

NEW DRUG EVALUATION

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TREDAPTIVE[®]▼

Tredaptive[®]▼ is a combination of nicotinic acid and the anti-flushing agent laropiprant. Nicotinic acid has favourable effects on lipid profiles, but flushing occurs in the majority of patients, limiting its use. Tredaptive[®]▼ improves lipid profiles significantly when given alone or in combination with a statin, and the incidence of flushing is reduced compared to extended release (MR) nicotinic acid. Tredaptive[®]▼ may be considered as an option for lipid modification, in addition to lifestyle changes, in those patients who fulfil the nicotinic acid criteria but are unable to tolerate it due to flushing.

What is it?

Tredaptive[®]▼ (Merck Sharp & Dohme) is a modified-release (MR) combination of nicotinic acid 1 g plus laropiprant 20 mg licensed for the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia or with primary hypercholesterolaemia.¹ The recommended starting dose is one tablet daily, increasing to two tablets daily as a maintenance dose.

Nicotinic acid is an established lipid regulating drug but its use has been limited by poor tolerability, in particular flushing.^{2,3} Tredaptive[®]▼ contains laropiprant, which is added to minimise flushing and acts by selectively blocking the prostaglandin D₂ (PGD₂) receptor.⁴

How effective is it?

Two double-blind, randomised controlled trials have compared the efficacy of Tredaptive[®]▼ with that of extended release (MR) nicotinic acid or placebo in patients with primary hypercholesterolaemia or mixed dyslipidaemia.^{5,6}

In a 24 week study, a total of 1,613 patients received Tredaptive[®]▼ (2 g / 40 mg), MR nicotinic acid (2 g) or placebo.⁵ Patients were recruited across all CHD risk categories, but those considered to be at high CHD risk received ongoing statin therapy; approximately 67% of patients were on stable statin therapy at the start of the study. Patients receiving Tredaptive[®]▼ had significant reductions in LDL-C (treatment difference 18%), increases in HDL (20%), and reductions in triglycerides (26%) compared to placebo (all $p < 0.001$). The lipid modifying efficacy of Tredaptive[®]▼ was comparable when administered alone or when added to ongoing statin therapy. Tredaptive[®]▼ was compared with MR nicotinic acid only with respect to its effects on flushing symptoms. During the maintenance phase (weeks 2-24) more patients receiving Tredaptive[®]▼ experienced no flushing compared with those receiving nicotinic acid (24% vs. 46%, $p = \text{not reported}$). The

incidence of discontinuation due to flushing was 10.2% vs. 22.2%, respectively ($p < 0.001$).⁵

A second 16 week study ($n = 1,455$) compared the flushing profile of Tredaptive[®]▼ with that of gradually titrated nicotinic acid (0.5g for four weeks titrated in 0.5g increments every four weeks to 2 g for the final four weeks).⁶ Patients receiving Tredaptive[®]▼ had significantly ($p < 0.001$) less flushing than those on nicotinic acid, as measured by days per week with moderate, severe, or extreme flushing. Overall, more patients receiving Tredaptive[®]▼ experienced no or mild flushing compared to those receiving nicotinic acid (47% vs. 22%, $p = \text{not reported}$). Fewer patients on Tredaptive[®]▼ discontinued treatment due to flushing than those on nicotinic acid (7.4% vs. 12.4%, $p = 0.002$).⁶

A further 12 week double blind study ($n = 1,398$) compared the efficacy of Tredaptive[®]▼ as add on treatment to simvastatin (20 or 40 mg) with Tredaptive[®]▼ or simvastatin alone in patients with primary hypercholesterolaemia or mixed hyperlipidaemia.⁷ High-risk patients were excluded. The combination of Tredaptive[®]▼ plus simvastatin produced significantly greater reductions in LDL-C compared with either treatment alone. The mean reduction (pooled across simvastatin doses) was -48% for the combined treatment vs. -17% with Tredaptive[®]▼ and -37% with simvastatin alone, $p < 0.05$ for combined vs. monotherapy.⁷

How safe is it?

In all trials, with the exception of flushing, the overall incidence of adverse events was generally similar between treatment groups.⁵⁻⁷ In the largest study comparing Tredaptive[®]▼ with MR nicotinic acid the most common adverse events were flushing (7.5% vs. 15.2%), nausea (2.9% vs. 2%), diarrhoea (2.6% vs. 1.8%), feeling hot (2.6% vs. 3.3%), parasthaesia (2.9% vs. 4.6%), pruritis (5.6% vs. 6.3%) and erythema (2.4% vs. 2.6%).⁵ Treatment with Tredaptive[®]▼ plus simvastatin

was generally well tolerated, with an overall adverse event profiles similar to that of Tredaptive[®] alone.⁷

In one study significantly more patients receiving Tredaptive[®] had consecutive elevations ($\geq 3 \times$ ULN) in liver enzymes compared to those receiving MR nicotinic acid (1.1% vs.0.1%, p=not reported).⁶ As with other nicotinic acid products, Tredaptive[®] is contraindicated in patients with significant or unexplained hepatic dysfunction.¹ Liver function tests are recommended before initiating treatment with Tredaptive[®], every six to 12 weeks for the first year, and periodically thereafter. Should elevations of liver enzymes persist ($\geq 3 \times$ ULN), reduction of dose or withdrawal is recommended.¹

All suspected adverse reactions to black triangle drugs such as Tredaptive[®] should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

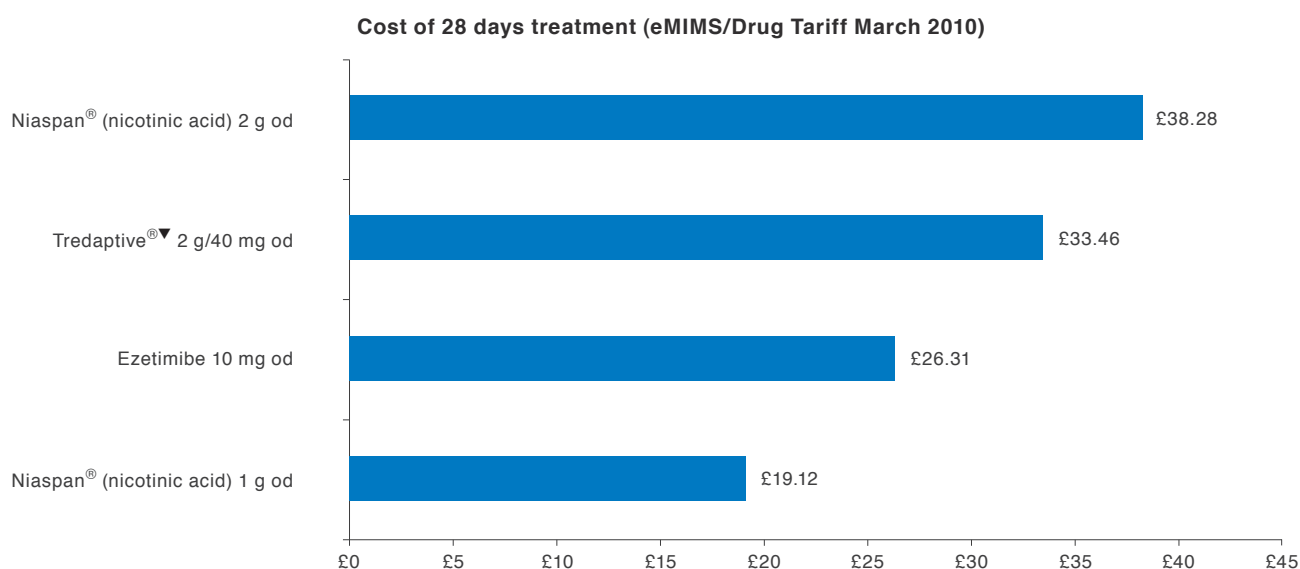
What other options are there?

In the treatment of primary dyslipidaemia, statins are the first line therapy.⁸ If lipid control is inadequate or statins are unsuitable; ezetimibe may be used as an add-on therapy or monotherapy.

When should it be used?

NICE recommends nicotinic acid for the secondary prevention of CVD as an alternative for those intolerant of statin therapy.⁸ The incidence and severity of flushing was significantly lower with Tredaptive[®] than MR nicotinic acid,^{5,6} and may be considered as an option for lipid modification in patients who fulfil the nicotinic acid criteria but are unable to tolerate it due to flushing. Tredaptive[®] should be initiated and titrated by specialists only.

How much does it cost?



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY: R - review, RCT - randomised controlled trial, G-guideline.

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