Drugs 2008; 68 (16): 2373-2386
0012-6667/08/0016-2373/$53.45/0

Niacin Extended-Release/Simvastatin

Mark Sanford and *Monique P. Curran*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Niacin extended-release (ER)/simvastatin is a once-daily, fixed-dose combination of the HMG-CoA reductase inhibitor simvastatin and an ER formulation of niacin (a B-complex vitamin).

▲ In healthy volunteers who were given niacin ER/simvastatin 2000 mg/40 mg, niacin exposure was similar to that with niacin ER 2000 mg, while simvastatin exposure was increased compared to that with simvastatin 40 mg.

▲ In patients with elevated non-high-density lipoprotein cholesterol (non-HDL-C) but with low-density lipoprotein cholesterol (LDL-C) at or below the National Cholesterol Education Program (NCEP) goal after a ≥2-week simvastatin 20 mg/day run-in period (SEACOAST I), 24 weeks of niacin ER/simvastatin 1000 mg/20 mg or 2000 mg/20 mg per day reduced median plasma non-HDL-C levels to a significantly greater extent than simvastatin 20 mg/day.

▲ In patients with elevated non-HDL-C and LDL-C at any level after a ≥2-week simvastatin 40 mg/day run-in period (SEACOAST II), 24 weeks of niacin ER/simvastatin 1000 mg/40 mg or 2000 mg/40 mg per day was noninferior to simvastatin 80 mg/day in reducing median plasma non-HDL-C levels.

▲ Compared with simvastatin monotherapy, there was no significant difference in reduction in plasma LDL-C levels with niacin ER/simvastatin in SEACOAST I, and the noninferiority criterion for LDL-C was not met in SEACOAST II. However, plasma HDL-C levels increased more and triglyceride levels were lowered more than with simvastatin monotherapy (SEACOAST I and II).

▲ Niacin ER/simvastatin was generally well tolerated, with flushing being the most common adverse reaction.

Table I. Features and properties of niacin extended-release/simvastatin (Simcor®)

Intended use	
Treatment of primary hypercholesterolaemia and mixed dyslipidaemia or hypertriglyceridaemia when monotherapy with simvastatin or niacin extended-release is considered inadequate	
Mechanism of action	
Simvastatin inhibits cholesterol synthesis and release of low-density lipoprotein (LDL). Niacin inhibits synthesis of LDL and triglycerides and catabolism of high-density lipoproteins	
Dosage and administration	
Starting dosage	500 mg/20 mg per day (in patients naive to or switching from niacin immediate-release)
Maintenance dosage	1000 mg/20 to 2000 mg/40 mg per day
Route of administration	Oral
Pharmacokinetic profile of a single dose of niacin extended-release/simvastatin 2000 mg/40 mg in healthy volunteers (niacin data not available for all parameters)	
Mean peak plasma concentration	Simvastatin acid 3.29 ng/mL
Mean time to peak plasma concentration	Simvastatin acid 6.56 h Niacin 4.6–4.9 h
Mean area under the plasma concentration-time curve	Simvastatin acid 30.81 ng • h/mL
Mean plasma terminal elimination half-life	Simvastatin acid 4.6–5.0 h
Adverse reactions (incidence ≥3%)	
Most common	Flushing, pruritus, headache, nausea, back pain, diarrhoea

HMG-CoA reductase inhibitors (statins) and niacin (nicotinic acid) are well established lipid-modifying agents that are used, along with therapeutic life-style changes, in the primary and secondary prevention of coronary heart disease (CHD), carotid artery disease and other atherosclerotic vascular diseases.[1-5] In patients with primary dyslipidaemias and in individuals with other risk factors for atherosclerosis, lipid-modifying drugs reduce the risk of major coronary events and coronary death.[6] Similarly, in patients already affected by atherosclerotic diseases, lipid-modifying drugs reduce disease recurrence, reduce the need for intensive interventions, such as coronary artery bypass graft surgery, and improve the patient's quality of life and survival.[5-7]

The 2001 US National Cholesterol Education Adult Treatment Panel III (NCEP ATP III) guidelines[8] (revised in 2004)[7] identify the lowering of low-density lipoprotein cholesterol (LDL-C) as the primary goal of lipid-modifying therapy in patients with atherosclerotic disease and those at risk for atherosclerotic disease due to dyslipidaemia. However, in patients with mixed dyslipidaemia (i.e. patients with high triglycerides, low high-density lipoprotein cholesterol [HDL-C] levels and small dense LDL particles), LDL-C levels may underestimate the cardiovascular risk.[4] Therefore, the NCEP ATP III recommends lowering both LDL-C and non-HDL-C in patients with hypertriglyceridaemia.[7] Non-HDL-C represents the total of atherogenic particles containing apolipoprotein B (apo B), including LDL-C, intermediate-density lipoprotein cholesterol and very low-density lipoprotein cholesterol (VLDL-C).

Of the available lipid-modifying drugs, statins are the most effective for lowering plasma LDL-C and are considered the cornerstone of treatment for dyslipidaemia.[4,8] Niacin also reduces LDL-C and it is the most effective drug for raising HDL-C and reducing lipoprotein (a).[2] Currently, there is interest in intensive lipid-modifying strategies, including use of high-dose or combination drug therapies for patients who are poorly responsive to standard drug monotherapy.[6,9] Therefore, the combination of niacin extended-release (ER) and simvastatin, which have complementary mechanisms of action,[1,2,10] may lead to the attainment of goal NCEP ATP III levels for risk-adjusted plasma LDL-C and non-HDL-C when monotherapy with simvastatin or niacin ER has failed. An earlier study suggested that combined treatments may provide important clinical benefits because slow-release niacin coadministered with simvastatin, as separate tablets, led to regression of coronary atherosclerosis in patients with CHD.[11] Furthermore, the combination of two lipid-lowering agents in one formulation should improve patient compliance, although this needs to be demonstrated in future studies.[12]

Niacin ER/simvastatin (Simcor®)[1] is a fixed-dose, combined formulation that incorporates niacin ER (referred to as prolonged-release nicotinic acid outside of the US) with simvastatin.[13] Once-daily niacin ER/simvastatin is approved in the US to reduce total cholesterol, LDL-C, apo B, non-HDL-C or triglycerides, or to increase HDL-C in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Frederickson type IIa and IIb hyperlipidaemia), and to reduce triglycerides in patients with hypertriglyceridaemia (Frederickson type IV hyperlipidaemia) when monotherapy with simvastatin or niacin ER is considered inadequate for these purposes.[13] The US FDA-approved label notes that, compared with simvastatin or niacin monotherapy, an incremental benefit of niacin ER/simvastatin on cardiovascular morbidity and mortality has not been established.[13] The label also stipulates that drug therapy is indicated as an adjunct to diet when dietary and other nonpharmacological measures alone have been inadequate.[13]

This profile reviews key data on the efficacy, tolerability and pharmacology of niacin ER/simvastatin in patients with these indications. Medical literature on the use of niacin ER/simvastatin in modifying blood lipids was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Addi-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

There are no published data specifically related to the pharmacodynamic properties of niacin ER/simvastatin, but the pharmacodynamic effects of simvastatin and niacin as monotherapy have been reviewed extensively.[1,2,14-16] The lipid-modifying effects of these drugs are thought to be key to the prevention of atherosclerotic diseases, although the exact pathways to these effects are complex, as both drugs have other atheroprotective pharmacodynamic actions.[1-3,15-17] This section provides a brief overview of the properties of the constituent drugs, drawing information chiefly from reviews.[1,2,16]

Simvastatin

- After absorption from the gastrointestinal tract, simvastatin is converted from the inactive, closed-ring lactone to the pharmacologically active β-hydroxyacid metabolite (simvastatin acid), a competitive and reversible inhibitor of HMG-CoA reductase.[1,14] As the conversion of HMG-CoA to mevalonic acid by HMG-CoA reductase is an early, rate-limiting step in the synthesis of cholesterol, inhibition of this enzyme reduces cholesterol production.[14]
- Simvastatin inhibition of HMG-CoA reductase leads to increased expression of hepatic LDL receptors that bind LDL particles, resulting in a lowering of circulating LDL-C and total cholesterol.[1] Simvastatin also enhances the removal of triglyceride-rich VLDL-C and chylomicron remnants in patients with hypertriglyceridaemia,[18] and reduces apo B and triglycerides, while increasing HDL-C levels in patients with mixed dyslipidaemia.[1,13]
- Simvastatin has been associated with a reduction in oxidized LDL *in vitro*[1] and in patients with hypercholesterolaemia.[19]
- Simvastatin, like other statins, improves endothelial function, increases nitric oxide bioavailability and has various endothelial anti-inflammatory effects that may reduce atherogenesis and susceptibility to plaque rupture.[17,20]
- Reductions in cholesterol synthesis with simvastatin are also associated with increased production of long-chain, polyunsaturated fatty acids that may improve vascular endothelial function.[21]

Niacin

- Niacin is a water-soluble B-complex vitamin[22] that reduces plasma total cholesterol, LDL-C, VLDL, apo B and triglycerides;[2,15,16] at high doses, niacin also reduces lipoprotein (a).[3] Niacin increases apo A-I and is the most potent available agent for increasing HDL levels.[16]
- In the liver, niacin reduces the synthesis of triglycerides.[16] As triglycerides are used in building VLDL and LDL particles, the secretion of these particles is also reduced.[16]
- Niacin reduces the mobilization of free fatty acids by modulating triglyceride lipolysis in adipose cells.[2,16] It inhibits the conversion of VLDL to LDL[2] and also increases the proportion of lipid molecules that are larger, more buoyant and less atherogenic.[2]
- Niacin inhibits hepatic catabolism of HDL and HDL-apo A-I, but not HDL-C esters.[16] These processes appear to account for the low levels of low-density lipids and high levels of HDL-C and apo A-I observed with niacin therapy.[16] HDL-C and apo A-I are essential to the release of cholesteryl esters from macrophages and to their transport to the liver where they are catabolized to free cholesterol and excreted in the bile.[16]
- In patients with coronary artery disease with low HDL-C, but with LDL-C in the normal range after treatment, niacin ER was associated with an increase in endothelium-dependent vasodilatation,[2] and the same effect was observed in patients with metabolic syndrome.[23,24]
- Recent studies suggest that niacin ER may have anti-inflammatory effects.[23,25] In patients with the metabolic syndrome (n = 50),[23] there was a significant reduction in C-reactive protein (CRP) after 52 weeks of therapy with niacin ER 1000 mg/day compared with placebo (−20% vs +1%; $p < 0.001$).

Similarly, when niacin ER 1000 mg/day was added to the lipid-lowering regimens of patients with CHD (n = 54), 3 months of combined treatment led to a significant lowering of the inflammatory markers CRP and lipoprotein-associated phospholipase A2 (by 15% and 20%; both $p < 0.05$ vs baseline), while no significant changes were observed with placebo.[25]

- Flushing, a common adverse reaction associated with niacin (section 4), appears to involve Langerhans cells. These cells express a G protein-coupled niacin receptor and respond to niacin with increased prostaglandin D_2 and E_2 production.[15]
- Niacin has been associated with increased blood glucose levels in patients with type 2 diabetes mellitus.[2] This effect may be due to the rebound in the levels of nonesterified fatty acids that occurs after niacin suppression of lipolysis in adipose tissue.[26] However, increases in fasting blood glucose levels with niacin ER were generally small,[2,26] were not accompanied by long-term decreases in insulin sensitivity[26] and, in most instances, were not considered to be clinically important.[2]

2. Pharmacokinetic Profile

The pharmacokinetics of fixed-dose niacin ER/simvastatin will be the focus of this section.[13] In addition, the pharmacokinetic parameters of simvastatin and niacin ER when administered as monotherapy will be briefly reviewed.[1,2,27-29] Data have been obtained mainly from the US manufacturer's prescribing information.[13,27,28]

Niacin Extended-Release (ER)/Simvastatin

- In a relative bioavailability study in 44 healthy volunteers administered two tablets of niacin ER/simvastatin 1000 mg/20 mg, niacin exposure was similar to that with two tablets of niacin ER 1000 mg.[13,30] However, based on area under the concentration-time curve (AUC) values, exposure to simvastatin and simvastatin acid increased by 23% and 41%, compared with administration of two tablets of simvastatin 20 mg.[13,30]
- The mean time to maximum concentration (t_{max}) for niacin, simvastatin and simvastatin acid following administration of niacin ER/simvastatin 2000 mg/40 mg was 4.6–4.9, 1.9–2.0 and 6.56 hours, respectively; the maximum concentration (C_{max}) and AUC of simvastatin acid were 3.29 ng/mL and 30.81 ng • h/mL.[13]
- Following administration of niacin ER/simvastatin 2000 mg/40 mg, 10.2%, 10.7% and 29.5% of the administered niacin dose was recovered in the urine as nicotinuric acid (NUA), N-methylnicotinamide (MNA) and N-methy-2-pyridone-5-carboxamide, respectively.[13]
- The mean terminal elimination half-life ($t_{1/2\gamma}$) values for simvastatin and simvastatin acid were 4.2–4.9 and 4.6–5.0 hours in healthy volunteers given niacin ER/simvastatin 2000 mg/40 mg.[13]

Simvastatin

- Simvastatin is rapidly absorbed after oral administration, with a t_{max} of 1.3–2.4 hours for the active and total inhibitors.[13,27] After a single dose of radiolabelled simvastatin 100 mg, the total plasma radioactivity t_{max} was 4 hours, which then declined to ≈10% of peak by 12 hours.[27]
- After oral administration of simvastatin in healthy volunteers, there was a linear increase in exposure to active metabolites for doses 5–120 mg,[1,27] and greater availability for pharmacodynamically inactive than active metabolites.[1]
- Simvastatin undergoes extensive first-pass metabolism in the liver, with the result that the bioavailability of simvastatin in the general circulation is <5%.[27] Simvastatin is readily hydrolyzed by hepatic/intestinal cytochrome P450 (CYP) 3A4, chiefly to simvastatin acid and to its 6′-hydroxy, 6′-hydroxymethyl and 6′-exomethylene derivatives.[27]
- In humans, simvastatin and simvastatin acid are ≈95% bound to plasma proteins.[27] Animal radioactivity studies show that simvastatin-derived radioactivity crosses the blood-brain barrier.[27]
- Simvastatin is cleared quickly by the body and is excreted in the urine and faeces. After radiolabelled simvastatin was administered orally, 13% of the radioactivity was recovered in the urine (<0.5% as

active metabolites) and 60% in the faeces.[1] The $t_{1/2\gamma}$ of simvastatin acid is 1.9 hours, while the total body clearance is 31.8 L/h.[1]

- In elderly patients (aged 70–78 years) treated with simvastatin, mean plasma levels of HMG-CoA reductase inhibitory activity was ≈45% higher than in younger patients (aged 18–30 years).[13] No dose adjustments are required for older patients.[1]
- Pharmacokinetic data for other statins suggest that exposure to simvastatin metabolites may be increased in patients with severe renal insufficiency (creatinine clearance [CL_{CR}] 10–30 mL/min [0.60–1.8 L/h]) and that dosage adjustments may be required.[27]
- Increased exposure may occur when simvastatin is coadministered with potent inhibitors of CYP3A4 (e.g. antifungal azoles such as ketoconazole, macrolide antibiotics, HIV protease inhibitors, nefazodone and large quantities of grapefruit juice). Ciclosporin, danazol, amiodarone and verapamil also increase the AUC of simvastatin active metabolites, presumably as a result of CYP3A4 inhibition.[27] Coadministration of simvastatin with any of these drugs should be avoided, as higher simvastatin exposure could increase the risk of myopathy and rhabdomyolysis (section 4).[13]
- Coadministration of gemfibrozil with simvastatin led to clinically important increases in exposure to simvastatin acid, perhaps as a result of inhibition of simvastatin glucuronidation, and could increase the risk of myopathy.[13] This effect occurred to a lesser extent when simvastatin was coadministered with other fibrates.[13]
- Simvastatin can potentiate the anticoagulant effect of coumarin anticoagulants.[13] In patients receiving coumarins, coagulation monitoring is required when first initiating treatment with niacin ER/simvastatin, and after dose adjustments.[13]
- Coadministration of simvastatin with digoxin was associated with a slight increase in plasma digoxin levels, so close monitoring is required when coadministering digoxin with niacin ER/simvastatin.[13]

Niacin

- After oral administration, niacin ER is rapidly absorbed, with 60–76% of the dose taken up from the gastrointestinal tract.[28]
- Oral administration of niacin ER leads to dose-dependent, but highly variable, niacin concentrations, attributable to extensive, saturable, first-pass metabolism. Mean steady-state niacin C_{max} values were 0.6, 4.9 and 15.5 μg/mL after niacin ER 1000, 1500 and 2000 mg/day.[2]
- During first-pass metabolism, niacin is conjugated with glycine in the liver to form NUA, most of which is excreted in the urine.[29] A second niacin metabolic pathway leads to the formation of nicotinamide adenine dinucleotide or MNA and nicotinamide-N-oxide. MNA is further metabolized to N-methyl-4- and N-methyl-2-pyridone-5-carboxamide.[29] These pyridine metabolites may be involved in niacin-induced hepatotoxicity[2] (section 4).
- Niacin was chiefly eliminated by the kidneys. After single and multiple doses of niacin ER 1500–2000 mg, ≈53–77% of the orally administered dose was detected in the urine, mostly as niacin metabolites; <8% was recovered as the unchanged drug after multiple doses of niacin ER 2000 mg.[13]
- Aspirin coadministered with niacin may decrease the metabolic clearance of niacin.[13] The clinical importance of this is unknown.[13]
- Niacin may also potentiate vasoactive and ganglion-blocking drugs, which could result in postural hypotension.[13]
- *In vitro*, the bile acid sequestrants, colestipol and cholestyramine, bind to niacin, thereby reducing exposure to the drug. At least 4–6 hours, or as long a time interval as possible, should be allowed to elapse before coadministering these drugs with niacin ER/simvastatin.[13]

3. Therapeutic Efficacy

The efficacy of niacin ER/simvastatin as a treatment for type II hyperlipidaemia or mixed dyslipidaemia was compared with that of simvastatin monotherapy in a 24-week, randomized, double-

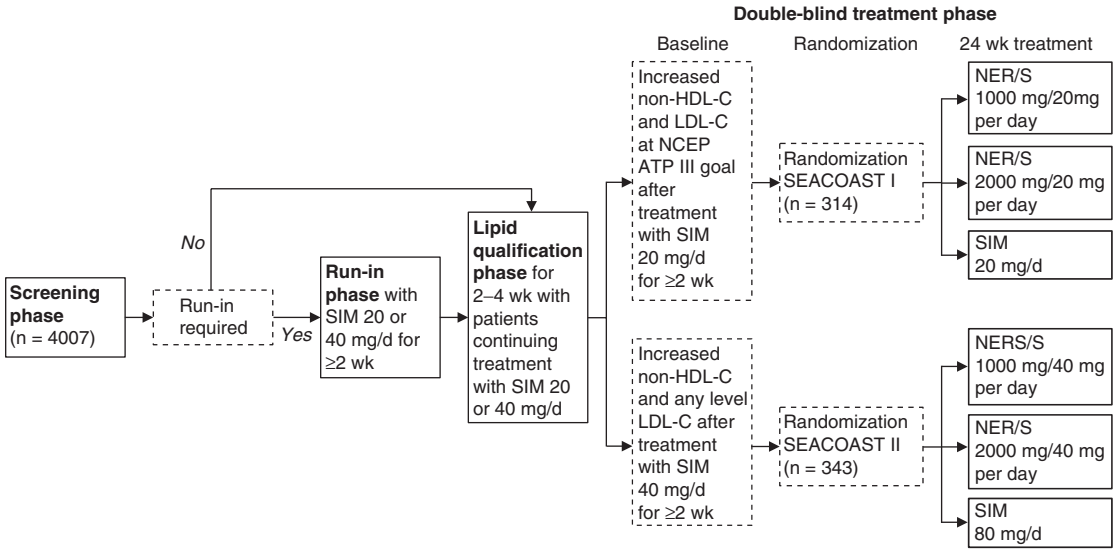

Fig. 1. Study design of the SEACOAST I[31] and II[32] randomized, double-blind trials that compared niacin extended-release/simvastatin (NER/S) with simvastatin (SIM) monotherapy in patients with mixed dyslipidaemia. Run-in was not required if non-high-density lipoprotein cholesterol (non-HDL-C) was raised and low-density lipoprotein cholesterol (LDL-C) was at the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) goal in patients who were treatment naive or currently taking SIM 20 mg/day (these patients went directly to SEACOAST I lipid qualification) or if non-HDL-C was raised with LDL-C at any level in patients currently taking SIM 40 mg/day (these patients went directly to SEACOAST II lipid qualification). Patients who did not meet NCEP ATP III LDL-C criteria after the SIM 20 mg/day run-in period were directed to the SIM 40 mg/day run-in and were randomized in the SEACOAST II trial if they then met SEACOAST II lipid qualification criteria.

blind, multicentre, phase III SEACOAST (Safety and Efficacy of a Combination of Niacin-Extended Release and Simvastatin in Patients with Dyslipidaemia) study.[31,32] OCEANS (Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients with Dyslipidaemia) was an open-label study that evaluated blood lipid changes at 24 and 52 weeks in patients randomized to one of two alternative niacin ER/simvastatin titration schedules.[33]

SEACOAST Study

The SEACOAST study consisted of two components; SEACOAST I (low-dose trial)[31] and II (high-dose trial).[32] SEACOAST I (n = 314 randomized patients) assessed whether once-daily niacin ER/simvastatin (1000 mg/20 mg or 2000 mg/20 mg) was superior to low-dose simvastatin 20 mg/day in reducing non-HDL-C in patients with elevated non-HDL-C, but with LDL-C at or below NCEP ATP III goals after a ≥2-week run-in period/lipid qualification phase with simvastatin 20 mg/day.[31] SEACOAST II (n = 343 randomized patients) evaluated whether once-daily niacin ER/simvastatin (1000 mg/40 mg or 2000 mg/40 mg) was noninferior to high-dose simvastatin 80 mg/day in reducing non-HDL-C in patients with elevated non-HDL-C levels after a ≥2-week run-in period/lipid qualification phase with simvastatin 40 mg/day.[32] SEACOAST II also evaluated whether either niacin ER/simvastatin dosage was nonferior to high-dose simvastatin in reducing LDL-C. In SEACOAST II, patients were included regardless of whether or not NCEP ATP III LDL-C goals had been met during the run-in phase.[32]

There were four phases to the SEACOAST study, screening, open-label simvastatin run-in period, lipid qualification and double-blind treatment (figure

1).[31,32] Before screening, patients were required to adhere reasonably to a standard cholesterol-lowering diet for ≥4 weeks and be willing to continue this diet.[31] Men and women aged ≥21 years were included if they had increased risk-adjusted NCEP ATP III non-HDL-C at screening. Anti-dyslipidemic treatment (other than simvastatin) was discontinued. During the lipid qualification phase, patients continued with simvastatin treatment until non-HDL-C at two consecutive weekly visits varied by <15%. Baseline lipid values were the means of the last two lipid profiles obtained during this phase.

Exclusion criteria for SEACOAST were elevated plasma AST, ALT or uric acid (≥1.3 times the upper limit of normal [ULN]), elevated plasma creatine phosphokinase (CPK) [≥3 times the ULN], active gout symptoms, blood glycosylated haemoglobin ≥9%, calculated CL_{CR} <30 mL/min,[31,32] and a number of medical conditions (including allergies to statins or niacin, unstable angina, poorly controlled diabetes and myopathies).[32]

In SEACOAST I after the run-in/lipid qualification phases, patients were randomized to niacin ER/simvastatin 1000 mg/20 mg or 2000 mg/20 mg per day or simvastatin 20 mg/day.[31] In SEACOAST II after the run-in/lipid qualification phases, patients were randomized to niacin ER/simvastatin 1000 mg/40 mg or 2000 mg/40 mg per day or simvastatin 80 mg/day.[32] During the double-blind treatment phase, niacin ER/simvastatin was initiated at a dosage of 500 mg/20 mg per day (SEACOAST I)[31] or 500 mg/40 mg per day (SEACOAST II),[32] with upward titrations every 4 weeks until the goal dosages were reached. Patients randomized to monotherapy with simvastatin 20 mg/day (SEACOAST I) or 80 mg/day (SEACOAST II) also received niacin immediate-release 50 mg/day to maintain study blinding.[31,32] Aspirin 325 mg, ibuprofen 200 mg or another NSAID could be taken approximately 30 minutes before the study medication to minimize flushing effects.[31,32]

The primary endpoint in SEACOAST I and II was the median percentage change in plasma non-HDL-C levels from baseline to week 24 of the double-blind treatment phase. Secondary endpoints included the percentage change from baseline to week 24 in plasma LDL-C, HDL-C, triglycerides, lipoprotein (a), apo A-I, apo B, apo A-I **:** apo B ratio and total cholesterol **:** HDL-C ratio.[31,32]

Patients were included in the modified intention-to-treat (ITT) analyses if they had one baseline non-HDL-C evaluation and a plasma lipid evaluation at 24 weeks.[31,32] In SEACOAST II, noninferiority of niacin ER/simvastatin 1000 mg/40 mg and 2000 mg/40 mg per day versus simvastatin 80 mg/day was established if the upper limit of the 95% confidence interval (CI) for the between-group difference in percentage change from baseline to 24 weeks for non-HDL-C (primary endpoint) was ≤6%.[32] The same noninferiority criterion was applied to between-group differences in LDL-C (secondary endpoint). If noninferiority was shown for either niacin ER/simvastatin dosage group compared with simvastatin monotherapy, then the superiority of niacin ER/simvastatin over simvastatin alone was also tested.[32]

Across the treatment groups in SEACOAST I and II, the median age of the patients was 55–62 years and 49–61% of the patients were male.[31,32] Most patients (89% in SEACOAST I[31] and 98% in SEACOAST II[32]) had CHD, CHD risk equivalent, or two or more CHD risk factors and so were considered to be at moderate or high risk for cardiovascular events. Overall, 21% of the patients in SEACOAST I[31] and 36% of patients in SEACOAST II[32] had diabetes. The 24-week discontinuation rates for simvastatin 20 mg, niacin ER/simvastatin 1000 mg/20 mg and 2000 mg/20 mg per day recipients were 19.8%, 33.1% and 30.3%, respectively (SEACOAST I), and for simvastatin 80 mg, niacin ER/simvastatin 1000 mg/40 mg and 2000 mg/40 mg per day recipients, they were 21.9%, 24.6% and 21.6% (SEACOAST II).

- Niacin ER/simvastatin was an effective lipid-modifying treatment in patients with mixed dyslipidaemias or type II hyperlipidaemia.[31,32]
- In SEACOAST I, patients receiving niacin ER/simvastatin 1000 mg/20 mg or 2000 mg/20 mg per day for 24 weeks experienced ≈2- and ≈3-fold greater median percentage reductions in plasma non-

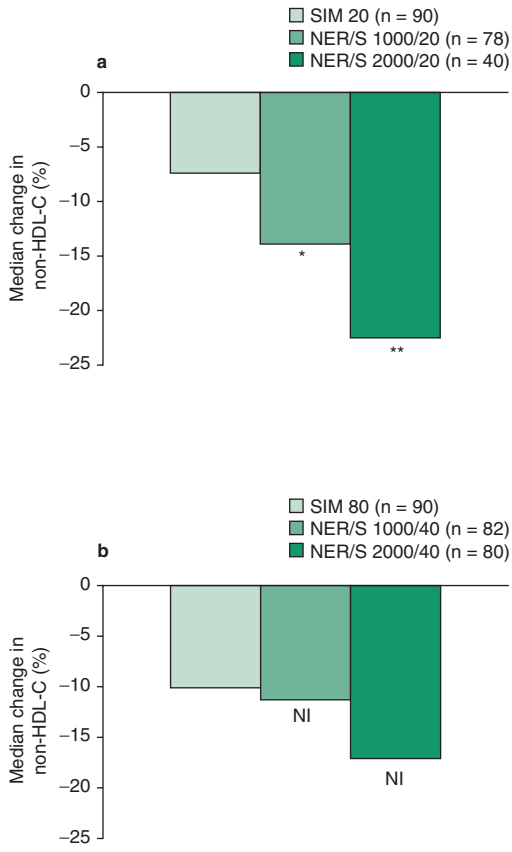

Fig. 2. Efficacy of niacin extended-release/simvastatin (NER/S) in the treatment of patients (pts) with dyslipidaemia. Median percentage change from baseline to week 24 in plasma non-high-density lipoprotein cholesterol (non-HDL-C) level [primary endpoint] in the randomized, double-blind, double-dummy, multicentre SEACOAST trials of (**a**) NER/S 1000 mg/20 mg or 2000 mg/20 mg per day vs simvastatin (SIM) 20 mg/day (SEACOAST I)[31] and (**b**) NER/S 1000 mg/40 mg or 2000 mg/40 mg per day vs SIM 80 mg/day (SEACOAST II).[32] Median non-HDL-C values at baseline were 156.5, 164.5 and 159.8 mg/dL in SIM 20 mg/day and NER/S 1000 mg/20 mg and 2000 mg/20 mg per day groups, respectively (SEACOAST I). In SEACOAST II, baseline non-HDL-C values at baseline were 130.5, 135.5 and 143.0 mg/dL in SIM 80 mg and NERS 1000 mg/40 mg and 2000 mg/40 mg per day groups, respectively. **NI** = meets noninferiority criterion. * $p < 0.01$, ** $p < 0.001$ vs SIM 20 mg/day.

HDL-C levels from baseline (primary endpoint) than simvastatin 20 mg/day recipients (figure 2).[31]

- Niacin ER/simvastatin 1000 mg/20 mg and 2000 mg/20 mg per day led to a significantly greater lowering of plasma triglycerides, lipoprotein (a) and apo B, total cholesterol **:** HDL-C ratio, and to significantly greater increases in plasma HDL-C and apo A-I **:** apo B ratio than simvastatin 20 mg/day (figure 3).[31]
- In SEACOAST II, both niacin ER/simvastatin dosage groups were noninferior to the high-dose simvastatin 80 mg/day treatment group, since the upper limit of the 95% CI for the between-group difference in percentage change from baseline in median plasma non-HDL-C (primary endpoint) at 24 weeks was less than the predefined margin of 6% (figure 2).[32]
- Compared with high-dose simvastatin 80 mg/day, both dosages of niacin ER/simvastatin produced significantly greater decreases in triglycerides, lipoprotein (a) and total cholesterol **:** HDL-C ratio and significantly greater increases in HDL-C and apo A-I (figure 3).[32]
- In SEACOAST I (patients at LDL-C NCEP ATP III goals), there was no significant difference between niacin ER/simvastatin and simvastatin monotherapy recipients in the median reductions in LDL-C levels from baseline to week 24.[31] In SEACOAST II (patients with any LDL-C level), niacin ER/simvastatin, compared with simvastatin, failed to met the noninferiority criterion for this endpoint.[32]
- A *post hoc* subgroup analysis of SEACOAST I data reported lipid responses in hypertriglyceridaemic (baseline triglycerides ≥200 mg/dL) and non-hypertriglyceridaemic (baseline triglycerides <200 mg/mL) patients. The median percentage changes in non-HDL-C (primary endpoint) in hypertriglyceridaemic patients were −10.2%, −18.8% and −28.9% in simvastatin 20 mg/day and niacin ER/simvastatin 1000 mg/20 mg and 2000 mg/20 mg per day recipients ($p < 0.01$ vs simvastatin 20 mg/day for both niacin ER/simvastatin dosages); corresponding values for non-hypertriglyceridaemic patients were −4.7%, −9.7% and −11.9% ($p < 0.05$ for niacin ER/simvastatin 2000 mg/20 mg per day vs simvastatin 20 mg/day).[31]
- According to *post hoc* analyses of the SEACOAST trials, a significantly higher percentage of

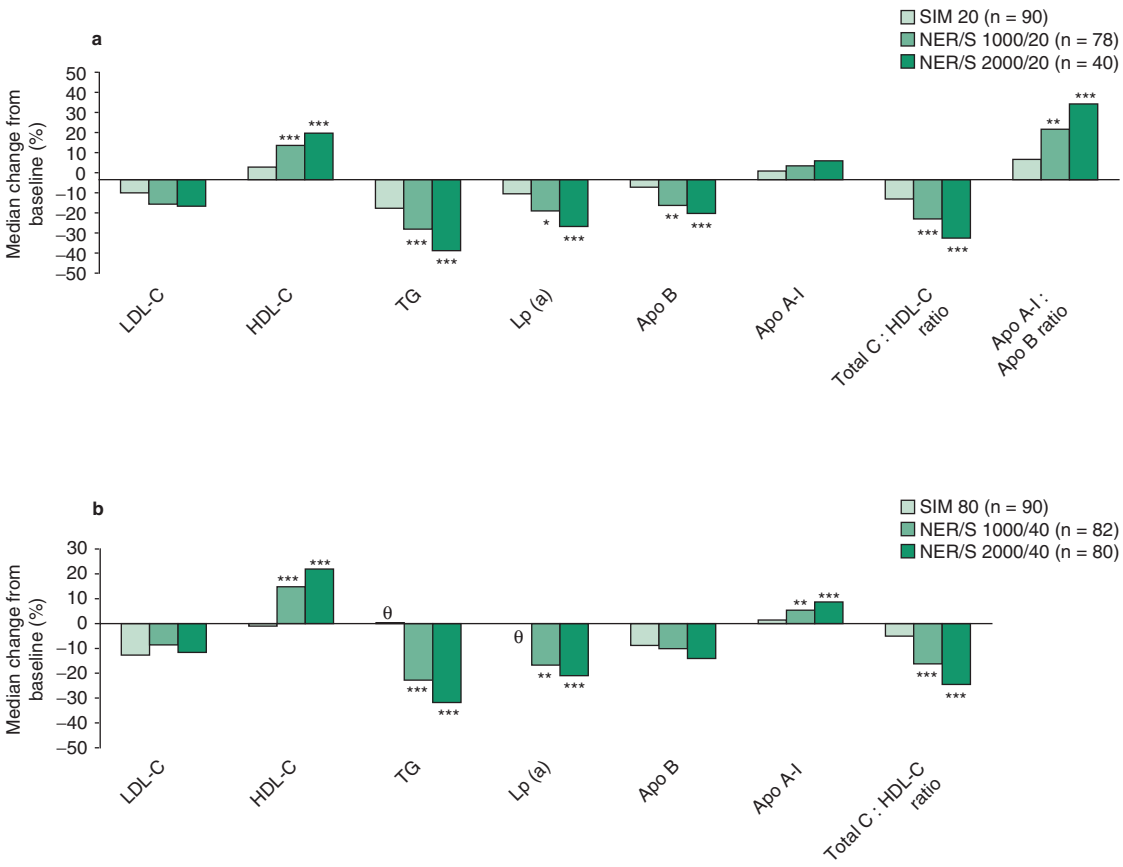

Fig. 3. Efficacy of niacin extended-release/simvastatin (NER/S) in the treatment of dyslipidaemia according to secondary endpoints. Median percentage change from baseline to wk 24 in plasma lipids in the randomized, double-blind, double-dummy, multicentre SEACOAST trials comparing (**a**) NER/S 1000 mg/20 mg or 2000 mg/20 mg per day vs simvastatin (SIM) 20 mg/day (SEACOAST I) and (**b**) NER/S 1000 mg/40 mg or 2000 mg/40 mg per day vs SIM 80 mg/day (SEACOAST II). In SEACOAST I, median low-density lipoprotein cholesterol (LDL-C) levels at baseline were 114.8, 117.5 and 111.5 mg/dL in the SIM 20 mg, NER/S 1000 mg/20 mg and 2000 mg/20 mg per day treatment groups, respectively; corresponding plasma triglyceride and high-density lipoprotein cholesterol (HDL-C) levels were 208.5, 209.5 and 214.3 mg/dL and 43.0, 41.3 and 40.9 mg/dL (SEACOAST I).[31] In SEACOAST II, median LDL-C levels at baseline were 98.5, 105.0 and 109.0 mg/dL in the SIM 80 mg, NER/S 1000 mg/40 mg and 2000 mg/40 mg per day treatment groups, respectively; corresponding plasma triglycerides and HDL-C levels were 140.5, 147.3 and 155.5 mg/dL and 46.5, 44.3 and 46.3 mg/dL (SEACOAST II).[32] **Apo A-I** = apolipoprotein A-I; **Apo B** = apolipoprotein B; **Lp (a)** = lipoprotein (a); **TG** = triglycerides; **Total C** = total cholesterol; θ = percentage change <1%; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs SIM 20 or 80 mg/day.

niacin ER/simvastatin recipients than simvastatin monotherapy recipients reached the trial combined lipid goals (risk-adjusted goals for non-HDL-C or LDL-C, HDL-C ≥40 mg/dL and triglycerides <150 mg/dL).[31,32] For instance, in SEACOAST I, in patients who did not meet goal plasma lipid levels after the simvastatin 20 mg/day run-in period, 16%, 25%, and 42% of simvastatin 20 mg/day, niacin ER/simvastatin 1000 mg/20 mg, and 2000 mg/20 mg per day recipients, respectively, met the combined plasma lipid goal at 24 weeks ($p < 0.001$ for niacin ER/simvastatin 2000 mg/20 mg per day vs simvastatin 20 mg/day) [data were estimated from a figure].[31]

- In the SEACOAST II trial, in patients who did not meet lipid goals after the simvastatin 40 mg/day run-in period, 20%, 30% and 50% of simvastatin 80 mg/day, niacin ER/simvastatin 1000 mg/40 mg, and 2000 mg/40 mg per day recipients, respectively,

met the combined plasma lipid goal at 24 weeks ($p < 0.05$ and $p < 0.001$ for niacin ER/simvastatin 1000 mg/40 mg and 2000 mg/40 mg per day vs simvastatin 80 mg/day) [data were estimated from a figure].[32]

OCEANS Study

The OCEANS study evaluated the efficacy of 52 weeks of treatment with niacin ER/simvastatin in patients aged ≥21 years with mixed dyslipidaemia.[33] After an initial screening visit, patients entered a simvastatin 40 mg/day run-in phase (4–6 weeks) and then a lipid qualification phase (1–2 weeks). Patients were randomized to an 8- or 12-week niacin ER/simvastatin titration schedule with a maximum dosage of 2000 mg/40 mg per day. Patients were eligible for randomization if the average of two non-HDL-C values was greater than the NCEP ATP III risk-adjusted treatment goals. Other inclusion/exclusion criteria were similar to those of the SEACOAST study. All patients were to be following a lipid-lowering diet during the entire course of the study, but compliance with the diet was not recorded at the screening visit or subsequently. Patients were withdrawn from the study if they did not reach LDL-C NCEP ATP III goals at 24 weeks. Although evaluation of the tolerability profile of niacin ER/simvastatin was the primary endpoint of this study (section 4), secondary endpoints evaluated efficacy parameters, including median percentage change in non-HDL-C from baseline to 24 and 52 weeks.[33]

The OCEANS study screened 1718 patients and 520 were randomized (171 patients [32.9%] were lipid-treatment naive).[33] Of those randomized, 244 (47%) discontinued treatment, leaving 268 who completed 24 weeks. A total of 161 patients were available for analysis at the 52-week follow-up, as the study sponsor shortened the trial duration from 52 to 24 weeks once 150 patients had completed the study.[33]

- Treatment with niacin ER/simvastatin 2000 mg/40 mg per day was associated with significant reductions in plasma non-HDL-C.[33] In the modified ITT population (n = 463) at 24 weeks, the median percentage reductions in non-HDL-C were 23% and 21% in the niacin ER/simvastatin 8- and 12-week titration groups ($p < 0.0001$ for both groups vs baseline).[33]
- A similar reduction in non-HDL-C was observed in the 24-week completer population (27% in both titration groups; both $p < 0.0001$ vs baseline).[33] In a subgroup analysis (n = 85[34]), patients who had been lipid-treatment naive prior to enrolment had a median decrease in non-HDL-C of 53.0% (8- and 12-week titration groups from the 24-week completer population were combined for this analysis).[33]
- In patients who did not meet NCEP ATP III lipid goals following the simvastatin 40 mg/day run-in period, 82% achieved the NCEP ATP III non-HDL-C goal and 65% achieved the trial combined lipid goal (LDL-C, HDL-C and triglyceride goals) by week 24 (n = 138 in non-HDL-C and n = 221 in combined lipid analyses).[33]
- In the 52-week completer population, median percentage reductions in non-HDL-C were 25% (95% CI 13, 35) and 28% (95% CI 15, 37) in the 8- and 12-week titration groups.[33]

4. Tolerability

Fixed-dose niacin ER/simvastatin (500 mg/20 mg to 2000 mg/40 mg per day) for 6–12 months was generally well tolerated in the SEACOAST and OCEANS studies, which are described in section 3. This review focuses on a pooled analysis of the SEACOAST study that is reported in the US manufacturer's prescribing information.[13]

- In the SEACOAST trials, flushing was the most common adverse reaction experienced by niacin ER/simvastatin recipients, followed by headache, pruritus, nausea, back pain and diarrhoea (see figure 4 for the incidence of non-flushing reactions).[13]
- Flushing is a known adverse effect of niacin that is uncomfortable but that does not endanger the patient, although in rare cases it may lead to syncope.[28] At least one episode of flushing was reported in up to 59% (SEACOAST)[13] and 71% (OCEANS)[33] of niacin ER/simvastatin recipients. Flushing was mostly mild to moderate in intensi-

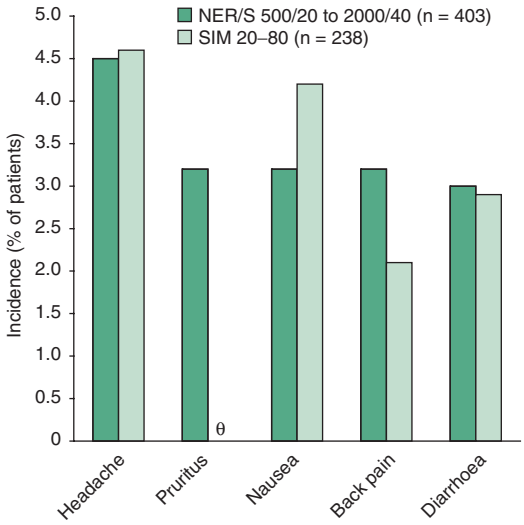

Fig. 4. Incidence of adverse reactions (excluding flushing) occurring at a frequency ≥3% in patients with mixed dyslipidaemia treated with niacin extended-release/simvastatin (NER/S) 500 mg/20 mg–2000 mg/40 mg per day or simvastatin (SIM) 20 to 80 mg/day. Pooled data from the randomized, double-blind, double-dummy SEACOAST trials.[13] Patients randomized to SIM monotherapy also received niacin immediate-release 50 mg/day to maintain study blinding.[31,32] Statistical analyses were not reported.[13] θ = zero incidence.

ty (>90% of cases in SEACOAST I and OCEANS,[31,33] and >78% of cases in SEACOAST II[32] in patients treated with niacin ER/simvastatin).

- Flushing tended to occur early in treatment and the incidence waned over time.[31-33] For instance, in the OCEANS study, 65% of patients experienced flushing during weeks 0–12, 39% during weeks 13–24 and 30% during weeks 41–52.[33] Among niacin ER/simvastatin recipients, discontinuations due to flushing occurred in 6.0% of patients in the SEACOAST study,[13] and 6.7% and 7.4% in the 8- and 12-week titration groups in the OCEANS study.[33]

- In the SEACOAST study, discontinuations due to adverse events were reported in 11–16% of niacin ER/simvastatin recipients and 4–5% of simvastatin recipients, with the between-group difference being significant for niacin ER/simvastatin 2000 mg/40 mg per day versus simvastatin 80 mg/day (12% vs 4%; $p < 0.05$).[31,32] In the OCEANS study, 23% of niacin ER/simvastatin recipients discontinued treatment due to an adverse event during the entire 52-week period.[33]

- Serious treatment-related adverse events occurred in <1% of niacin ER/simvastatin or simvastatin monotherapy recipients in the SEACOAST[31,32] and OCEANS studies.[33]

- Simvastatin (as with other statins) is occasionally associated with myopathy, including rhabdomyolysis. The concomitant administration of some other drugs (e.g. inhibitors of CYP3A4) with simvastatin appears to increase the risk of rhabdomyolysis (section 2).[35,36] However, across the SEACOAST and OCEANS studies, no patients developed myopathy or rhabdomyolysis;[31-33] one patient reported myalgia (OCEANS study), but this resolved after therapy was discontinued.[33] No patient treated with niacin ER/simvastatin had a CPK elevation >10 times the ULN (CPK criterion for rhabdomyolysis).[31-33]

- Niacin can lead to reversible increases in plasma uric acid, but in the SEACOAST and OCEANS studies, there was only one report of a new case of gout (SEACOAST II).[32]

- In patients with diabetes, niacin can reduce glucose tolerance (section 2), although most patients can be successfully managed with dietary and exercise adjustments.[35] In SEACOAST I and II, there were three cases of new-onset diabetes in niacin ER/simvastatin recipients, but glucose tolerance had been abnormal at baseline in these patients.[31,32] In the OCEANS study, 11 patients developed new-onset diabetes, but baseline laboratory findings were indicative of undiagnosed diabetes.[33]

- Both simvastatin and niacin may also increase hepatic transaminases, but when used at recommended doses clinically significant elevations are uncommon and hepatotoxicity is rare.[35] In the SEACOAST and OCEANS studies, niacin ER/simvastatin was not associated with clinically important changes in hepatic enzymes.[31-33]

5. Dosage and Administration

The recommended maintenance dosage of niacin ER/simvastatin in patients with primary hypercholesterolaemia and mixed dyslipidaemia or with

hypertriglyceridaemia is 1000 mg/20 mg to 2000 mg/40 mg per day, taken once daily at bedtime.[13] Higher dosages have not been studied and are not recommended.[13] In patients who are naive to, or who are switching from all niacin formulations other than niacin ER, the starting dose for niacin ER/simvastatin is 500 mg/20 mg once daily. In patients who are already receiving niacin ER, the initial dose should not exceed 2000 mg/40 mg per day. The daily dose of niacin ER should not be increased by more than 500 mg in a 4-week period.[13] In order to reduce flushing, pruritus and gastrointestinal distress, niacin ER/simvastatin should be taken with a low-fat snack and dosage titration recommendations should be followed.[13] Pretreatment with aspirin or another NSAID approximately 30 minutes before taking niacin ER/simvastatin may reduce the frequency and severity of flushing.[13]

Niacin ER/simvastatin is contraindicated in patients with active liver disease, active peptic ulcer disease or arterial bleeding.[13] As there is an increased risk of hepatotoxicity when switching between niacin formulations, niacin ER/simvastatin should only be substituted for equivalent doses of niacin ER.[13]

It is recommended that niacin ER/simvastatin is not used in patients with severe renal insufficiency, unless they are known to tolerate simvastatin dosages ≥10 mg/day.[13] Close monitoring is necessary in these patients.[13]

Niacin can increase fasting blood glucose and serum uric acid.[13] Patients with, or at risk for, diabetes, should be monitored closely during treatment with niacin ER/simvastatin, so that treatments can be adjusted if necessary.[13] Niacin ER/simvastatin should be used only with caution in patients at increased risk for gout.[13]

Coadministration of niacin ER/simvastatin with drugs that are CYP3A4 inhibitors should be avoided, as the risk of myopathy and rhabdomyolysis is increased (section 2).[13] In general, patients receiving niacin ER/simvastatin should be monitored for muscle pain, tenderness or weakness, especially during the first month of treatment, or after dosage increases.[13]

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Niacin ER/Simvastatin: Current Status

Niacin ER/simvastatin is approved in the US to reduce elevated total cholesterol, LDL-C, apo B, non-HDL-C or triglycerides, or to increase HDL-C in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Frederickson type IIa and IIb hyperlipidaemia), and to reduce triglycerides in patients with hypertriglyceridaemia (Frederickson type IV hyperlipidaemia) when treatment with simvastatin or niacin ER monotherapy is considered inadequate.[13]

To date, it is not established whether niacin ER/simvastatin has an incremental benefit over simvastatin or niacin monotherapy in reducing cardiovascular morbidity and mortality. However in the SEACOAST randomized trials, which compared niacin ER/simvastatin with simvastatin monotherapy in patients with mixed dyslipidaemias who had not responded fully to a simvastatin monotherapy run-in, 24 weeks of treatment with niacin ER/simvastatin led to clinically-relevant improvements in plasma lipid profiles, including lowering of non-HDL-C levels (primary endpoint). In the open-label OCEANS study, niacin ER/simvastatin also led to improvements in non-HDL-C over baseline levels. In these studies, niacin ER/simvastatin was generally well tolerated.[31,32]

Acknowledgements and Disclosures

The manuscript was reviewed by: **D.G. Hackam**, Division of Clinical Pharmacology, Department of Medicine, University of Western Ontario, London, Ontario, Canada; **M.A. Lincoff**, Department of Cardiovascular Medicine, The Cleveland Clinic, Cleveland, Ohio, USA; **A. Saraste**, Nuclear Medicine Clinic and Polyclinic, Technical University of Munich, Munich, Germany; **A. Tavridou**, Laboratory of Pharmacology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturers of the agent under review were offered an opportunity to comment on this article. Changes resulting from any

comments received were made on the basis of scientific and editorial merit.

References

1. Plosker GL, McTavish D. Simvastatin: a reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolaemia. Drugs 1995; 50 (2): 334-63
2. McCormack PL, Keating GM. Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidaemia. Drugs 2005; 65 (18): 2719-40
3. Scanu AM, Bamba R. Niacin and lipoprotein(a): facts, uncertainties, and clinical considerations. Am J Cardiol 2008 Apr 17; 101 Suppl.: 44-7B
4. Cannon CP. Combination therapy in the management of mixed dyslipidaemia. J Intern Med 2008 Apr; 263 (4): 353-65
5. Smith Jr SC, Allen J, Blair SN, et al. AHA/ACC Guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular diseases: 2006 update (writing group for the American Heart Association/American College of Cardiology). Circulation 2006 May 16; 113 (19): 2363-72
6. Hackam DG. Intensive reduction of low-density lipoprotein-cholesterol: implications of recent trials. Am J Cardiovasc Drugs 2006; 6 (6): 367-71
7. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004 Jul 13; 110 (2): 227-39
8. National Cholesterol Education Program. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001 May 16; 285 (19): 2486-97
9. Taylor AJ. Evidence to support aggressive management of high-density lipoprotein cholesterol: implications of recent imaging trials. Am J Cardiol 2008 Apr 17; 101 Suppl.: 36-43B
10. Hvizdos KM, Goa KL. Management of dyslipidaemias: the role of simvastatin. Dis Manage Health Outcomes 2000; 7 (2): 83-109
11. Brown GB, Zhao X-Q, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001 Nov 29; 345 (22): 1583-92
12. Sleight P, Pouleur H, Zannad F. Benefits, challenges, and registerability of the polypill. Eur Heart J 2006 Jul; 27 (14): 1651-6
13. Abbott. Simcor®: prescribing information [online]. Available from URL: http://www.fda.gov/cder/foi/label/2008/022078lbl.pdf [Accessed 2008 Sep 30]
14. Todd PA, Goa KL. Simvastatin: a review of its pharmacological properties and therapeutic potential in hyperchlosterolaemia. Drugs 1990 Oct; 40 (4): 583-607
15. Gille A, Bodor ET, Ahmed K, et al. Nicotinic acid: pharmacological effects and mechanisms of action. Annu Rev Pharmacol Toxicol 2008; 48: 79-106
16. Kamanna VS, Kashyap M. Mechanism of action of niacin. Am J Cardiol 2008 Apr 17; 101 Suppl.: 20-6B
17. Tesfamariam B. The effects of HMG-CoA reductase inhibitors on endothelial function. Am J Cardiovasc Drugs 2006; 6 (2): 115-20
18. vanWijk JPH, Buirma R, vanTol A, et al. Effects of increasing doses of simvastatin on fasting lipoprotein subfractions, and the effect of high-dose simvastatin on postprandial chylomicron remnant clearance in normotriglyceridemic patients with premature coronary sclerosis. Atherosclerosis 2005 Jan; 178 (1): 147-55
19. Tavridou A, Efthimiadis A, Efthimiadis I, et al. Antioxidant effects of simvastatin in primary and secondary prevention of coronary heart disease. Eur J Clin Pharmacol 2006 Jun; 62 (6): 485-9
20. Giurgea AG, Margeta C, Maca T, et al. Simvastatin reduces serum level of vascular endothelial growth factor in hypercholesterolemic patients. J Cardiovasc Pharmacol 2006 Jan; 47 (1): 30-6
21. Jula A, Marniemi J, Rönnemaa T, et al. Effects of diet and simvastatin on fatty acid composition in hypercholesterolemic men: a randomized controlled trial. Arterioscler Thromb Vasc Biol 2005 Sep; 25 (9): 1952-9
22. McEvoy GK, Snow EK, editors. AHSF drug information 2008. Bethesda (MD): American Society of Health-System Pharmacists, Inc. 2008
23. Thoenes M, Oguchi A, Nagamia S, et al. The effects of extended-release niacin on carotid intimal media thickness, endothelial function and inflammatory markers in patients with the metabolic syndrome. Int J Clin Pract 2007 Nov; 61 (11): 1942-8
24. Sorrentino SA, Besler C, Bahlmann FH, et al. Extended-release niacin improves endothelial function, restores re-endothelialization capacity of endothelial progenitor cells and augments vasoprotective properties of HDL in patients with metabolic syndrome [abstract no. 189]. Circulation 2007 Oct 17; 116 (16): 16
25. Kuvin JT, Dave DM, Sliney KA, et al. Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. Am J Cardiol 2006 Sep 15; 98 (6): 743-5
26. Vega GL, Cater NB, Meguro S, et al. Influence of extended-release nicotinic acid on nonesterified fatty acid flux in the metabolic syndrome with atherogenic dyslipidemia. Am J Cardiol 2005 Jun 1; 95 (11): 1309-13
27. Merck and Co. Inc. Zocor®: prescribing information [online]. Available from URL: http://www.merck.com/product/usa/pi_circulars/z/zocor/zocor_pi.pdf [Accessed 2008 Jul 7]
28. Abbott. Niaspan®: prescribing information [online]. Available from URL: http://www.fda.gov/cder/foi/label/2007/020381s034lbl.pdf [Accessed 2008 Jul 2]
29. Menon RM, Adams MH, Gonzáles MA, et al. Plasma and urine pharmacokinetics of niacin and its metabolites from an extended-release niacin formulation. Int J Clin Pharmacol Ther 2007; 45 (8): 448-54
30. US FDA Center for Drug Evaluation and Research. Simcor® summary review [online]. Available from URL: http://www.fda.gov/cder/foi/nda/2008/022078s000_SumR.pdf [Accessed 2008 Sep 16]
31. Ballantyne CM, Davidson MH, McKenney J, et al. Comparison of the safety and efficacy of a combination tablet of niacin extended release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I Study). Am J Cardiol 2008 May 15; 101 (10): 1428-36
32. Ballantyne CM, Davidson MH, McKenney JM, et al. Comparison of the efficacy and safety of a combination tablet of niacin extended-release and simvastatin with simvastatin 80 mg monotherapy: the SEACOAST II (high-dose) study. J Clin Lipidol 2008 Apr; 2 (2): 79-90

33. Karas RH, Kashyap ML, Knopp RH, et al. Long-term safety and efficacy of a combination of niacin extended release and simvastatin in patients with dyslipidemia. Am J Cardiovasc Drug 2008; 8 (2): 69-81
34. Karas RH, Bajorunus DR, Davidson MH, et al. The combination of niacin extended-release with simvastatin improves lipid levels in treatment-naive patients [abstract no. 219]. J Clin Lipidol 2008; 2 (3): 221-2. Plus poster presented at the National Lipid Association 2008 Annual Scientific Sessions; 2008 May 29-Jun 1; Seattle (WA)
35. Bays H. Safety of niacin and simvastatin combination therapy. Am J Cardiol 2008 Apr 17; 101 (8A): 3-8B
36. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003 Apr 2; 289 (13): 1681-90

Correspondence: *Mark Sanford*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz