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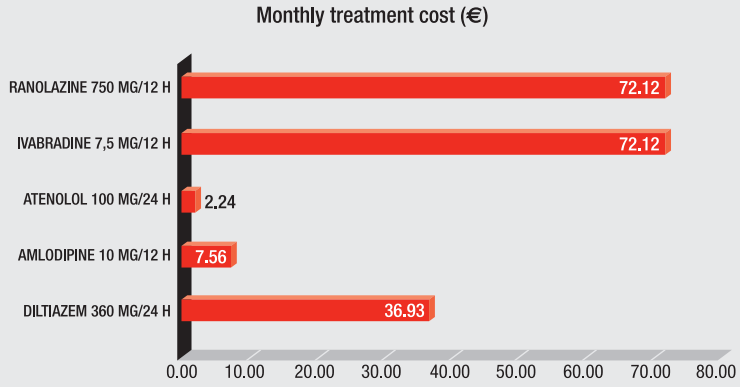
Ranolazine▲ (Ranexa®) in stable angina

A lot of inconveniences for no relevant benefit



- Ranolazine is indicated as an adjunct for stable angina in those patients who do not tolerate or are not adequately managed with first line treatments.
- It presents modest efficacy in exercise tolerance (24 seconds more) and reduction in the frequency of angina (0.4 episodes less, in 7 weeks). Studies have only compared it to placebo.
- No reduction in coronary morbidity or mortality has been shown.
- It presents a risk of prolonged QT intervals and a large variety of interactions with other medication employed in cardiovascular disease.
- The modest efficacy of ranolazine does not compensate for the risk of severe adverse effects.

Therapeutic indications[1]

Ranexa is indicated as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as betablockers and/or calcium antagonists).

Mechanism of action and pharmacokinetics[1]

The action mechanism of this drug is practically unknown. It appears to reduce cellular calcium levels, increasing myocardial relaxation and reducing the rigidity of the left ventricle. These effects do not depend on changes in heart rate, blood pressure or even vasodilation.

Continue with betablockers and calcium channel blockers

Maximum plasma concentrations (Cmax) are reached after 2-6 hours and a steady state is achieved after 3 days. The bioavailability is 25-50%, with high interindividual variability. Ranolazine is 62% protein bound. Elimination occurs through urine and feces.

Posology and administration[1]

Adults. The inicial dose is 375 mg twice daily. After 2-4 weeks the dose may be increased to 500 mg and, depending on the response, a maximum dose of 750 mg twice daily may be given. In case of adverse reactions, the dose should be reduced to 500 mg or 375 mg twice daily. If the symptoms persist then treatment should be discontinued. The tablets should be swallo-

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.

wed wholly, and may be taken with or without food.

Patients should carry an alert card indicating all their medication.

Safety and precautions

Adverse reactions

Withdrawals due to adverse effects ocurred in 9% of the cases. The adverse effects were dose-dependent. The most frequent (>10%) were dizziness, constipation, nausea, asthenia, and headache. This frequency increased in patients >75 years[8].

The most frequent severe adverse effect were unstable angina, infarction and angina pectoris. A very rare adverse effect, though severe was syncope[7].

Ranolazine can provoke increases in QT intervals, which could lead to arrhythmia[8]. Available data indicates that the arrhythmogenic effect is relatively low, although high serum concentrations could prove dangerous.

Contraindications

Hypersensitivity to the main active substance or any of the excipients, severe renal failure, moderate and severe hepatic failure, concomittant treatment with potent CYP3A4 inhibitors (grapefruit juice, itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone), and CYP3A4 inducers (rifampicin, phenytoin, carbamazepine, hypericum or St. John's wort). Neither should ranalozine be employed in patients with prolonged QT intervals (including congenital prolonged QT syndrome or uncorrected hypokaliemia), known history of ventricular tachycardia and patients under treatment with drugs that may prolong the QT interval such as some antipsychotics (ziprasidone) and class IA (quinidine) and class III (dofetilide, sotalol) antiarrhythmic agents.

Precautions

Concomitant use with moderate CYP3A4 inhibitors (diltiazem, fluconazole, erithromycin), P-gp (P glycoprotein) inhibitors (verapamil, cyclosporine, quinidine) or CYP2B6 inhibitors (bupropion, efavirenz, ciclophosphamide), mild liver failure, mild to moderate renal failure, elderly patients, patients with low body weight (≤ 60 kg) and patients with congestive heart failure (Class III and IV, NYHA).

Interactions[1]

Inhibitors of CYP3A4, P-gp, and CYP2D6 can increase serum levels of ranolazine, while inducers such as CYP3A4 can reduce ranolazine concentrations.

Ranolazine can increase plasma concentrations of drugs that are substrates of CYP3A4, P-gp, and CYP2D6 (tricyclic antidepressants and antipsychotics). The CYP2B6 inhibition produced has not been evaluated and so precaution is advised. Ranolazine also produces increments in plasma concentrations of digoxin and simvastatin.

Special situations

Pregnancy and lactation. It should not be used. **Women.** The effects on the frequency of angina and exercise tolerance was considerably lower in women than in men. **Elderly patients,** with renal failure and/or low weight. Adverse reactions in these patients were more frequent. **Children and adolescents:** this drug should not be employed in patients under 18 years of age. **Motor vehicle driving.** Ranolazine can provoke dizziness and blurred vision.

Place in therapeutics

Initial management of angina includes recommending a healthy lifestyle and control of co-morbidities. In patients with mild to moderate stable angina, beta blockers are the first choice. If monotherapy is not sufficient to control symptoms then calcium channel blockers and/or long-acting nitrates can be combined with the initial treatment. Patients who do not attain adequate control of symptoms under maximum doses of antianginal treatment should be referred to a cardiologist.

In the CARESA trial, the only one responding to the indication of the drug, the patients in the ranolazine group showed an increased exercise tolerance of 24 seconds (basal value = 7 minutes). One limitation of the study was the low doses of baseline antianginal therapy employed beforehand. The ERICA study found a difference of 0.4 less episodes of angina in the ranolazine group after 7 weeks of treatment. The MERLIN-TIMI 36 trial showed a lack of benefit in a composite endpoint of morbidity and mortality in patients with acute coronary syndrome.

Ranolazine presents the risk of prolonging the QT interval and a considerable amount of interactions with other durgs, which could potentiate the risk of arrhythmia. Patients should always carry the list of treatments they are taking.

Given the modest efficacy and the risk of severe adverse reactions, it is recommended to employ first line treatments, beta blockers and/or calcium channel blockers.

Presentations

RANEXA® (Menarini LTD) 375 mg 60 tablets (77.27 €), 500 mg 60 tablets (77.27 €) y 750 mg 60 tablets (77.27 €). Prescription medicine only.

References

A complete report on ranolazine can be consulted at: http://www.dtb.navarra.es

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