CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-078

SUMMARY REVIEW

2/17/08

Summary Review for Regulatory Action

Date	February 17, 2008
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	NDA 22-078
Applicant Name	Abbott
Date of Submission	April 17, 2007
PDUFA Goal Date	February 17, 2008
Proprietary Name / Established (USAN) Name	Simcor Simvastatin/niacin extended-release
Dosage Forms / Strength	500/20 mg, 750/20 mg, and 1000/20 mg tablets
Proposed Indication(s)	Treatment of primary hypercholesterolemia and type IIa, IIb —— hypercholesterolemia
Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Iffat Chowdhury, MD
Statistical Review	Janice Derr, PhD
Pharmacology Toxicology Review	Karen Davis Bruno, PhD
CMC Review/OBP Review	John Hill, PhD
Microbiology Review	Not applicable
Clinical Pharmacology Review	Sang Chung, PhD
DDMAC	Michael Brony
DSI	Andrea Slavin, RN
CDTL Review	Not applicable
OSE/DMETS	Kellie Taylor, PharmD, MPH
OSE/DDRE	Vicky Borders-Hemphill, PharmD
OSE/DSRCS	Not applicable
Other	Not applicable

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

With submission of this 505b2 NDA, Abbott seeks approval of a 500/20 mg, 750/20 mg, and 1000/20 mg fixed-dose combinations of simvastatin (Zocor) and niacin extended-release (Niaspan) for the treatment of primary hypercholesterolemia, mixed dyslipidemia,

hypertriglyceridemia,

Although this is a 505b2 application based on data from the Zocor and Niaspan NDAs, a randomized, controlled clinical trial (SEACOAST) comparing the efficacy and safety of Simcor to simvastatin monotherapy was conducted by the sponsor. The findings from this study have been extensively reviewed by Dr. Iffat Chowdhury. In addition serving as a secondary review of the controlled trial data, this memorandum will discuss some of the clinical pharmacology data, the rationale for granting a waiver for pediatric studies, and the reasons for limiting the indications of Simcor to patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia who have an inadequate response to simvastatin or niacin extended-release monotherapy.

2. Background

Simvastatin was approved in 1992; Niaspan in 1997. Simvastatin is indicated for the treatment of primary hypercholesterolemia, type IIa, IIb, III, and IV hyperlipidemia, and to reduce the risk of CHD mortality and cardiovascular events in patients at high risk for coronary events. Niaspan is indicated for the treatment of primary hypercholesterolemia, type IIa, IIb, IV, and V hyperlipidemia, and to reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia.

3. CMC

There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

This NDA relied on the review of the nonclinical pharmacology/toxicology data from the Zocor and Niaspan NDAs. Dr. Karen Davis Bruno has recommended minor revisions to the sponsor's proposed labeling.

5. Clinical Pharmacology/Biopharmaceutics

In a relative bioavailability study, the C_{max} and AUC values for niacin were comparable in subjects who received two 1000/20 mg tablets of Simcor, two 1000 mg Niaspan tablets, and co-administered simvastatin (2 x 20 mg) and Niaspan (2 x 1000 mg). The C_{max} and AUC values for simvastatin and simvastatin acid after two 1000/20 mg tablets of Simcor were 23% and 41% higher, respectively, compared with levels after administration of two simvastatin 20 mg tablets. Although not evaluated in the same individuals, the absolute values of simvastatin and simvastatin acid following administration of two 1000/20 mg tablets of Simcor were considerably lower than the absolute values observed after administration of 80 mg simvastatin in a previous study.

Dr. Chung, the clinical pharmacology reviewer, has deemed the 500/20 mg and the 1000/20 mg Simcor dosage strengths acceptable. Because the 750/20 mg Simcor tablet was not evaluated in a clinical pharmacology study and it does not qualify for a biowaiver because formulation proportionality among the three strengths has not been established, Dr. Chung deferred a decision on the acceptability of this dosage strength to the clinical team.

The 750/20 mg tablet was used, without any apparent problems, in an open-label comparative titration-scheme study (OCEANS), which has been reviewed by Dr. Chowdhury. Given the acceptability of the 500/20 and 1000/20 mg dosage strengths and the fact that the efficacy of Simcor will be assessed clinically through monitoring of lipid levels, I believe it is reasonable to approve the 750/20 mg dosage strength based on the available data.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

SEACOAST was a double-blind, randomized, multi-center, multi-national, active-controlled, 24-week study of the lipid effects of SIMCOR compared to simvastatin 20 mg and 80 mg in 641 patients with type II hyperlipidemia or mixed dyslipidemia. Following a lipid qualification phase, patients entered one of two treatment groups. In Group A, patients on simvastatin 20 mg monotherapy with elevated non-HDL levels and LDL-C levels at-goal per the NCEP guidelines were randomized to one of three treatment arms: SIMCOR 1000/20 mg, SIMCOR 2000/20 mg, or simvastatin 20 mg. In Group B, patients on simvastatin 40 mg monotherapy with elevated non-HDL levels per the NCEP guidelines regardless of LDL-C goal status were randomized to one of three treatment arms: SIMCOR 1000/40 mg, SIMCOR 2000/40 mg, or simvastatin 80 mg. SIMCOR was initiated at the 500 mg dose of niacin extended-release and increased by 500 mg every four weeks. Thus subjects were titrated to the 1000 mg dose of SIMCOR after four weeks and to the 2000 mg dose of SIMCOR after 12 weeks. All subjects randomized to simvastatin monotherapy received 50 mg immediate-release niacin daily in an attempt to keep the study from becoming unblinded due to flushing in the SIMCOR groups only. All subjects were instructed to take aspirin or a NSAID 30 minutes prior to study drug administration.

In Group A, the primary efficacy analysis was a comparison of the mean percent change in non-HDL levels between the SIMCOR 2000/20 mg and simvastatin 20 mg groups, and if statistically significant, then a comparison between the SIMCOR 1000/20 mg and simvastatin 20 mg groups. In Group B, the primary efficacy analysis was a determination of whether the mean percent change in non-HDL in the SIMCOR 2000/40 mg group was non-inferior (i.e., non-inferiority margin -6%) to the mean percent change in the simvastatin 80 mg group, and if so, whether the mean percent change in non-HDL in the SIMCOR 1000/40 mg group was non-inferior (i.e., -6%) to the mean percent change in the simvastatin 80 mg group.

As shown in Table 1, in Group A, the non-HDL-C lowering with SIMCOR 2000/20 and SIMCOR 1000/20 was statistically significantly greater than that achieved with simvastatin 20 mg after 24 weeks.

Table 1. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 20-mg Treated Baseline Group A

Week	Simcor 2000/20 n[a]	Simcor 2000/20 dose (mg/mg)	Simcor 2000/20 non-HDL[b]	Simcor 1000/20 n[a]	Simcor 1000/20 Dose (mg/mg)	Simcor 1000/20 non-HDL[b]	Simvastatin 20 n[a]	Simvastatin 20 Dose (mg/mg)	Simvastatin 20 non-HDL[b]
Baseline	56	---	163.1 mg/dL	108	---	164.8 mg/dL	102	---	163.7 mg/dL
4	52	500/20	-12.9%	86	500/20	-12.8%	91	20	-8.3%
8	46	1000/20	-17.5%	91	1000/20	-15.5%	95	20	-8.3%
12	46	1500/20	-18.9%	90	1000/20	-14.8%	96	20	-6.4%
24	40	2000/20	-19.5%†	78	1000/20	-13.6%†	90	20	-5.0%
Dropouts by week 24:	28.6%			27.8%			11.8%		

[a] n=number of subjects with values in the analysis window at each timepoint
[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.
†significant vs. simvastatin 20 mg at the primary endpoint (Week 24), $p<0.05$

In Group B, the lowering of non-HDL-C in the two Simcor groups was non-inferior to the lowering observed in the simvastatin 80 mg group (Table 2).

Table 2. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 40-mg Treated Baseline Group B

Week	Simcor 2000/40 n[a]	Simcor 2000/40 dose (mg/mg)	Simcor 2000/40 non-HDL[b]	Simcor 1000/40 n[a]	Simcor 1000/40 Dose (mg/mg)	Simcor 1000/40 non-HDL[b]	Simvastatin 80 n[a]	Simvastatin 80 Dose (mg/mg)	Simvastatin 80 non-HDL[b]
Baseline	98	---	144.4 mg/dL	111	---	141.2 mg/dL	113	---	134.5 mg/dL
4	96	500/40	-6.0%	108	500/40	-5.9%	110	80	-11.3%
8	93	1000/40	-15.5%	100	1000/40	-16.2%	104	80	-13.7%
12	90	1500/40	-18.4%	97	1000/40	-12.6%	100	80	-9.5%
24	80	2000/40	-7.6%[c]	82	1000/40	-6.7%[d]	90	80	-6.0%
Dropouts by week 24:	18.4%			26.1%			20.4%		

[a] n=number of subjects with values in the analysis window at each timepoint
[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.
[c] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for Simcor 2000/40 vs. Simvastatin 80 is (-7.7%, 4.5%)
[d] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for Simcor 1000/40 vs. Simcor 80 is (-6.6%, 5.3%)

Compared with simvastatin 20 mg, treatment with Simcor 1000/20 and 2000/20 mg was associated with favorable improvements in TC, LDL-C, Apo B, HDL-C, and TG. Compared with simvastatin 80 mg, treatment with Simcor 1000/40 and 2000/40 mg was associated with favorable improvements in HDL-C and TG. The absolute reductions in TC and LDL-C were greater in the simvastatin 80 mg group vs. the Simcor 1000/40 and 2000/40 mg groups. Changes in Apo B were similar in the simvastatin 80 mg and high-doe Simcor arms.

8. Safety

The safety profiles of simvastatin and niacin extended-release are well known. The major concerns include myotoxicity (both), hepatitis (niacin), decreased glucose tolerance (niacin), and increased uric acid levels (niacin). In terms of combination therapy, the risk for muscle toxicity and transaminitis will be expected to be greater compared with the single-agent use of simvastatin or niacin.

In SEACOAST, there were no cases of myopathy or hepatitis reported in any of the treatment groups. Mild CPK elevations less than 3X ULN occurred in about 30% of patients taking Simcor and 27% of patients taking simvastatin. Seven patients (1.7%) from the Simcor groups had a CPK elevation between 3X ULN and 5X ULN, as compared with one patient (0.4%) in the simvastatin groups. No Simcor patients had CPK values between 5X and 10X ULN. A patient treated with 80 mg of simvastatin had a single CPK value greater than 10X ULN. A total of 79 (20%) patients in the Simcor treatment arms had AST values greater than normal compared to 29 (12.2%) of the patients in the simvastatin treatment arms. Two patients who received Simcor 1000/20mg had AST > 3X ULN (104 u/L and 108 u/L). No treatment arm had any patient with two consecutive AST elevations greater than 3X ULN. Fifty-seven (14.4%) patients who received Simcor had an abnormal ALT value compared to 33 (13.9%) patients who received simvastatin monotherapy. Three patients who received Simcor had an ALT elevation greater than 3X ULN. One patient who received simvastatin 80 mg had an ALT elevation greater than 3X ULN. The highest of the four values was 148 u/L. No patient in any of the treatment groups had two consecutive elevations of ALT greater than 3X ULN.

These findings are in agreement with data from previous studies of statin-niacin co-administration therapy. The Simcor labeling adequately addresses potential risks and provides guidance on appropriate clinical monitoring.

9. Advisory Committee Meeting

The Division did not believe that this NDA required discussion at an Advisory Committee meeting.

10. Pediatrics

The Division waived the requirement for pediatric studies with Simcor. Statins are the pharmacologic mainstay of lipid disorder treatment in pediatric patients. Professional organizations such as the American Heart Association indicate that niacin may be an option for pediatric patients over the age of 10 years who have extrememly high TG levels (e.g., $\geq$ 700 mg/dl). However, compliance with niacin is notoriously poor due to flushing. This would likely pose a significant obstacle to effective long-term treatment in a pediatric patient population. Furthermore, pre-treatment with aspirin, often recommended to reduce niacin-induced flushing, would be ill advised in pediatric patients due to the potential risk for Reye's syndrome in the face of fever-causing illnesses. Although in theory alert patients and their parents could discontinue use of aspirin at the first sign or symptom of illness, in practice compliance with such action would be less than perfect. Moreover, one has to question the risk-benefit profile of long-term use of aspirin (or a NSAID which may also reduce niacin-induced flushing) from a gastrointestinal perspective in pediatric patients.

I agree with Dr. Chowdhury's recommendation that Simcor 500/20 mg, 750/20 mg, and 1000/20 mg be approved.

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Eric Colman, MD
Deputy
DMEP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
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MEDICAL OFFICER