction to a 50 mg dose, though in Spain this presentation is not available on the market.

Precaution should be taken with drugs that are substrates of CYP3A4 with a narrow therapeutic index (cisapride, halofantrine, pimozide, ergotic derivatives) and with simvastatin due to the increments in their plasmatic concentrations when associated with cilostazol.

Special situacions[1]

Renal impairment: contraindicated when creatinine clearance is ≤ 25 ml/min; **hepatic impairment:** contraindicated in moderate or severe hepatic impairment. **Children:** no population studies available in these age groups. **Pregnancy:** contraindicated. **Breastfeeding:** do not employ.

Place in therapy

The treatment of intermitent claudication (IC) is a combination of preventive measures to avoid cardiovascular events along with symptomatic treatment of IC[9,11]. These preventive measures include lifestyle modifications (mainly smoking cessation), physical exercise programs and antiaggregant therapy. Supervised physical exercise programs represent the best treatment option in patients with intermitent claudication, as they reduce cardiovascular risk and improve claudication symptoms[11,12]. Among the drugs employed in symptomatic treatment of IC there are pentoxifylline, naftidrofuryl and buflomedil that provide only a very modest benefit.

Cilostazol has only been compared to pentoxifylline and given the clinical trials available, it has not been shown more effective. The only clinical trial in which endpoints evaluated included morbidity and mortality did not show better results than placebo and a considerable amount of withdrawals from the trial occurred, more than 60%.

Patients with intermitent claudication are often polymedicated and are at high cardiovascular risk. This drug presents frequent cardiovascular adverse effects, numerous contraindications and precautions, in addition to interactions with other drugs like antihypertensives, anticoagulants, antiaggregants and proton pump inhibitors, all of which are frequently employed in these patients.

For all these reasons, adding cilostazol to their treatment regimen may considerably increase the risk the patients bear for only a modest benefit which has only been observed for a short term period.

Presentations

Brands: Ekistol® (Lacer, S.A.) and Pletal® (Otsuka Pharmaceutical, S.A.). Cilostazol 100 mg 56 tablets (34.97 €). Prescription only medicine.

References

All references can be consulted at: www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INFORMATION:
Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta - 31002 Pamplona **T** 848429047 **F** 848429010