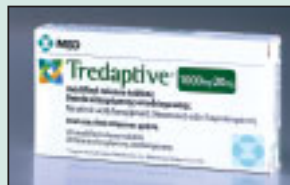


# Nicotinic acid/laropiprant: a new lipid-modifying therapy

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## KEY POINTS

- Tredaptive is a combined formulation of nicotinic acid and laropiprant, which inhibits flushing caused by nicotinic acid
- licensed for the treatment of dyslipidaemia and primary hypercholesterolaemia as an adjunct to a statin or as monotherapy when a statin is inappropriate
- available as modified-release tablets containing 1000mg nicotinic acid and 20mg laropiprant; 28=£16.73, 56=£33.46
- starting dose is 1 tablet daily increasing after 4 weeks to the maintenance dose of 2 tablets daily
- Tredaptive lowers LDL cholesterol and triglycerides and raises HDL cholesterol in adults with primary hypercholesterolaemia regardless of concurrent statin therapy
- the combination of Tredaptive plus simvastatin lowers LDL-cholesterol and triglycerides more than simvastatin monotherapy, and increases HDL-cholesterol more than Tredaptive monotherapy
- flushing affecting the head, neck and upper torso occurs in 12% of patients and results in treatment discontinuation in 7-10%
- the addition of Tredaptive to ongoing statin therapy has been shown to significantly increase HDL-cholesterol and reduce LDL-cholesterol and triglycerides



**Tredaptive is a combination of nicotinic acid and laropiprant for the treatment of dyslipidaemia and primary hypercholesterolaemia. In our New products review, Steve Chaplin discusses the clinical data relating to its efficacy and side-effects, and Dr Marc Evans describes its place in therapy.**

The National Institute for Health and Clinical Excellence (NICE) recommends statins for patients with clinical evidence of cardiovascular disease (CVD) and as primary prevention in those whose 10-year CVD risk is at least 20 per cent.<sup>1</sup> The drug of first choice is simvastatin 40mg per day. Combined treatment with a statin and other agents is not recommended for primary prevention, though the addition or substitution of ezetimibe (Ezetrol) is an alternative for patients with primary hypercholesterolaemia.<sup>2</sup>

For primary prevention, no target for a reduction in LDL-choles-

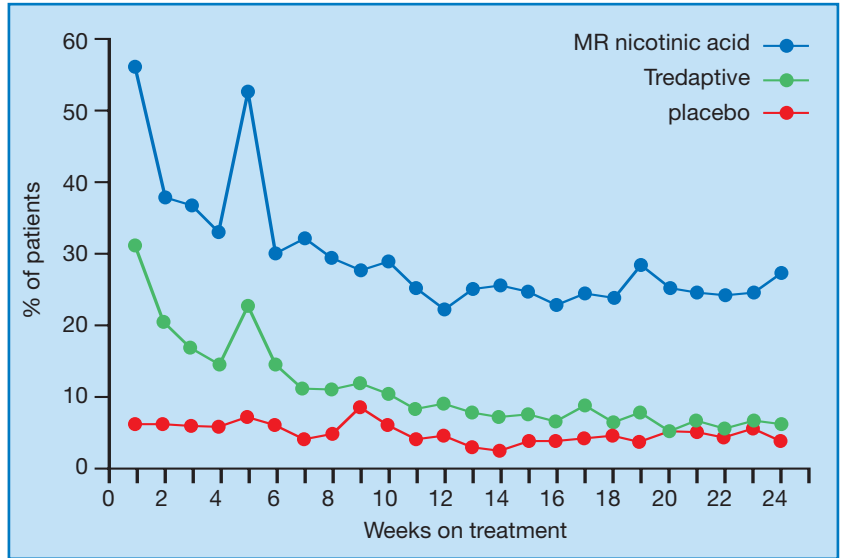
terol is recommended, and consideration of the effectiveness of treatment is left to clinical judgement and patient preference. In secondary prevention, if total cholesterol remains above 4mmol per litre and LDL-cholesterol above 2mmol per litre, a dose increase to simvastatin 80mg per day should be considered. This dose is also recommended for patients with acute coronary syndrome.

Patients who cannot tolerate a statin may consider a fibrate, nicotinic acid (Niaspan) and anion exchange resins instead or, for those with primary hypercholesterolaemia, ezetimibe.

NICE offers no specific guidance on what to do if target lipid levels are not achieved with simvastatin 80mg per day, though it does indicate 'high-intensity statins', *ie* those offering reductions in LDL-cholesterol comparable with simvastatin 80mg per day, as options.

## The technology

Tredaptive is a modified-release (MR) formulation combining nicotinic acid 1000mg and laropiprant 20mg. Nicotinic acid reduces triglycerides, LDL-cholesterol and total cholesterol and



**Figure 1.** Percentage of patients with moderate, severe or extreme flushing with Tredaptive, MR nicotinic acid and placebo<sup>7</sup>

raises HDL-cholesterol by multiple mechanisms. In the Coronary Drug Project trial, secondary prevention with nicotinic acid was associated with a reduction in non-fatal MI after five years (8.9 *vs* 12.2 per cent with placebo).<sup>3</sup> Mortality was no different from placebo at five years, but after 15 years (and nine years after stopping treatment) mortality was 11 per cent lower among recipients of nicotinic acid compared with those randomised to placebo (52 *vs* 58 per cent).<sup>4</sup>

The utility of nicotinic acid is limited by a high incidence of flushing, even with the MR formulation. This phenomenon is mediated by the prostaglandin D<sub>2</sub> receptor subtype 1 (DP<sub>1</sub>) and can be reduced by treatment with aspirin.<sup>5</sup> Laropiprant is an antagonist at DP<sub>1</sub> receptors and this action inhibits nicotinic acid-induced flushing when administered concurrently.<sup>6</sup> Laropiprant may affect platelet function but no clinically relevant effects have been noted at therapeutic doses.<sup>7</sup>

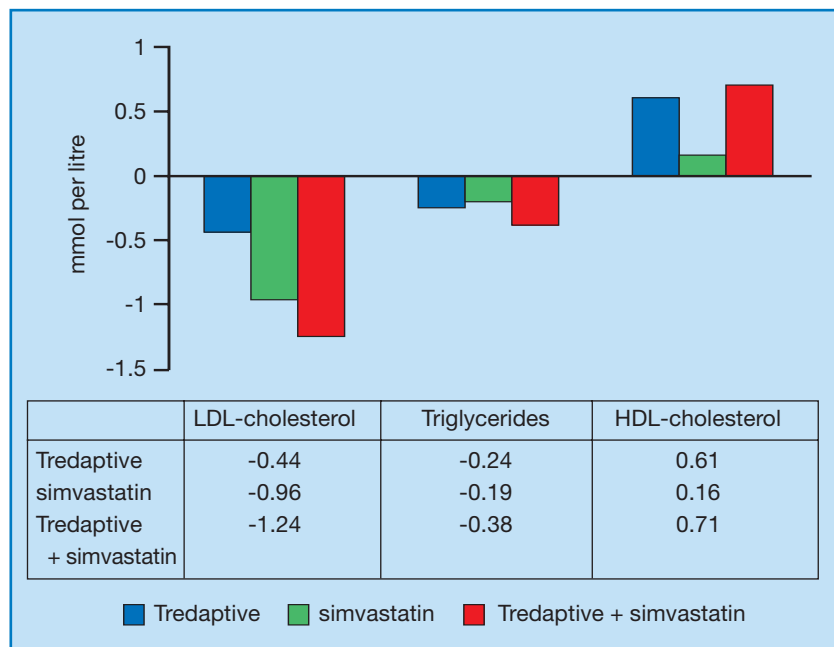
Tredaptive is licensed for the treatment of dyslipidaemia, particularly in patients with mixed dyslipid-

aemia (characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol) and in patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial). It is indicated as monotherapy only for patients unable to tolerate a statin or for whom a statin is not appropriate, and in combination with a statin when target lipid levels are not achieved.

The recommended dose of Tredaptive is initially 1000mg/20mg (one tablet) once daily with food in the evening or at bedtime, increasing after four weeks to two tablets once daily. If treatment is interrupted for more than seven days, it should be retitrated from the initial dose. No dose adjustment is required for older people; caution is required in patients with renal impairment because nicotinic acid and its metabolites are primarily excreted by the kidneys. Tredaptive is contraindicated in patients with significant or unexplained hepatic dysfunction, active peptic ulcer and arterial bleeding.

**Clinical trials**

Two randomised trials (one currently unpublished) provide the



**Figure 2.** Changes in LDL-cholesterol, triglycerides and HDL-cholesterol over 12 weeks with Tredaptive, simvastatin and Tredaptive plus simvastatin<sup>8</sup>

key clinical data for Tredaptive.<sup>7,8</sup> Both included adults with primary or mixed hypercholesterolaemia and used the licensed dose.

Tredaptive was compared with MR nicotinic acid 1000mg per day, increased to 2000mg per day after four weeks, in a 24-week placebo-controlled trial in 1613 patients.<sup>7</sup> Mean baseline LDL-cholesterol was 2.94mmol per litre; 67 per cent of patients were taking a statin. The primary end-points were the change in LDL-cholesterol over weeks 12–24 for Tredaptive *vs* placebo and severity of flushing during the first week for all groups. Secondary end-points included changes in other lipids.

A total of 28 per cent of patients did not complete the trial; this included withdrawals due to flushing (Tredaptive 10.2 per cent, MR nicotinic acid 22.2 per cent, placebo 0.7 per cent).

Tredaptive reduced mean LDL-cholesterol significantly compared with placebo (-0.49 *vs* -0.01mmol per litre).<sup>8</sup> This was associated with a significant increase in HDL-

cholesterol (0.52mmol per litre) and significant reductions in triglycerides (0.29mmol per litre) and LDL/HDL-cholesterol ratio (-28.9 *vs* 2.3).<sup>8</sup> Similar changes occurred in the subgroup of patients not taking a statin.<sup>8</sup>

The severity of flushing in the first week was less with Tredaptive than with MR nicotinic acid.<sup>7</sup> The proportion of patients with moderate, severe or extreme flushing with Tredaptive was initially about half that associated with MR nicotinic acid and declined to almost placebo levels after 20 weeks (see Figure 1).<sup>7</sup>

In the second trial, 1398 patients were randomised to treatment with Tredaptive plus placebo or simvastatin 20 or 40mg per day, or simvastatin alone, for 12 weeks.<sup>8</sup> Mean baseline LDL-cholesterol was 3.9mmol per litre. The primary end-point was the change in LDL-cholesterol. A total of 18 per cent of patients did not complete the trial; this included withdrawals due to flushing (Tredaptive 9 per cent, Tredaptive

plus simvastatin 5 per cent, simvastatin 0.3 per cent) and other adverse effects (14, 12 and 5 per cent respectively).

Mean reductions in LDL-cholesterol and triglycerides, and the increase in HDL-cholesterol, were significantly greater with combined treatment than with simvastatin monotherapy (see Figure 2). Despite the large reduction in LDL-cholesterol (1.24mmol per litre), in this trial simvastatin plus Tredaptive did not achieve the NICE target of <2mmol per litre.

### Adverse effects

Data pooled from all trials suggest that flushing affecting the head, neck and upper torso occurs in about 12 per cent of patients on Tredaptive compared with 17 per cent of those taking MR nicotinic acid and 0.4 per cent allocated placebo. Flushing resulted in treatment discontinuation in 7 per cent of patients taking Tredaptive (but in 9 and 10 per cent in the key efficacy trials).<sup>9</sup>

Fasting plasma glucose increased by an average of 0.22mmol per litre with both Tredaptive and nicotinic acid. In the published trial, the incidence of new-onset diabetes was 0.8 per cent with Tredaptive, 0.4 per cent with MR nicotinic acid and 0 with placebo; the incidence of worsening diabetes was 17, 24 and 5 per cent respectively.<sup>7</sup> Diet or hypoglycaemic therapy may therefore need to be adjusted in patients with diabetes treated with Tredaptive.<sup>8</sup>

Other common adverse effects included gastrointestinal events (17 per cent; diarrhoea, dyspepsia, nausea and vomiting), CNS events (12 per cent; dizziness, headache and paraesthesia), skin reactions (16 per cent) and elevations in uric acid, alanine transaminase (ALT) and aspartate transaminase (AST).<sup>8,9</sup>

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## Place in therapy

Cardiovascular disease, in particular CHD, remains the leading cause of death in the industrialised world,<sup>1</sup> with the disease burden set to continue increasing in association with the rapid increase in CHD risk factors.<sup>2</sup> The evidence that incrementally lower cholesterol is better in terms of cardiovascular disease risk comes both from epidemiological studies and clinical trials. Every major clinical end-point trial of lipid-lowering therapy<sup>3</sup> has demonstrated that lower LDL-cholesterol levels are associated with a reduced risk of cardiovascular events.

However, in all cholesterol-lowering studies, there remains a substantial risk in the treated groups. This may relate to low baseline levels of HDL-cholesterol, which remain predictive of cardiovascular events even during treatment with statins. A recent *post-hoc* analysis of the Treating to New Targets (TNT) data demonstrated that the relationship between HDL-cholesterol and cardiovascular risk was maintained, even at very low LDL-cholesterol concentrations.<sup>4</sup> Data from statin trials have been stratified for HDL-cholesterol at baseline,<sup>5</sup> with the incidence of cardiovascular events being inversely proportional to baseline HDL-cholesterol levels.

The role of triglyceride and HDL-cholesterol levels in determining vascular risk has been demonstrated by large population-based studies.<sup>6</sup> Within each LDL-cholesterol subgroup the risk of MI increased with increasing triglyceride levels and reduced HDL-cholesterol levels, an effect that was most pronounced in subjects with lower LDL-cholesterol levels. Addition of drugs effective in raising HDL-cholesterol and reducing plasma triglyceride levels to statins may thus provide a rational approach to reducing cardiovascular risk beyond that achieved by statin monotherapy.

In the Coronary Drug Project trial, changes in fasting plasma glucose did not appear to negatively impact on the outcome benefits seen with nicotinic acid either with respect to MI in the six-year follow-up period or with respect to long-term outcome in the 15-year follow-up period.

Nicotinic acid may be a rational choice for such an agent as it is currently the most effective drug available for increasing HDL-cholesterol, while also producing significant effects on LDL-cholesterol and triglycerides. A 'rule of 20s' may be applied to the therapeutic effects seen with nicotinic acid, with a 20 per cent increase in HDL-cholesterol, a 20 per cent reduction in LDL-cholesterol and a 20 per cent reduction in plasma triglycerides occurring with the

optimal therapeutic dose of 2000mg daily.<sup>7</sup> The potential outcome benefits of LDL-cholesterol reduction combined with increasing HDL-cholesterol with nicotinic acid-based regimens is supported by a variety of studies. Nicotinic acid utility is limited, however, by side-effects, in particular flushing.

Tredaptive is a combination of nicotinic acid with laropiprant, a prostaglandin receptor antagonist that significantly improves the tolerability of nicotinic acid. The addition of Tredaptive to ongoing statin therapy has been shown to produce significant and durable improvements in multiple lipid parameters beyond that achieved by statin therapy alone, and may thus contribute to additional cardiovascular risk reduction.

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