



### **Combination nicotinic acid/laropirant: effective with reduced flushing**

While nicotinic acid (niacin) is effective in raising HDL cholesterol, the main side effect of flushing can be problematic. It is thought that nicotinic acid induces the flushing response by triggering the release of prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), a chemical that causes vasodilation in the skin and flushing symptoms. Data from a Phase III study presented at the European Society of Cardiology Annual Congress 2007 show that treatment with the combination of extended release (ER) nicotinic acid and laropirant, a PGD<sub>2</sub> antagonist, provided effective overall lipid control with significantly less flushing than reported with ER nicotinic acid alone in patients with dyslipidaemia.<sup>1</sup>

The study was a double-blind trial that evaluated the lipid efficacy and flushing profile of ER nicotinic acid/laropirant, either as monotherapy or added to a statin, in 1,613 patients with primary hypercholesterolaemia or mixed dyslipidaemia. Patients (about 65% on statin therapy) were randomized to ER nicotinic acid/laropirant 1 g/20 mg day (n=800), ER nicotinic acid 1 g/day (n=543), or placebo (n=270). After 4 weeks, dosage was increased to 2 g/day in patients treated with the combination or ER nicotinic acid. Treatment was continued for a further 20 weeks.

Across weeks 12 to 24 of the study, treatment with ER nicotinic acid/laropirant 2 g/day resulted in significant changes from baseline in low-density lipoprotein (LDL) cholesterol (-18%), HDL cholesterol (+20%) and triglycerides (-26%) compared with placebo (p<0.001). The 2 g dose of the combination also significantly reduced both non-HDL cholesterol (another measure of lipids which includes a broader spectrum of atherogenic lipoproteins) by 20% and apolipoprotein B (apo B, a component of LDL cholesterol) by 19%, and raised apolipoprotein A-I (apo A-I, a component of HDL cholesterol) by 6.9%, compared with placebo. These effects occurred irrespective of concomitant statin therapy.

Flushing was measured by the Global Flushing Severity Score (GFSS). Patients treated with ER nicotinic acid/laropirant reported significantly less flushing both at initiation of therapy and during maintenance therapy, compared with patients on ER nicotinic acid alone (p<0.001). During the first week of treatment, 69% of patients treated with ER nicotinic acid/laropirant 1 g/day reported either none or mild flushing symptoms, compared with 44% of patients treated with ER nicotinic acid alone. Moderate or greater flushing was reported by 27% of patients treated with ER nicotinic acid/laropirant but 49% of patients in the ER nicotinic acid group. By week 24, the frequency of moderate or greater flushing was 0.2 days/week in patients receiving ER nicotinic acid/laropirant 2 g/day but 0.7 days/week in patients treated with ER niacin 2 g/day or a placebo. More than twice as many patients on ER

nicotinic acid than the combination discontinued treatment because of flushing (22% vs. 10%).

The combination of ER nicotinic acid/laropiprant was well tolerated. There was no statistically significant difference seen between the group treated with ER nicotinic acid/laropiprant and the group treated with ER nicotinic acid with respect to elevation in liver enzymes  $\geq 3$ x upper limit of normal range (ULN) (1.4% vs. 1.0%) and creatine kinase  $\geq 10$ x ULN. There were no reports of hepatitis, myopathy or rhabdomyolysis observed in this study.

While many LDL cholesterol-lowering drugs have been shown to reduce major coronary events and stroke, most patients continue to be at risk for cardiovascular events. Nicotinic acid has been shown in previous outcome studies to reduce the risk of cardiovascular events, but the flushing side effect can influence patient compliance. The authors concluded that the improved tolerability of this combination should allow more patients to reach and maintain a 2 g therapeutic dose of ER nicotinic acid.

### **Reference**

1. Maccubbin D, Sirah W, Betteridge A et al. Lipid-altering efficacy and tolerability profile of extended release niacin/laropiprant in patients with primary hypercholesterolemia or mixed hyperlipidemia. Eur Heart J 2007;28 (abstract suppl): 108. Abstract P715