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Extended-Release Niacin (Nicotinic Acid)/Laropiprant

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Contents

Abstract

▲ Extended-release (ER) niacin (nicotinic acid)/laropiprant is a once-daily fixed-dose combination tablet that has been evaluated (with or without an HMG-CoA reductase inhibitor [statin]) in the treatment of adults with dyslipidaemia or primary hypercholesterolaemia. Niacin (vitamin B3) is a lipid-modifying drug and laropiprant is an anti-flushing agent, which reduces flushing induced by niacin.

▲ In a randomized, double-blind, placebo-controlled, multicentre, 24-week trial, a significant ($p < 0.001$) reduction (18.4%) in plasma low-density lipoprotein cholesterol (LDL-C) levels (primary endpoint) was achieved with ER niacin/laropiprant 2000 mg/40 mg once daily (after an initial 4-week 1000 mg/20 mg once-daily regimen) compared with placebo (weeks 12–24) in adults with primary hypercholesterolaemia or mixed dyslipidaemia.

▲ ER niacin/laropiprant 2000 mg/40 mg plus simvastatin 20 mg or 40 mg once daily (after an initial 4-week lower-dose regimen) produced significant ($p < 0.05$) improvements, from baseline, in LDL-C levels (primary endpoint) compared with once-daily ER niacin/laropiprant 2000 mg/40 mg or simvastatin alone at week 12 in a randomized, double-blind, multicentre, factorial trial in adults with primary hypercholesterolaemia or mixed dyslipidaemia.

▲ The incidence and intensity of flushing (an efficacy endpoint) were significantly ($p < 0.05$) reduced with ER niacin/laropiprant compared with ER niacin in randomized trials.

▲ ER niacin/laropiprant, alone or in combination with a statin, was generally well tolerated for up to 24 weeks by adults with dyslipidaemia or primary hyercholesterolaemia.

Features and properties of extended-release (ER) niacin (nicotinic acid)/laropiprant (Tredaptive™)	
Indication	
Treatment of adults with dyslipidaemia, particularly combined mixed dyslipidaemia, or primary hypercholesterolaemia (heterozygous familial and non-familial). May be used in patients in combination with HMG-CoA reductase inhibitors, when the cholesterol lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate. Used as monotherapy only in patients in whom HMG-CoA reductase inhibitors are considered inappropriate or not tolerated	
Mechanism of action	
Niacin inhibits the synthesis of low-density lipoprotein and triglycerides, and selectively blocks the hepatic catabolic uptake of high-density lipoprotein particles containing apolipoprotein A-I	
Dosage and administration	
Initial dosage	ER niacin/laropiprant 1000 mg/20 mg once daily
Maintenance dosage	ER niacin/laropiprant 2000 mg/40 mg once daily
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile after administration of ER niacin/laropiprant (2000 mg/40 mg: two fixed-dose [1000 mg/20 mg] combination tablets taken with food) in adults	
Mean maximum plasma concentration	20.2 μmol/L (niacin); ≈1.6 μmol/L (laropiprant)
Median time to maximum plasma concentration	4 h (niacin); 1 h (laropiprant)
Mean area under the plasma concentration-time curve (AUC)	58 μmol • h/L (niacin [AUC_{last}]); ≈13 μmol • h/L (laropiprant [AUC_{∞}])
Apparent terminal elimination half-life	17 h (laropiprant)
Treatment-related adverse experiences	
Most common (incidence ≥2% over 24 weeks)	Flushing, pruritus, paraesthesia, nausea, diarrhoea, feeling hot, erythema

Niacin (nicotinic acid), one of the naturally occurring B-complex vitamins (vitamin B3), is a well established treatment for hyperlipidaemia. At therapeutic dosages, niacin produces beneficial effects on lipids, including decreases in plasma low-density lipoprotein (LDL) cholesterol (LDL-C) levels, increases in high-density lipoprotein (HDL) cholesterol (HDL-C) levels, decreases in triglyceride (TG) levels and decreases in lipoprotein(a) [Lp(a)] levels.[1,2] Niacin is the most effective drug available for elevating HDL-C levels[1] and was the first lipid-modifying drug to significantly decrease cardiovascular events in the Coronary Drug Project.[3] In the Guidelines from the US National Cholesterol Education Adult Treatment Panel III (NCEP ATP III)[4] updated in 2004,[5] the primary goal of therapy for patients with atherosclerotic disease due to dyslipidaemia is the lowering of LDL-C levels.

The beneficial effects of niacin on the lipid profile are dose related, with a dosage of 2000 mg/day producing markedly greater improvements in various lipid parameters than lower dosages of the drug.[6] However, dose-related niacin-associated adverse effects, such as flushing (or 'hot flashes') of the face and trunk, occur in more than 90% of patients receiving treatment with immediate-release formulations of niacin. Flushing is mainly the result of vasodilation, which is caused by niacin-mediated release of prostaglandin (PG)-D_2, and is independent of its lipid-modifying effects.[6]

Studies have shown a reduced incidence and intensity of flushing in patients receiving treatment with an extended-release (ER) formulation of niacin (while retaining lipid-modifying efficacy) compared with the immediate-release formulation.[7,8] Nevertheless, flushing remains a problem for many patients and gradual upwards titration of the dose over weeks or months to an effective therapeutic dose may be required to reduce flushing. Moreover, flushing can remain a problem for many patients and discontinuation of niacin treatment is fairly common.[6] With the aim of improving the tolerability profile of niacin, potentially improving adherence to treatment, and allowing a simplified and accelerated dose-advancement regimen,[9,10] a fixed-dose combination tablet containing ER niacin and laropiprant, an anti-flushing agent, ER niacin/laropiprant (Tredaptive™), has been developed and is now approved for use in the EU and some other countries, including Switzerland, Mexico, Norway, Iceland, Peru, Hong Kong, New Zealand, Macau, the Phillipines, Singapore, Croatia, Australia and South Korea.

This article provides an overview of the pharmacological properties of ER niacin/laropiprant and examines the clinical profile of this fixed-dose combination in patients with dyslipidaemia (including mixed dyslipidaemia) and in patients with primary hypercholesterolaemia (heterozygous familial and non-familial).

Medical literature on the use of ER niacin/laropiprant in mixed dyslipidaemia or primary hypercholesterolaemia was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference list of published articles.

1. Pharmacodynamic Profile

Data on the pharmacodynamic properties of niacin or laropiprant, administered as the fixed-dose combination (ER niacin/laropiprant) or as single agents, are derived from various sources, including published studies,[11-15] the manufacturer's prescribing information[16] and reviews.[2,17,18]

Niacin (Nicotinic Acid)

- Although the mechanism of action of niacin in terms of modifying lipid levels in patients with hyperlipidaemia or primary dyslipidaemia is not yet completely understood, it has been suggested that niacin inhibits free fatty acid (FFA) release from adipose tissue[16] by modulating TG lipolysis in adipose cells[17] (although decreases in FFA levels may be transient, being followed by a rebound increase, in humans[19]). This results in a reduction in the synthesis of TG and very low-density lipoprotein (VLDL) particles in the liver and the secretion of smaller VLDL particles containing less TG.[18] Conversion of VLDL to LDL particles is inhibited and

there is an increase in the proportion of less atherogenic lipid molecules.[17]

- Recent data indicate that niacin produces direct and noncompetitive inhibition of hepatocyte diacylglycerol acyltransferase-2, an important enzyme required for TG synthesis, thereby accelerating intracellular hepatic apolipoprotein B (apo B) degradation and decreasing the secretion of VLDL and LDL particles.[2]
- Niacin increases HDL-C levels by selectively blocking the hepatic catabolic uptake of HDL particles containing apoliprotein A-I (apo A-I) [the cardioprotective subfraction of HDL] without cholesterol ester removal being affected.[17,18] Inhibition of *de novo* lipogenesis or esterification of fatty acids into TG in the liver are other possibly clinically relevant mechanisms of action of the drug.[2,16]
- Increases in the vascular endothelial cell redox state, leading to the inhibition of oxidative stress and vascular inflammatory genes (cytokines involved in atherosclerosis), have been observed in *in vitro* studies of niacin.[2]
- In patients with dyslipidaemia, niacin produces beneficial effects on various components of the lipid profile, including increases in HDL-C and apo A-I plasma levels and reductions in LDL-C, total cholesterol, VLDL-C, apo B, TG and Lp(a) levels.[17,18]
- Flushing induced by niacin in adults with dyslipidaemia (see sections 3 and 4) is primarily mediated by niacin-induced PGD_2 release from skin Langerhans cells, which stimulates the PGD_2 receptor-1 subtype (DP1) in dermal blood vessels.[8] Niacin-induced flushing also results from the stimulation of PGE_2 by subcutaneous Langerhans cells via the G protein-coupled receptor 109A niacin receptor.[2]
- Coadministered low-dose aspirin does not appear to have a marked effect on ER niacin-associated flushing when added to niacin plus laropiprant.[13] In a phase I, randomized, double-blind, double-dummy, placebo-controlled, crossover study, residual flushing symptoms occurring with ER niacin/laropiprant 2000 mg/40 mg were neither attenuated nor exacerbated by oral aspirin 325 mg once daily (administered 30 minutes before ER niacin/laropiprant) in healthy volunteers.[13] Study participants were healthy nonsmoking men (n = 56) and women (n = 21) [age range 18–75 years; body mass index 35 ± 3 kg/m^2].[13]
- A *post hoc* analysis of data from the pivotal 24-week randomized placebo-controlled trial[6] (section 3) showed that ER niacin had blood pressure (BP) lowering effects in patients with dyslipidaemia.[12] In this analysis, significant placebo-adjusted reductions from baseline in systolic BP (SBP) and diastolic BP (DBP) were evident in patients receiving ER niacin, administered alone or in combination with laropiprant, in normotensive or hypertensive patients with hyperlipidaemia.[12]
- At week 24, placebo-adjusted changes from baseline in SBP measurements for the ER niacin and ER niacin/laropiprant groups were −2.2 ($p < 0.05$) and −3.1 ($p < 0.001$) mmHg; corresponding placebo-adjusted changes from baseline in DBP were −2.7 and −2.5 mmHg (both $p < 0.001$ vs baseline).[12] The effects on BP were broadly similar to those achieved in an earlier trial of niacin in the Coronary Drug Project trial.[20] Given that the BP-lowering effect of ER niacin was not affected by concomitantly administered laropiprant, the effect of ER niacin on BP does not appear to be mediated by PGD_2. Prospective, randomized trials are required to fully evaluate the effects of niacin treatment on BP in patients with dyslipidaemia.[12,21]

Laropiprant

- Laropiprant is a selective and potent antagonist of DP1 and has been shown to reduce both the incidence and intensity of flushing caused by niacin.[11,16] Laropiprant selectively blocks PGD_2 from binding to its receptor, thereby inhibiting niacin-associated flushing,[11] without affecting the beneficial effects of niacin on the lipid profile.[9] Laropiprant 100 mg reduced the symptoms of flushing and the increase in skin perfusion induced by immediate-release oral niacin 500 mg in 12 healthy men and women.[8,14]
- Laropiprant has shown good efficacy in reducing flushing symptoms induced by niacin. In a 'proof-of-concept' placebo-controlled study designed to

evaluate the effects of laropiprant on niacin-induced vasodilation of the skin, adults with dyslipidaemia receiving laropiprant with ER niacin 1500 mg had improvements in the subjective and objective manifestations of niacin-induced vasodilation.[11] Patients receiving laropiprant 30, 100 or 300 mg with ER niacin 1500 mg had a significant reduction (by about 50% or more) from baseline in flushing symptom scores as well as a significant reduction in malar skin blood flow, as measured by laser Doppler perfusion imaging.[11] Of note, the 100 mg and 300 mg doses of laropiprant evaluated are higher than those currently approved for use when the drug is administered as the fixed-dose ER/laropiprant combination tablet.

- Detectable off-target antagonistic activity at the thromboxane A2 receptor (TP) has been demonstrated with laropiprant *in vitro*.[16] The activity of laropiprant at the TP receptor is substantially less than that for DP1. No clinically relevant effects on platelet aggregation induced by collagen or on bleeding time have been observed.[15,16]

2. Pharmacokinetic Profile

Pharmacokinetic data reviewed in this section relate to the individual components of the ER niacin/laropiprant fixed-dose combination and have been obtained from the manufacturer's prescribing information,[16] fully published studies[15,22] and reviews.[17,18]

Niacin

- Niacin is rapidly and well absorbed after oral administration.[17] When administered as an ER formulation, as expected, time to reach the maximum plasma concentration (C_{max}) is longer than after administration of the immediate-release formulation (based on historical data[18]). After administration of ER niacin/laropiprant 2000 mg/40 mg (two 1000 mg/20 mg fixed-dose combination tablets taken with food) to adults, a mean niacin C_{max} of 20.2 μmol/L was achieved in a median time (t_{max}) of 4 hours and the mean area under the plasma concentration-time curve (AUC) from time zero to the last measurement (AUC_{last}) was 58 μmol • h/L.[16] Based on amounts of niacin recovered in the urine, the bioavailability of the drug (after administration with food [including a high-fat meal] or without food) was at least 72%. Serum protein binding of niacin is low (<20%).[16]
- Niacin undergoes extensive first-pass metabolism via two different metabolic pathways that are dependent on both the dose and dose-rate of the drug. Nicotinamide adenine dinucleotide (NAD) and nicotinamide are products of the first pathway, which is the main pathway for low doses of niacin or lower absorption; nicotinamide is then mainly metabolized to *N*-methylnicotinamide and *N*-methyl-2-pyridone-5-carboxamide. After higher doses or higher absorption rates of niacin, the NAD pathway is saturable, leading to an increasing proportion of the oral dose as unchanged drug in the bloodstream.[16]
- The second metabolic pathway for niacin leads to the production of nicotinuric acid (NUA) as a result of the conjugation of the drug with glycine; unlike the first pathway, the glycine conjugation pathway does not become saturated, with dose-proportional increases in plasma NUA concentrations observed after niacin doses ranging from 1000 to 2000 mg.[16] Niacin is eliminated, predominantly as metabolites, in the urine. Neither niacin nor its metabolites were shown to inhibit reactions mediated by numerous cytochrome P450 (CYP) enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D, CYP2E1 or CYP3A4 or UGT1A1-mediated 3-glucuronidation of estradiol, *in vitro*.[16]

Laropiprant

- After administration of a single oral 40 mg dose of laropiprant (as two ER niacin/laropiprant 1000 mg/20 mg tablets), the mean absolute bioavailability of laropiprant is approximately 71%.[16] Laropiprant has a linear approximately dose-proportional pharmacokinetic profile.[15,16]
- Laropiprant is rapidly absorbed after oral administration,[15,16] with C_{max} values of 0.88 to 2.74 μmol/L achieved in a t_{max} of 0.8–1.0 hour after single doses (close to therapeutic doses) ranging from 12 to 50 mg in healthy male volunteers.[15]

After a single oral 40 mg dose of laropiprant (as two ER niacin/laropiprant 1000 mg/20 mg tablets), the median t_{max} was 1 hour, the mean AUC from time zero to infinity (AUC_∞) was approximately 13 μmol • h/L and the mean C_{max} was about 1.6 μmol/L.[16]

- Neither the rate nor the extent of absorption of laropiprant are affected by administration of the drug with a high-fat meal.[16] The pharmacokinetic profile of laropiprant after 10 days' multiple dose administration (30–450 mg once daily) was similar to that after single doses ranging from 3 to 900 mg, indicating that laropiprant does not accumulate over time. After single doses ranging from 12 to 50 mg, administered with or without food, the AUC_∞ ranged from 4.10 to 18.18 μmol • h/L.[15]
- The volume of distribution of laropiprant was approximately 70 L in health volunteers who received a single intravenous 40 mg dose of the drug. Laropiprant is extensively bound to plasma proteins and this is independent of its concentration in the plasma. In animal studies, laropiprant has been shown to cross the placenta.[16]
- Laropiprant is predominantly metabolized via acyl glucuronidation and the major components circulating in plasma are laropiprant and the acyl glucuronide conjugate. A smaller proportion of laropiprant undergoes oxidative metabolism.[16] As the main metabolite has substantially less affinity for DP1 than laropiprant, it is unlikely that it contributes to the overall antiflushing activity of laropiprant.[16] The acyl glucuronide conjugate of laropiprant is excreted in the faeces (via bile) and the urine. About 68% of an administered dose was recovered in the faeces. After administration of ER niacin/laropiprant 2000 mg/40 mg (as two fixed-dose combination tablets with food), the apparent terminal elimination half-life of laropiprant was 17 hours.[16]

Special Populations

Pharmacokinetic data are not yet available for ER niacin/laropiprant in elderly patients (aged ≥65 years) or patients with hepatic insufficiency. Age (over the 18–65 year range), sex or race (White, Hispanic, Black, Asian, Native American) had no appreciable effect on the pharmacokinetics of niacin or laropiprant. Because niacin and its metabolites are excreted via the renal route, ER niacin/laropiprant should be administered with caution to patients with renal impairment.[22]

- Although systemic exposure to laropiprant and its inactive acyl glucuronide metabolite increased in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2 [1.8 L/h/1.73 m^2]) compared with that in healthy volunteers, the extent of the increase was considered to be not clinically significant.[22]
- The pharmacokinetics of laropiprant are significantly affected in patients with moderate hepatic disease: 2.8-fold and 2.2-fold increases in the AUC and C_{max} of laropiprant have been reported in such patients.[16]

Drug Interactions

- Although modest increases in simvastatin acid (the active moiety of simvastatin) AUC and C_{max} values were observed in patients receiving concomitant niacin, the clinical relevance and mechanism of this interaction is not yet known.[16]
- Bile acid sequestrants may reduce the bioavailability of coadministered acidic drugs, including niacin; thus, the manufacturer recommends that ER niacin/laropiprant should be administered more than 1 hour before or more than 4 hours after a bile acid sequestrant is administered.[16]
- The pharmacokinetics of midazolam, a CYP3A4 substrate, are not affected by multiple doses of coadministered laropiprant, indicating that laropiprant is neither an inducer nor an inhibitor of CYP3A4. By contrast, the plasma concentration of 1′-hydroxymidazolam, an active metabolite of midazolam, increased approximately 2-fold during multiple dose coadministration of midazolam or laropiprant.[16]
- The pharmacokinetic profile of warfarin (single dose) was not altered to a clinically relevant extent by coadministered laropiprant (multiple doses).[23] The manufacturer's prescribing information should be referred to for further information on drug interactions.[16]

3. Therapeutic Efficacy

The efficacy of orally administered once-daily ER niacin/laropiprant in the treatment of adults with mixed dyslipidaemia (across all coronary heart disease [CHD] risk categories) and adults with primary hypercholesterolaemia (heterozygous familial and non familial) has been evaluated in two fully published large (n = 1613;[6] n = 1398[24]) worldwide phase III trials. Both trials were randomized, double-blind and multicentre in design, and enrolled men and women aged 18–85 years;[6,24] one of the trials was a 24-week placebo-controlled trial[6] and the other was a 12-week active comparator, factorial design trial.[24] The trials were designed to assess the effects of treatment with ER niacin/laropiprant, alone or in combination with an HMG-CoA reductase inhibitor (statin), on multiple lipid/lipoprotein parameters.[6,24] In addition, the lipid-modifying efficacy of ER niacin/laropiprant, alone or in combination with ongoing statin therapy, has been evaluated in Asian patients with primary hypercholesterolemia or mixed hyperlipidemia in a smaller, phase III, randomized, double-blind study.[25] The flushing profile of ER niacin/laropiprant (flushing was an efficacy endpoint) was also evaluated in the placebo-controlled trial,[6] and in three other randomized studies.[9,10,26]

At baseline, patients enrolled in the placebo-controlled trial[6] who were at high CHD risk or who had multiple risk factors had to be receiving ongoing statin therapy and have LDL-C levels at or below their current NCEP ATP III LDL-C treatment goal: <100 mg/dL (2.59 mmol/L) for patients at high risk; for patients with multiple (at least two risk factors) the LDL-C goal was <130 mg/dL (3.37 mmol/L). Patients categorized as at low CHD risk (0–1 risk factors) were required to have LDL-C levels within the 130 to 190 mg/dL (3.37 to 4.92 mmol/L) range.[6] TG levels at baseline were ≤350 mg/dL (3.96 mmol/L). Exclusion criteria included levels of creatinine >1.7 mg/dL (176 μmol/L), ALT >1.5 × the upper limit of normal (ULN) and AST >1.5 × ULN; new onset (<3 months), poorly controlled or unstable type 1 or 2 diabetes mellitus and menopausal hot flashes were among the other exclusion criteria. Eligible patients were randomized in a 3 : 2 : 1 ratio to receive once-daily treatment (with food in the evening) with ER niacin/laropiprant 1000 mg/20 mg (n = 800), ER niacin 1000 mg (n = 543) or placebo (n = 270): doses of active drugs were doubled after the initial 4-week treatment period. Excluded drugs included lipid-modifying therapy initiated within 6 weeks of the first visit, aspirin >100 mg/day or long acting NSAIDs. However, patients were permitted to take low-dose aspirin (≤100 mg 8 hours before or after study medication) for cardioprophylaxis.[6]

Baseline characteristics and demographics were similar for the three groups in the placebo-controlled trial.[6] Of the overall randomized population of patients, 61% were male, 33% had mixed dyslipidaemia and 67% had primary hypercholesterolaemia; 1609 patients completed the trial. Statins (including simvastatin, atorvastatin, pravastatin, fluvastatin, rosuvastatin and lovastatin) were being taken by approximately 67% of patients at the start of the trial. Based on NCEP ATP III guidelines, 29% of patients in the overall population had low levels of HDL-C (<40 mg/dL [1.03 mmol/L] for men; <50 mg/dL [1.30 mmol/L] for women) and 38% had elevated TG levels (>150 mg/dL [1.70 mmol/L]). At baseline, across the three groups, the mean LDL-C level was 113.5 mg/dL (2.94 mmol/L), the mean HDL-C level was 50.8 mg/dL (1.32 mmol/L) and the median TG level was 145.7 mg/dL (1.65 mmol/L).[6]

In the active comparator, factorial trial (n = 1398), designed to assess the efficacy of ER niacin/laropiprant plus simvastatin, at baseline, patients at low CHD risk (0–1 risk factors) had an LDL-C level of between 130 and 190 mg/dL (3.37 and 4.92 mmol/L) and those with multiple NCEP ATP III risk factors had an LDL-C level of between 130 and 160 mg/dL (3.37 and 4.14 mmol/L). As in the other trial, TG levels at baseline were ≤350 mg/dL (3.96 mmol/L).[24] High-risk (CHD/CHD risk equivalent) patients were excluded from the study; levels of creatinine >2 mg/dL (176.8 μmol/L), ALT and/or AST >1.5 × ULN and creatinine kinase >2 × ULN were among the other exclusion criteria. After

a lipid therapy washout period of 6–8 weeks, patients were randomized to one of seven treatment groups (all drugs were taken once daily with the evening meal): ER niacin/laropiprant 1000 mg/20 mg plus simvastatin 10, 20 or 40 mg (n = 609), ER niacin/laropiprant 1000 mg/20 mg (n = 195), or simvastatin 10, 20 or 40 mg (n = 594) [for 4 weeks]. Thereafter, with the exception of simvastatin 40 mg (as a single agent or in combination with ER niacin/laropiprant), doses were doubled and treatment was continued for a further 8 weeks. Excluded drugs included lipid-modifying therapy initiated within 6 weeks of the first visit. The treatment groups had similar characteristics at baseline. For all treatment groups, the baseline mean LDL-C level was 150.8 mg/dL (3.9 mmol/L), the mean HDL-C level was 54.1 mg/dL (1.4 mmol/L) and the median TG level was 132.8 mg/dL (1.5 mmol/L).[24]

Effects on Lipids

Placebo-Controlled Trials

The primary lipid endpoint in the placebo-controlled trial[6] was the efficacy of ER niacin/laropiprant 2000 mg/40 mg compared with placebo in terms of the percentage change from baseline in plasma LDL-C levels over the 12- to 24-week treatment period.[6] Other lipid endpoints included the efficacy of ER niacin/laropiprant compared with placebo on the percentage change from baseline in HDL-C, non-HDL-C, LDL-C : HDL-C ratio, TG and apo B. In addition, the lipid-modifying efficacy of ER niacin/laropiprant 2000 mg/40 mg was evaluated over weeks 12–24 for the subsets of statin-naive and statin-treated patients. All randomized patients who took at least one dose of study drug after randomization were included in the efficacy analysis; last observation carried forward imputation was used for missing lipid endpoint results.

- Sustained beneficial effects on LDL-C levels (at week 4 and across weeks 12–24) as well as on multiple other lipid/lipoprotein parameters were achieved in adults with primary hypercholesterolaemia or mixed dyslipidaemia (across all risk categories) who received treatment with ER niacin/laropiprant in the placebo-controlled trial (figure 1).[6] During weeks 12–24, a significant ($p < 0.001$) reduction (18.4%) in LDL-C levels was achieved with ER niacin/laropiprant 2000 mg/40 mg compared with placebo (primary endpoint) [figure 1]. After about 12 weeks (8 weeks for ER niacin/laropiprant 2000 mg/40 mg or ER niacin 2000 mg) lipid levels had a tendency to plateau in both active treatment groups and thereafter were stable for the rest of the 24-week trial.[6]

- The efficacy of ER niacin/laropiprant administered alone (as assessed by effects on each lipid parameter) did not significantly differ from that of ER niacin/laropiprant added to ongoing statin therapy. In addition, ER niacin/laropiprant and ER niacin showed comparable lipid-modifying efficacy (i.e. no significant between-group differences in changes in lipid parameters).[6] ER niacin/laropiprant showed consistent efficacy across subpopulations of patients as defined by sex, race (Caucasian, Black, Hispanic or other), baseline LDL-C, HDL-C and TG levels, diabetes status, NCEP ATP III risk level and age.[6,16] However, placebo-adjusted changes in LDL-C, HDL-C and TG responses appeared to be greater in women than in men and in patients aged ≥65 years compared with those aged <65 years.[16]

- In a *post hoc* analysis of efficacy data for the subgroups of patients with or without metabolic syndrome[27] included in the placebo-controlled trial,[6] ER niacin/laropiprant was effective in improving LDL-C, HDL-C and TG parameters in both groups with no significant between-group differences evident (reported in an abstract).

- At week 12, significant ($p < 0.001$) improvements versus baseline (relative to placebo) in multiple lipid/lipoprotein parameters (including LDL-C [a 14.7% reduction relative to placebo] the primary endpoint) were observed in dyslipidaemic Asian patients who received treatment with ER niacin/laropiprant alone or in combination with a statin. Patients were randomized to receive once-daily ER niacin/laropiprant 1000 mg/20 mg (n = 322) or placebo (n = 324) for 4 weeks and then once-daily ER niacin/laropiprant 2000 mg/40 mg or placebo for 8 weeks (after a 4-week placebo run-in period).

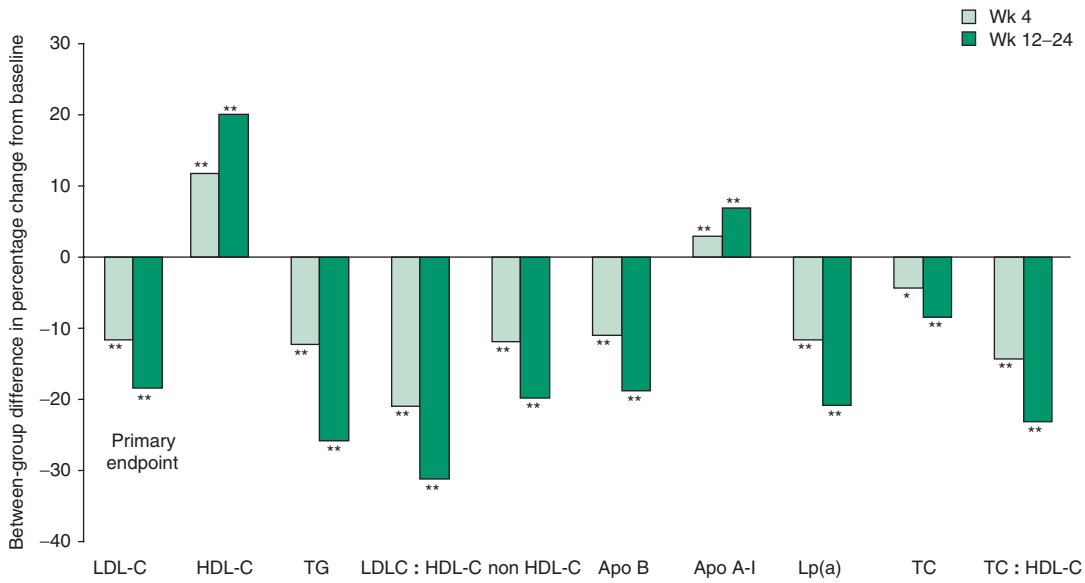

Fig. 1. Efficacy of extended-release (ER) niacin/laropiprant in adults with primary hypercholesterolaemia or mixed hyperlipidaemia. Results (for ER niacin/laropiprant vs placebo) of a randomized, double-blind, placebo (PL)-controlled, multicentre, 24-week trial. Patients were randomized in a 3 : 2 : 1 ratio to receive once-daily treatment (after food in the evening) with ER niacin/laropiprant 1000 mg/20 mg (n = 800), ER niacin 1000 mg (n = 543) or PL (n = 270): doses of active drugs were doubled after the initial 4-week treatment period. At baseline, for the entire study cohort, the mean low-density lipoprotein cholesterol (LDL-C) plasma level was 113.5 mg/dL (2.9 mmol/L), the mean high-density lipoprotein (HDL-C) plasma level was 50.8 mg/dL (1.3 mmol/L) and the mean triglyceride (TG) plasma level was 127.0 mg/dL (1.4 mmol/L). Bars show between-group differences (for ER niacin/laropiprant vs PL) in the percentage changes from baseline in lipid parameters at weeks 4 and 24. Values are least squares means for all parameters except TG and lipoprotein (a) [Lp(a)] (medians). See introduction to section 3 for further details of patient inclusion and exclusion criteria. Results for ER niacin monotherapy are not shown.[6] **Apo A-I** = apolipoprotein A-I; **Apo B** = apolipoprotein B; **TC** = total cholesterol; * $p < 0.05$, ** $p < 0.001$ vs PL.

Results were similar for recipients of ER niacin/laropiprant alone or with a statin.[25]

Active Comparator, Factorial Trial

The primary efficacy endpoint in the active comparator, factorial trial, was the efficacy of ER niacin/laropiprant 2000 mg/40 mg plus simvastatin (pooled across doses of 20 mg and 40 mg) on the mean percentage change from baseline in LDL-C levels compared with that of ER niacin/laropiprant 2000 mg/40 mg at week 12.[24] The main secondary efficacy endpoints were the efficacy of ER niacin/laropiprant 2000 mg/40 mg plus simvastatin (pooled across doses of 20 mg and 40 mg) compared with simvastatin (pooled doses) on the mean percentage change from baseline in LDL-C, HDL-C, TG, ratio of LDL-C : HDL-C, non-HDL-C apo B and apo A-I.[24]

- ER niacin/laropiprant plus simvastatin produced significant ($p < 0.05$) improvements from baseline in LDL-C levels (primary endpoint) and other lipid/lipoprotein parameters compared with ER niacin/laropiprant or simvastatin alone at week 12 (figure 2).[24] At this timepoint, the mean reduction in LDL-C was 47.9% in the ER niacin/laropiprant 2000 mg/40 mg plus simvastatin (pooled doses) group compared with mean reductions of 17% and 37% for the ER niacin/laropiprant or simvastatin groups, respectively. The beneficial lipid-modifying effects of ER niacin/laropiprant plus simvastatin compared with the comparator groups was generally consistent across various subgroup populations defined by age (≥65 years or <65 years), sex, region (US or ex-US) or race (Caucasian, Hispanic, Black or other).

Effects on Flushing

The flushing profile (flushing was an efficacy endpoint) of ER niacin/laropiprant has been evaluated in patients with dyslipidaemia (over a period of up to 24 weeks) in several randomized trials, including the large placebo-controlled trial discussed previously,[6] a phase II dose-ranging trial,[9] a double-blind, parallel group trial in patients with or without ischaemic cardiovascular disease[10] and a placebo-controlled trial in Asian patients.[26]

Assessments were made using the Flushing Symptom Questionnaire, consisting of 11 questions to assess aspects of the severity, frequency, duration and bother of flushing.[6,9,10,26] The intensity of all four flushing symptoms (warmth, tingling, itching and skin redness) is measured by one of the 11 questions, using a validated numerical scale called the 'Global Flushing Severity Score' (GFSS) labelled as follows: no flushing (score 0); mild (1–3); moderate (4–6); severe (7–9); extreme (10).[6,9,10,26]

- Patients receiving treatment with ER niacin/laropiprant 1000 mg/20 mg compared with recipients of ER niacin 1000 mg had significantly ($p < 0.001$) less flushing, as assessed by the shift in the distribution of the maximum GFSS categorized as none/mild, moderate, severe or extreme, during

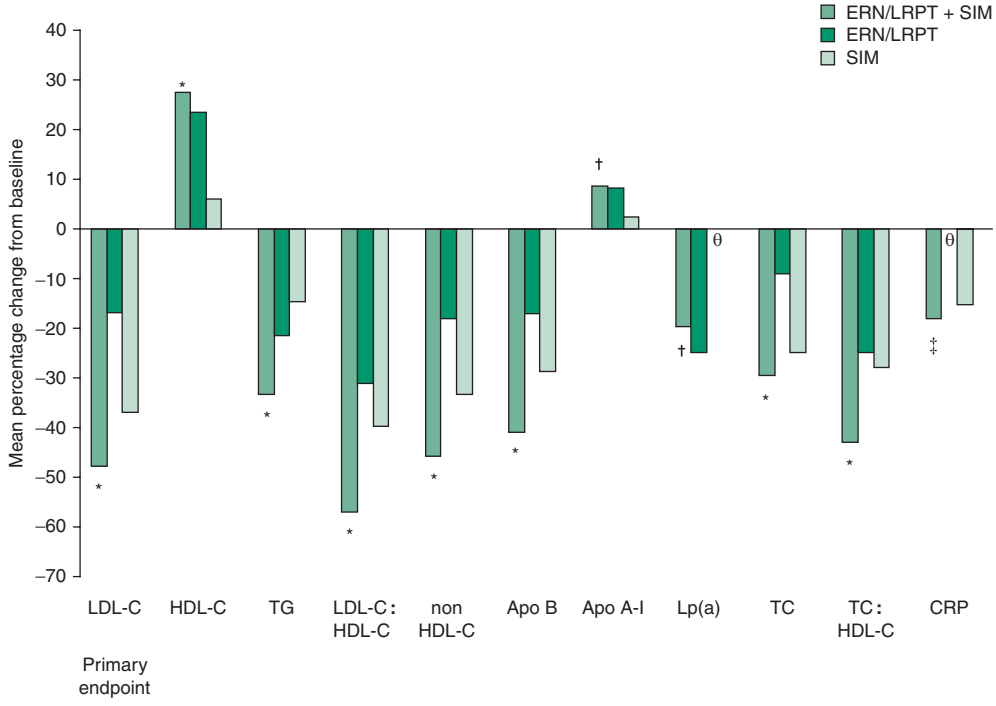

Fig. 2. Efficacy of extended-release niacin/laropiprant (ERN/LRPT) plus simvastatin (SIM) [ERN/LRPT + SIM] in adults with primary hypercholesterolaemia or mixed hyperlipidaemia. Results (pooled across SIM 20 mg and 40 mg doses) of a randomized, double-blind, multicentre, active comparator, factorial, 12-week trial. Patients were randomized to one of seven treatment groups (all drugs were taken once daily with the evening meal): ERN/LRPT 1000 mg/20 mg plus SIM 10, 20 or 40 mg (n = 609), ERN/LRPT 1000 mg/20 mg (n = 195), or SIM 10, 20 or 40 mg (n = 594) [for 4 weeks]. Thereafter, with the exception of SIM 40 mg (alone or in combination with ERN/LRPT), doses were doubled and treatment was continued for a further 8 weeks. At baseline, the mean low-density lipoprotein cholesterol (LDL-C) plasma level was 3.9 mmol/L for the ERN/LRPT + SIM, ERN/LRPT and SIM groups; corresponding baseline plasma levels of high-density lipoprotein (HDL-C) and triglycerides (TG) were 1.4 mmol/L (for each group) and 1.5 mmol/L (median, for each group). Bars show mean percentage changes from baseline for multiple lipid/lipoprotein parameters at week 12. Values are least squares means for all parameters except TG, lipoprotein (a) [Lp(a)] and C-reactive protein (CRP) [medians].[24] See introduction to section 3 for further details of patient inclusion and exclusion criteria. **Apo A-I** = apolipoprotein A-I; **Apo B** = apolipoprotein B; **TC** = total cholesterol; * $p < 0.05$ vs ERN/LRPT or SIM; † $p < 0.05$ vs SIM; ‡ $p < 0.05$ vs ERN/LRPT.

the initiation phase (week 1) [primary endpoint] in the large, placebo-controlled trial.[6]

- In the ER niacin/laropiprant 1000 mg/20 mg treatment group, the least squares mean maximum daily GFSS score was 2.5 (95% CI 2.2, 2.8) and the corresponding score in the ER niacin group was 4.3 (95% CI 4.0, 4.6); the between-group difference was −1.8 (95% CI −2.2, −1.5; $p < 0.001$). In addition, significantly ($p < 0.001$) smaller proportions of patients treated with ER niacin/laropiprant 1000 mg/20 mg compared with recipients of ER niacin 1000 mg had moderate, severe or extreme flushing (GFSS ≥4) during the first week of treatment (31% vs 56%). Moreover, during the first week, the maximum duration of flushing episodes was significantly shorter (1 minute vs 60 minutes; $p < 0.001$) with ER niacin/laropiprant 1000 mg/20 mg than with ER niacin 1000 mg.[6]

- During the maintenance phase of this placebo-controlled trial, significantly ($p < 0.001$) less flushing (assessed by the number of days per week with moderate, severe or extreme flushing) was experienced by recipients of ER niacin/laropiprant 2000 mg/40 mg than by those who received ER niacin 2000 mg. Moderate, severe or extreme flushing occurred on average 0.2 days per week for ER niacin/laropiprant recipients (and for recipients of placebo) and 0.7 days per week for ER niacin recipients. A significantly ($p < 0.001$) smaller proportion of patients in the ER niacin/laropiprant 2000 mg/40 mg treatment group than in the ER niacin 2000 mg group discontinued treatment because of flushing (10.2% vs 22.2%); the majority of flushing-related treatment discontinuations occurred during the first 12 weeks of the study.[6]

- Patients with dyslipidaemia receiving treatment with ER niacin/laropiprant (laropiprant dosages of 18.75–150 mg once daily) had a significant reduction in flushing compared with recipients of ER niacin alone during the first week of treatment and during weeks 2–8 weeks in the phase II, dose-ranging trial.[9] In this trial, 154 patients aged 18–75 years with dyslipidaemia were randomized to receive laropiprant 150 mg once daily (an off-label dosage) or placebo in an initial 9-week, two-period crossover trial (4 weeks of treatment, then 1-week washout, then 4 weeks of treatment) [part A of the trial, not discussed further].[9] Thereafter, after a 2-week washout period, 122 patients who had completed the 9-week trial and a further 290 additional patients were randomized to receive once-daily ER niacin 1000 mg (n = 72), ER niacin 1000 mg plus laropiprant 18.75, 37.5, 75 or 150 mg (n = 272), or placebo (n = 68) for 4 weeks followed by a further 4-week treatment period when the dosage of ER niacin was increased to 2000 mg once daily for both active treatment groups (part B).[9] In part B, the flushing intensity was the main endpoint both during the first week of treatment and during the maintenance treatment period (weeks 2–8). Exclusion criteria included the use of aspirin (except aspirin 81 mg/day for cardioprotection) and NSAIDs. Study medication was taken with evening meals.[9]

- Patients treated with ER niacin 1000 mg and laropiprant (across all doses) had a significant ($p < 0.001$) reduction in the intensity of ER niacin-associated with flushing (the percentage of patients with mild or greater flushing [maximum GFSS ≥1]) during week 1 of the initial 4-week treatment period in part B of the study (numerical data not reported).[9] In addition, at the same timepoint, a smaller proportion of patients treated with ER niacin and laropiprant (across all doses) experienced flushing of moderate or greater (GFSS ≥4) intensity.[9]

- In a randomized, 16-week study in 1455 patients with dyslipidaemia with or without ischaemic cardiovascular disease, patients treated with ER niacin/laropiprant (n = 726) experienced significantly ($p < 0.001$) less flushing (as measured by the number of days each week with a GFSS indicating moderate, severe or extreme flushing across the treatment period [primary endpoint]) than those who received ER niacin (n = 729) at a more gradually titrated dosage regimen.[10] In addition, at least twice as many ER niacin/laropiprant than ER niacin recipients (47% vs 22%) experienced no episodes of moderate, severe or extreme flushing (GFSS ≥4). In this study, after a 2-week placebo run-in period, patients in the ER niacin/laropiprant group received 1000 mg/20 mg once daily for 4 weeks and then

2000 mg/40 mg once daily for 12 weeks; ER niacin was administered at a gradually titrated regimen of 500 mg once daily for 4 weeks, then 1000 mg once daily for 4 weeks, thereafter increasing the dose by 500 mg every 4 weeks to a maximum dose of 2000 mg administered once daily for the last 4 weeks.[10]

- During the first week of therapy (after a 1-week placebo run-in period), patients from China, Korea and Singapore with dyslipidaemia treated with ER niacin/laropiprant 1000 mg/20 mg once daily had significantly ($p < 0.001$) less flushing than those treated with ER niacin 1000 mg in a placebo-controlled trial ($n = 322$).[26] Moderate or more severe flushing was documented in 23.8% of patients in the ER niacin/laropiprant group and in 50% of patients treated with ER niacin.[26]

4. Tolerability

The tolerability profile of ER niacin/laropiprant has been evaluated over periods of up to 24 weeks in two large, fully published, randomized, controlled clinical trials.[6,24] Tolerability data have also been reported in several other smaller randomized trials.[9,10,25,26] Additional data on the tolerability of ER niacin/laropiprant reviewed in this section are derived from the manufacturer's prescribing information.[16] Preliminary information on the tolerability of ER niacin/laropiprant over up to 12 months has also been reported.[28]

- ER niacin/laropiprant was generally well tolerated by adults with dyslipidaemia or primary cholesterolaemia, with adverse reactions generally being mild and transient.[6,9,10,16,24-26]

- Flushing, predominantly of the head, neck and upper torso, is the most common adverse reaction experienced by adults receiving treatment with ER niacin/laropiprant. In an analysis of pooled data from four randomized trials ($n = 2548$), flushing, considered by the investigator to be possibly, probably or definitely related to treatment, occurred in 12.3% of ER niacin/laropiprant recipients.[16] In the patients treated with ER niacin/laropiprant, ER niacin or pooled placebo/simvastatin, rates of discontinuation because of flushing were, respectively, 7.2%, 16.6% and 0.4%. Discontinuation of ER niacin/laropiprant treatment because of other specific adverse reactions occurred in <1% of patients.[16]
- In the randomized, placebo-controlled, 24-week trial that compared the efficacy of ER niacin/laropiprant with that of ER niacin (see section 3 for details of treatment regimens), flushing (reported as a treatment-related adverse experience) occurred in approximately twice as many ER niacin than ER niacin/laropiprant recipients (15.2% vs 7.5%).[6] However, with the exception of flushing, the tolerability profile of ER niacin/laropiprant was broadly similar to that of ER niacin.[6] Treatment-related adverse experiences (considered by the investigator to be possibly, probably or definitely related to treatment) occurring in ≥2% of recipients of ER niacin/laropiprant recipients are shown in figure 3.
- Three deaths were reported (two in the ER niacin/laropiprant treatment group and one in the ER niacin group) but were not considered by the investigators to be treatment related.[6] No adverse experiences related to hepatitis were reported. In addition, there were no reports of rhabdomyolysis or myopathy.[6]
- Increases in blood glucose levels (approximately 0.2 mmol/L) were similar in the ER niacin/laropiprant and ER niacin treatment groups; in the subset of patients with diabetes at the start of the study ($n = 253$), median increases in fasting serum glucose of 0.2 mmol/L, 0.5 mmol/L and a decrease of <0.03 mmol/L were recorded for ER niacin/laropiprant, ER niacin and placebo recipients, respectively.[6] Five recipients of ER niacin/laropiprant and two recipients of ER niacin were diagnosed with 'new onset diabetes' (based on a clinical adverse experience of diabetes and/or the initiation of antidiabetes therapy) during the study; pre-existing diabetes became worse in 16.8% and 24.4% of patients in the ER niacin/laropiprant and ER niacin groups, respectively.[6]
- An apparent hypersensitivity reaction, characterized by numerous symptoms, including pruritus, erythema, angio-oedema, vomiting and dyspnoea, has been documented in <1% of patients treated with ER niacin/laropiprant.[16] In addition, infre-

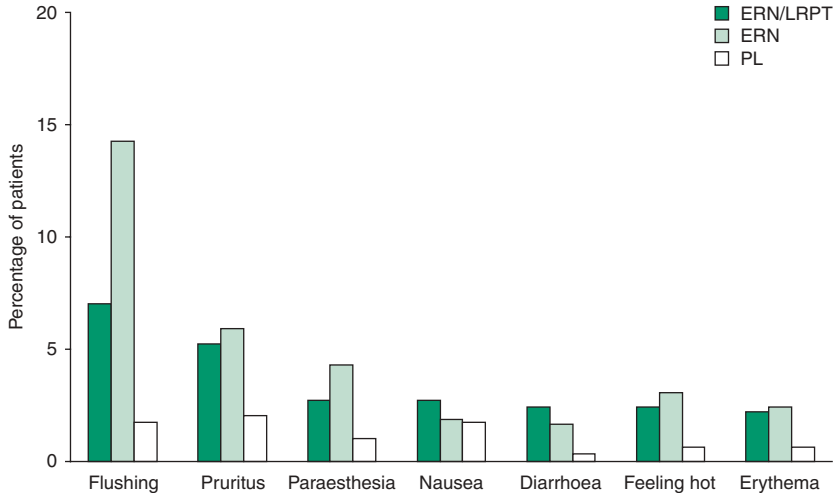

Fig. 3. Tolerability of extended-release niacin/laropiprant (ERN/LRPT) in adults with dyslipidaemia or primary hypercholesterolaemia. Treatment-related adverse experiences occurring in ≥2% of patients in a randomized, double-blind, placebo-controlled, multicentre, 24-week trial. Patients were randomized in a 3 : 2 : 1 ratio to receive once-daily treatment (after food in the evening) with ERN/LRPT 1000 mg/20 mg (n = 800 [for tolerability results, n = 798]), extended-release niacin (ERN) 1000 mg (n = 543 [n = 541]) or placebo (PL) [n = 270]: doses of active drugs were doubled after the initial 4-week treatment period.[6]

quent clinically important elevations in serum transaminases (ALT and/or AST of ≥3 × ULN) have been documented in 1.0% of patients receiving ER niacin/laropiprant with or without a statin in clinical trials.[16] In the placebo-controlled trial, similar (p = 0.6) proportions of patients treated with ER niacin/laropiprant or ER niacin had consecutive elevations in ALT and/or AST of ≥3 × ULN.[6] These elevated levels were asymptomatic and returned to normal after treatment discontinuation[6] or with the continuation of treatment.[16]

- In the randomized, 12-week, factorial trial (see section 3 for details of dosage regimens), ER niacin/laropiprant plus simvastatin was generally well tolerated, with a tolerability profile similar to that of ER niacin/laropiprant alone.[24] Rates of adverse experiences and discontinuation rates are shown in figure 4. Rates of adverse experiences related to glycaemic control were low in all treatment groups (≤0.5%).[24]
- In a pooled analysis of safety data from three phase III trials and three phase II 12-month extension trials in 4747 adults with dyslipidaemia, ER niacin/laropiprant, administered at approved dosages, was generally well tolerated (reported in an abstract and poster).[28] Over a period of up to 12 months, the incidence of flushing was numerically lower (statistical analysis not reported) in recipients of ER niacin/laropiprant than in those who received ER niacin (12.5% vs 23.3%). Treatment discontinuation due to flushing occurred in 7.2% and 16.6% of patients treated with ER niacin/laropiprant or ER niacin, respectively; corresponding rates of treatment discontinuation because of clinical adverse events were 9.7% and 7%. The incidences of treatment-related clinical and laboratory adverse events were similar in the two treatment groups.[28]

5. Dosage and Administration

ER niacin/laropiprant is available as a fixed-dose tablet containing modified-release niacin 1000 mg and laropiprant 20 mg.[16] ER niacin/laropiprant is indicated for the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia (characterized by elevated levels of LDL-C and triglycerides and low HDL-C) and in patients with primary hypercholesterolaemia (heterozygous familial and non-familial). ER niacin/laropiprant should be used in patients in combination

with HMG-CoA reductase inhibitors, when the cholesterol-lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate. It can be used as monotherapy only in patients in whom HMG-CoA reductase inhibitors are considered inappropriate or not tolerated. Diet and other non-pharmacological treatments (e.g. exercise, weight reduction) should be continued during therapy with ER niacin/laropiprant.[16]

The tablet should be taken whole (with food) in the evening or at bedtime; to reduce the possibility of flushing, it should not be taken with alcohol and/or hot drinks. The recommended initial dosage of ER niacin/laropiprant is 1000 mg/20 mg once daily. After 4 weeks of treatment, the dosage should be increased to a maintenance dosage of 2000 mg/40 mg (two tablets) once daily. If treatment is missed for <7 days, it may be resumed at the same dosage; however, in the event of treatment omission for ≥7 days, the dosage should be reduced to 1000 mg/20 mg for 1 week and then increased to 2000 mg/40 mg once daily. Dosage modification is not required for elderly patients.[16]

Local prescribing information should be consulted for additional guidance on dosage recommendations in patients switching to ER niacin/laropiprant from prolonged-release or immediate-release niacin regimens. The effects of ganglionic blocking agents and vasoactive drugs, such as calcium channel blockers, adrenergic receptor blocking drugs or nitrates, may be potentiated (leading potentially to postural hypotension) by coadministered niacin. Contraindications include hypersensitivity to the active substances or to any of the excipients, significant or unexplained hepatic dysfunction, active peptic ulcer disease, and arterial bleeding. The prescribing information should also be referred to for details of special warnings and precautions for use.[16]

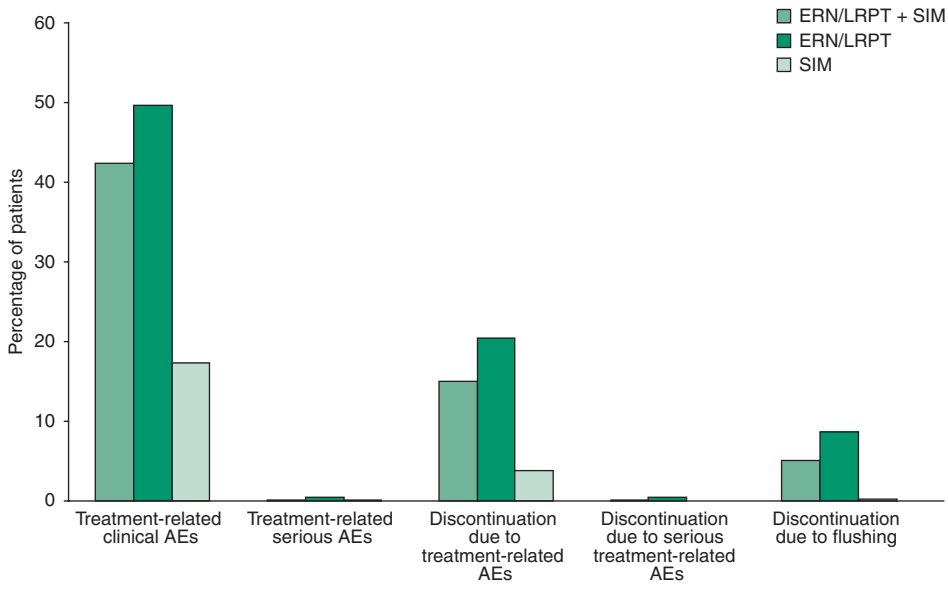

Fig. 4. Tolerability profile of extended-release niacin/laropiprant (ERN/LRPT) plus simvastatin (SIM) [ERN/LRPT + SIM] in adults with mixed dyslipidaemia or primary hypercholesterolaemia. Rates of adverse experiences (AEs) and discontinuation rates in a randomized, double-blind, multicentre, active comparator, factorial, 12-week trial. Patients were randomized to one of seven treatment groups (all drugs were taken once daily with the evening meal): ERN/LRPT 1000 mg/20 mg plus SIM 10, 20 or 40 mg (n = 609), ERN/LRPT 1000 mg/20 mg (n = 195) or SIM 10, 20 or 40 mg (n [for tolerability] = 593) [for 4 weeks]. Thereafter, with the exception of SIM 40 mg (alone or in combination with ERN/LRPT), doses were doubled and treatment was continued for a further 8 weeks.[24] Treatment-related clinical AEs and treatment discontinuation due to treatment-related AEs, serious treatment-related AEs, or flushing were determined by the investigator to be possibly, probably or definitely treatment-related clinical AEs. Simvastatin data pooled across doses.[24]

6. Extended-Release Niacin (Nicotinic Acid)/Laropiprant: Current Status

ER niacin/laropiprant is approved in the EU and some other countries, including Switzerland and Mexico, for the treatment of adults with mixed dyslipidaemia or primary hypercholesterolaemia. Administered once daily as a fixed-dose combination, ER niacin/laropiprant, with or without a statin, was an effective treatment for adults with mixed dyslipidaemia or primary hypercholesterolaemia and produced improvements in several lipid/lipoprotein parameters for up to 24 weeks in two large, randomized, controlled trials. Patients who received ER niacin/laropiprant experienced less flushing than recipients of ER niacin alone. ER niacin/laropiprant with or without a statin was generally well tolerated.

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