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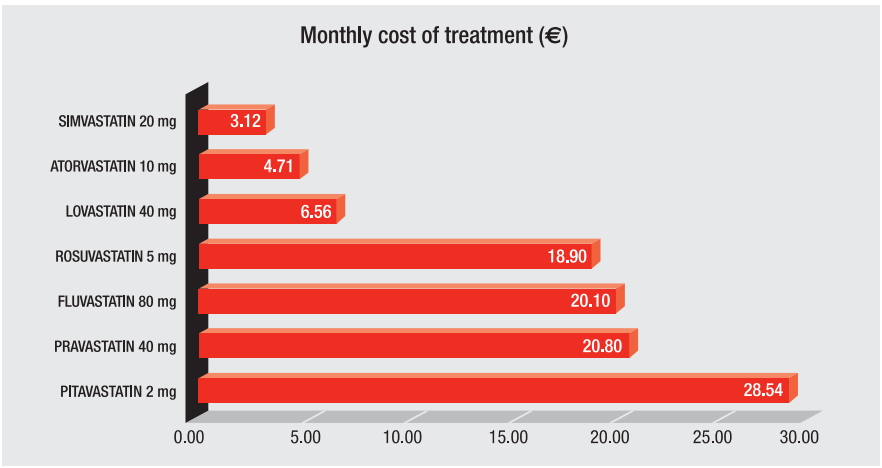
Pitavastatin (▲Alipzal®, ▲Livazo®) in dyslipidemia

The eighth statin but no results on morbidity and mortality



Simvastatin is still the elective choice, given the evidence and price

- Pitavastatin has not been shown to be superior to other compared statins in the reduction of lipid levels. Unlike these other statins, there are no trials on mortality and morbidity with respect to pitavastatin.
- Adverse reactions are similar to the rest of the statins and the incidence tends to be dose-dependent.
- Clinically significant interactions have been observed with ciclosporin, erythromycin, rifampicin, warfarin and fibrates. Like fluvastatin and pravastatin, it is minimally metabolized via P450 cytochrome.
- It is more expensive than simvastatin and atorvastatin.

Indications[1]

Pitavastatin is indicated for the reduction of elevated total cholesterol (TC) and low density lipoprotein cholesterol (LDL-c), in adult patients with primary hypercholesterolemia, including heterozygous familial hypercholesterolemia, and combined (mixed) dyslipidemia, when response to diet and other non-pharmacological measures are inadequate.

Mechanism of action and pharmacokinetics[1]

This agent is a competitive HMG-CoA reductase inhibitor. The bioavailability is 51% and the elimination half-life is 8.9 hours. The main metabolite is an inactive lactone derived from the conjugation of glucuronide and the hydroxilation. Metabolism via P450 cytochrome is minimal and therefore this drug is considered free of interactions through this metabolic pathway, just as the cases of fluvastatin and pravastatin. However, it is actively transported to hepatocytes by carriers such as OATP1B1 and OATP1B3 whose activation or inhibition can produce interactions.

Posology and method of administration[1]

The inicial dose is 1 mg once daily. Dose adjustments should be made over 4 or more weeks. The dose should be individualized in relation to LDL-c levels, the objectives of treatment, and patients' response. The majority of patients need a 2 mg dose. The maximum daily dose is 4 mg. Pitavastatin can be taken at any hour of the day, although preferably at the same hour daily.

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.

Clinical efficacy

The evaluation report issued by the Medicines and Healthcare products Regulatory Agency (MHRA)[2] in the United Kingdom included 5 double-blind short-term trials (12 weeks, except one of only 8 weeks) controlled with placebo and 5 double-blind trials with an active comparator. Some of these studies have a long-term extension phase. So, there are 7 long-term studies with a maximum duration of 104 weeks. Two of them were interrupted prematurely due to adverse effects, and therefore only offer data on safety. These trials included patients with primary hypercholesterolemia or mixed dyslipidemia and excluded high risk patients. The efficacy was measured by lipid profiles. The majority of these studies are not published. No studies with results on morbidity and mortality have been carried out[1].

The MHRA[2] report concludes that pitavastatin is not inferior to atorvastatin in the reduction of LDL-c at the corresponding dose. There are three studies in special populations (high cardiovascular risk, diabetes patients and elderly patients >85 years). In secondary prevention, pitavastatin 4 mg is not different to simvastatin 40 mg, and in elderly patients, pitavastatin is not inferior in the reduction of LDL-c when compared to pravastatin (pitavastatin 1 mg vs pravastatin 20 mg and pitavastatin 2 mg vs pravastatin 40 mg). In diabetes patients non inferiority of pitavastatin was not demonstrated, but this could be due to lack of statistical power.

In addition, 3 other double-blind, randomized trials have been evaluated. Two of them were non-inferiority, multicenter double-blind trials carried out on patients with primary hyperlipidemia or mixed dyslipidemia. The first study[3] compared pitavastatin to simvastatin in 857 patients. The reductions in LDL-c after 12 weeks were not inferior for pitavastatin 2 mg compared to simvastatin 40 mg (39% and -35%) and pitavastatin 4 mg compared to simvastatin 40 mg (-44% and -43%). The second study[4] compared pitavastatin with atorvastatin in 821 patients. Reductions of LDL-c after 12 weeks were not inferior for pitavastatin 2 mg compared to atorvastatin 10 mg (-44,6% and -43,5%). The limits of non-inferiority was established at 6% in both trials. The third study[5], a double-blind multicenter trial, compared pitavastatin 2 mg to pravastatinn 10 mg in 240 patients with primary hyperlipedemia. The results after 12 weeks showed superiority with regard to pitavastatin 2 mg in the reductions of LDL-c (-37,6% and -18,4%), and total cholesterol (-28% and -13,8%). The dose of pitavastatin was not equipotential to that of pravastatin. Following EMA recommendations, open trials or studies of less than 12 weeks have not been taken into account[6-16].

Safety

Adverse reactions[1]

Frequent (1-10%) cefalea, constipation, diarrhoea, dypepsia, nausea, myalgia, arthralgia. Increases in creatin kinase (CK) 3 times higher than normal values were observed in 1.8% of the patients. In a study after commercialization, 7.4% of patients under either 1 or 2 mg pitavastatin discontinued treatment due to adverse reactions. The incidence of myalgia was 1.08%. Two cases of rhabdomyolysis were reported and required admission to hospital (0.01%).

Contraindications[1]

Patients with severe liver impairment, active liver failure or persistently high and unjustified levels of transaminases (>3 times the upper normal limit). Patients with myopathy or concomitant treatment with ciclosporin, and during pregnancy, lactation and women in fertiles age that do not employ adequate contraceptive methods.

Warnings and precautions[1]

Just like other statins there is a possibility of developing myalgia, myopathy, and in rare cases, rhabdomyolysis. CK levels should be detemined in all patients that report muscle pain, or complain of muscle pain on palpation or muscle weakness, especially if accompanied by general malaise or fever. Liver function tests should be performed before intitating treatment and periodically during treatment. Statin therapy should be discontinued whenever there is suspicion of interstitial pulmonary disease.

Use in special situations[1]

Pregnancy and lactation: contraindicated. **Renal impairment:** precaution. The 4 mg dose is not recommended in severe renal failure. **Mild to moderate liver impairment:** use a maximum dose of 2 mg and monitor liver function. Contraindicated in **severe liver failure. Children under 18 years:** not authorized. **Elderly:** no dose adjustments necessary.

Interactions[1]

Pitavastatin should be discontinued temporarily during treatment with macrolids and fusidic acid. Precaution should be taken when used concomitantly with fibrates and niacin due to a possible increase in myopathy and rhabdomyolysis. Administration in conjunction with rifampicin can cause a 1.3 times increase in the AUC of pitavastatin due to the reduction in liver capture. Prothrombin times and INR values should be controlled in patients receiving warfarin or acenocoumarol when pitavastatin is added to patient treatment.

Risk plan of the European Medicines Agency (EMA)[1]

Once commercialized, the EMA has petitioned vigilance trials to evaluate:

· The risk of rhabdomyolysis with pitavastatin 4 mg in the European population to confirm the scarce data available in the phase II and III studies and in post-marketing studies in Japan as well (favourable for pitavastatin 4 mg vs atorvastatin 20 and 40 mg).

· To identify and quantify the less frequent adverse effects: psychiatric morbidity and other effects on the CNS.

· Data on clinical events and effects on morbidity and mortality in the long term especially in high risk patients.

Place in therapeutics

Pitavastatin is the eighth statin commercialized in Spain (included the withdrawn cerivastatin). It reduces total cholesterol and LDL-c to a similar extent to the rest of statins at equipotential doses. There are only data available on the reduction of lipid levels. However, other statins have shown a reduction in coronary morbidity and mortality. The most efficient one currently is simvastatin.

The greatest benefit obtained with statins has been observed in patients at high cardiovascular risk in secondary prevention, a population excluded from the majority of the clinical trials with pitavastatin.

New drugs in chronic diseases should show better results and significant improvements with respect to the reference treatment in relation to morbidity and mortality and /or quality of life. For the moment, pitavastatin has not proved to be better than the reference therapy.

Presentations

Alipzal® (Esteve) y Livazo® (Recordati Spain) 1 mg 28 tablets (20.79 €), 2 mg 28 tablets (28.54 €), 4 mg 28 tablets (42.80 €)

References

A complete report on pitavastatin can be found at: http://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