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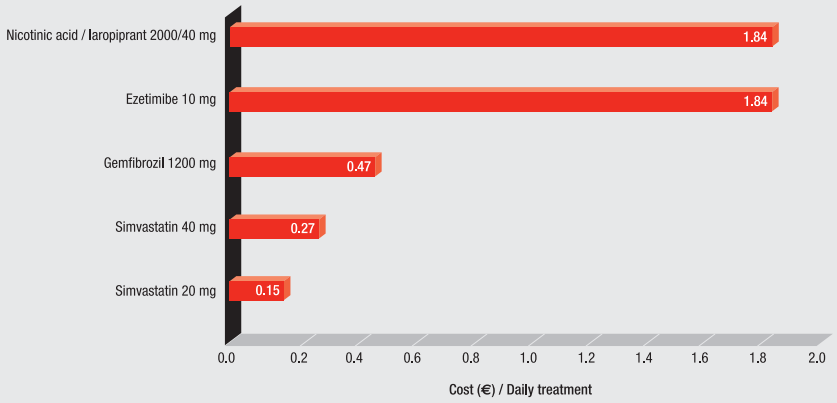
Nicotinic acid/laropiprant (Tredaptive®)

A new look at old junk



- Nicotinic acid/laropiprant is indicated in the treatment of dyslipidaemia.
- No comparative data on efficacy is available between nicotinic acid/laropiprant and the different statins. The administration of this drug in combination with statin therapy at low to medium doses produces a greater reduction in LDL-c levels than in monotherapy. There is no data available on the combination with high dose statins.
- There is no evidence available on the efficacy of nicotinic acid/laropiprant with regard to the reduction in morbimortality.
- Flushing still remains the most frequent undesirable effect related to nicotinic acid, despite its association with laropiprant.

Therapeutic indications[1]

Nicotinic acid/laropiprant is indicated in the treatment of dyslipidaemia, especially in those patients with combined mixed dyslipidaemia (characterised by elevated levels of LDL-c and triglycerides and low levels of HDL-c) and in those patients with primary hypercholesterolaemia (heterozygous familial and non-familial). This agent should be employed in patients in combination with statins, when the cholesterol lowering effect achieved is not sufficient. It may only be used in monotherapy in patients in whom statins are considered inappropiate or are not tolerated.

Statins and/or fibrates are the elective management options for treating dyslipidaemia

Mechanism of action and pharmacokinetics[1]

The mechanism of action of nicotinic acid is still not fully known. It inhibits the release of free fatty acids from adipose tissue, which could contribute to the reduction in concentrations of LDL-c, total cholesterol, very low density lipoproteins (VLDL-c), apolipoprotein b, triglycerides and Lipoprotein(a), and the increments in HDL-c and apo A-I. In addition it inhibits *de novo* lypogenesis or the esterification of fatty acids to triglycerides in the liver. Laropiprant is a potent and selective antagonist of DP_1 receptors on which the D_2 prostaglandin acts

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.

and is responsible for the shortness of breath induced by nicotinic acid.

The bioavailability of nicotinic acid is 72%. It undergoes an extense first step metabolism through two pathways. In high doses or with high absorption rates, the main pathway is saturated and a greater percentage of the dosis reaches blood with no modification. It is excreted mainly in urine in metabolite form.

Posology and method of administration[1]

The starting dose is one tablet (1,000 mg nicotinic acid and 20 mg laropiprant) once a day for four weeks after which the dose is increased to two tablets daily. If Tredaptive is missed for one complete week, therapy should be resumed as done initially, that is one tablet daily for one week, before increasing to the maintenace dose of two tables daily.

The tablets should be taken whole, with food, in the evening or at bedtime. To preserve the modified-release properties, the tablets should not be split, broken, crushed, or chewed before swallowing. To reduce the possibility of flushing, hot drinks or alcohol should not be taken at the time of ingestion.

Clinical efficacy

Data on the efficacy of nicotinic acid / laropiprant is available form two clincal trials carried out for 24 and 12 months, including 1,613 and 1,398 patients respectively[5,6]. The main variable of the trials was the efficacy in reducing LDL-c levels. The characteristics of the patients were as follows: ages betwen 18 and 80 years, with either primary hypercholesterolaemia or combined mixed hyperlipidaemia if TG levels were ≤ 350 mg/dL (3.95 mmol/L). Patients excluded were type 1 diabetes or recently diagnosed with type 2 diabetes. Those diabetes patients with inadequate glycaemic controls or who presented recent modifications in treatment were also excluded.

In the first study[5] the patients presented mean basal LDL-c levels of 113.5 ± 40.2 mg/dL (2.93 ± 1.0 mmol/L). The group under nicotinic acid/laropiprant showed a statistically significant reduction in LDL-c of -18,4% (95% CI, -21.4% to -15%) with respect to the placebo group. In the second study[6], the combination with a statin was compared with monotherapy. Patients had average basal levels of LDL-c of 151.3 ± 16.5 mg/dL (3.91 ± 0.43 mmol/L). Relative risk reduction was significant for the combination of nicotinic acid / laropiprant plus simvastatin compared to nicotinic acid / laropiprant alone, (RR = -10,8%; 95% CI, -13,2% to -8,4%). No data on the comparison of nicotinic acid/laropiprant and different doses of simvastatin were available from this study.

There is no data available with regard to nicotinic acid/laropiprants efficacy on reducing morbidity and mortality in patients with dyslipidaemia. The only data available on efficacy is from an older study, the *Coronary Drugs Project*[3], carried out between 1966 and 1975 in patients with previous myocardial infarction. Nicotinic acid showed a modest reduction in the incidence of recurrent non-fatal myocardial infarctions, but not in mortality.

Adverse effects[1,2]

Flushing is the most common adverse reaction of Tredaptive (12.3%). In clinical trials, 7.2% of the patients discontinued due to symptoms related to flushing (redness, warmth, itching and tingling). Other frequent adverse effects (1-10%) include: increase in liver transaminases, fasting glucose, uric acid; dizziness, headache and paraesthesia; diarrhoea, nausea, vomiting and dyspepsia; erythema, pruritus, exanthema and urticaria. Clinically relevant increments in creatin kinase (CK) levels were observed in 0.3% of the patients.

Contraindications and precautions[1]

Tredaptive is contraindicated in cases of hypersensitivity to the active substances or to any excipients, severe liver dysfuntion or of unknown aetiology, active peptic ulcer disease and arterial bleeding.

It should be employed with precaution in patients who consume important quantities of alcohol and those with a history of liver disease. Liver function tests should be performed before initiating treatment, after 6 to 12 weeks for the first year of treatment and then periodically in the following years.

If muscle pain, weakness or cramps appear during Tredaptive administration with a statin then, CK levels should be determined as rhabdomyolysis may be associated. Caution should be taken in patients with a history of gout or a predisposition for it.

Use in special situations[1]

Renal impairment: as no studies are available, precaution is advised. **Liver impairment:** no studies are available, though it is contraindicated in cases of severe dysfuntion. **Pregnancy, lactation and children under 18 years:** not recommended. **Elderly:** no dose adjustments are necessary.

Interactions[1]

Nicotinic acid can potentiate the effects of ganglionic blockers and **vasoactive agents** (nitrates, calcium channel blockers and adrenergic receptor antagonists) resulting in hypotension. When **simvastatin** was combined with nicotinic acid a moderate increase in serum levels of simvastatin was observed. **Bile acid sequestrants** can reduce the bioavailabilty of nicotinic acid. Tredaptive administration is recommended one hour before or 4 hours after the bile acid sequestrant. False positive reactions may be produced in urine glucose tests with Benedicts reagent. Plasmatic levels of the active metabolite of **midazolam** were increased two-fold with the administration of multiple doses of laropiprant. Precaution should be taken when nicotinic acid / laropiprant is taken with drugs predominantly metabolised by uridine diphosphate-glucuronosyltransferases 2B4 and 2B7, for example **zidovudine**. In one study a moderate increase in the inhibition of collagen induced platelet aggregation by **clopidogrel** was observed, though tis clinical relevance remains unknown.

Place in therapeutics

No data is available on nicotinic acid / laropiprants efficacy in the reduction of morbidity and mortality in patients with combined mixed dyslipidaemia and primary hypercholesterolemia. There is only one very old study, carried out before the introduction of statins, in which nicotinic acid in monotherapy showed modest efficacy in the reduction of the incidence of recurrent non-fatal myocardial infarctions in patients with a history of infarction, though no reduction in mortality was observed.

Although the combination of nicotinic acid with laropiprant reduced the episodes of flushing associated with nicotinic acid, this undesirable effect is still frequent. In one study, a greater reduction on LDL-c was observed after combination with a statin. Given that there are no comparative studies with either high dose statins or with combinations of the elective treatments, it is recommended that first line treatments should be employed in these patients: statins and/or fibrates. There is more data available on the efficacy and long-term safety of these agents.

Presentations

TREDAPTIVE® (Merck Sharp & Dome) 1.000 mg / 20 mg modified-release tablets. 28 and 56 tablets (25.79 € and 51.58 € respectively). Requieres medical prescription.

References

The complete report on nicotínic acid / laropiprant is available at: http://www.navarra.es/medicamento

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