CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-078

PHARMACOLOGY REVIEW(S)

1/26/08

Signed into DFS on 1/16/2008 .

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-078.
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	4/17/2007
PRODUCT:	Simcor (fixed dose combination of Niacin ER and simvastatin)
INTENDED CLINICAL POPULATION:	Patients with hyper-cholesterolemia, mixed dyslipidemia and hyper-triglyceremia.
SPONSOR:	Abbott Laboratories, Abbott Park, IL.
DOCUMENTS REVIEWED:	e-CTD submission.
REVIEW DIVISION:	Division of Metabolism and Endocrinology Products.
PHARM/TOX REVIEWER:	Indra Antonipillai
PHARM/TOX SUPERVISOR:	Karen Davis bruno
DIVISION DIRECTOR:	Mary parks
PROJECT MANAGER:	Kati Johnson

Date of review submission to Division File System (DFS): 1/16/2008

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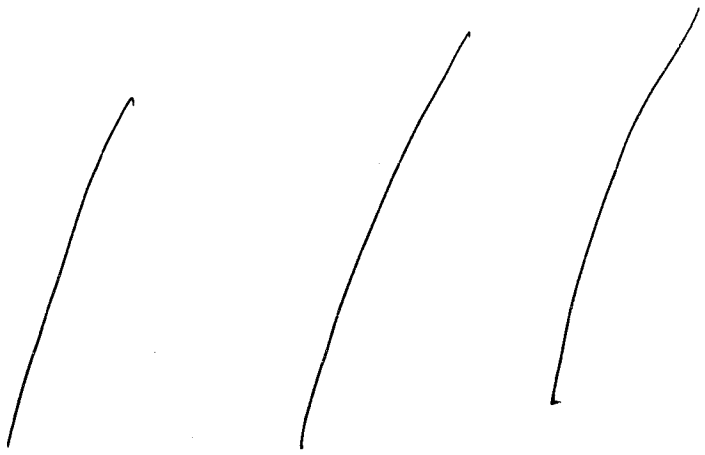
Executive Summary

1. Recommendations

A. **Recommendation on approvability**
Pharmacology recommends approval of this drug for proposed indications

B. **Recommendation for Nonclinical Studies**:
The preclinical studies are adequate to support the recommended doses up to 1000/20 mg of niacin ER/simvastatin. No further pre-clinical studies are required

C. **Recommendation on Labeling**: The preclinical sections of the label for the fixed dose combination are similar to the approved niacin extended release (Niaspan) label and Simvastatin (Zocor) label. Therefore, no major changes in the label are required. However, following changes in labeling are recommended:



II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies
Both niacin extended release (ER) and simvastatin are approved drugs for oral use in USA as Niaspan (NDA 20-381) and Zocor (NDA 19-766). Extensive nonclinical studies have been conducted with the approved zocor. No non-clinical pharmacology/toxicology studies have been conducted with Simcor, but there is extensive clinical experience with both drugs in humans.

B. Pharmacologic activity
Both are lipid lowering drugs. Niacin is a B-complex vitamin, and an antihyperlipidemic agent. Simvastatin is an HMG-CoA reductase inhibitor. Combination of two drugs will have additive effects on lowering LDL-cholesterol and increasing HDL-cholesterol in patients.

C. Nonclinical safety issues relevant to clinical use

There are no new non-clinical safety issues relevant to the clinical use with the current drug product.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-078
Review Number: 1

Sequence number/date/type of submission: 4/17/2007 (original application), it is an e-CTD submission. It is a 505(b)(2) application.

Information to sponsor: Yes ( ) No (X)

Sponsor: Abbott, Laboratories, Abbott Park, IL. Previous holder of this NDA was Kos Pharmaceuticals, which became a wholly owned subsidiary of Abbott Laboratories.

Manufacturer for drug substance: Niacin is manufactured at [redacted]
[redacted] Simvastatin is manufactured at [redacted]

Reviewer name: Indra Antonipillai, Ph.D., Pharmacology Reviewer.
Division: Division of Metabolism and Endocrinology Products (DMEP).
Review completion date: 12/20/2007

Drug:
Trade name**: simcor** It is a fixed dose combination of extended release (ER) niacin and simvastatin tablets (caplets). Both niacin ER and simvastatin are approved drug products.

Generic name: **Niacin** ER is niaspan, nicotinic acid; **simvastatin** is also called synvinolin, velastatin, simvastatinum.

Code name: The combination of niacin ER and simvastatin is also called NS tablets.

Chemical Name: Niacin's chemical name is pyridine-3-carboxylic acid, or 3-pyridinecarboxylic acid. **Simvastatin's chemical name** is 1,2,6,7,8,8a-hexahydro-B-gamma-dihydroxy-2,6-dimethyl-8-(2,2,-dimethyl-oxobutyoxy)-1-naphthaleneheptanoic acid lactone.

CAS Registry Number: **Niacin** CAS # is 59-67-6, **simvastatin** CAS # is 79902-63-9

Molecular formula/molecular weight:: Niacin is $C_6H_5NO_2$ / MW 123.11. Simvastatin: $C_{24}H_{38}O_5$, MW 418.57.

Structure: See Figures 1 and 2

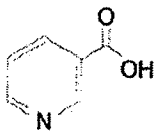


Figure 1. The Structural Formula of Niacin

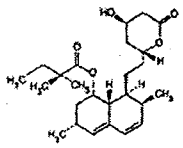


Figure 2. The Structural Formula of Simvastatin

Relevant INDs/NDAs/DMFs: Niacin (NDA 20-381) and simvastatin (NDA 19-766, zocor, Merck) are both approved drugs. IND 65,187 (Simcor), sponsor had previously submitted clinical study proposals with this combination NS tablets (or Simcor) in patients with type II hyperlipidemia under the above IND. IND 34,613 (Niaspan); DMF —— for Niacin, IND 56,027/NDA 21-249 (Advicor), DMF —— for simvastatin. DMF

Drug class: Lipid altering agent. Niacin is an antihyperlipidemic agent and soluble vitamin B; Simvastatin is total and LDL- cholesterol lowering agent, an HMG-CoA reductase Inhibitor.

Intended clinical population: The fixed dose combination drug is indicated for use in patients with primary hyper-cholesterolemia, mixed dyslipidemia and hyper-triglyceremia.

Clinical formulation: Simcor tablets are blue, capsule shaped tablets and contain extended release (ER) niacin/simvastatin in strengths of 500/20, 750/20 and 1000/20 mg

The formulation containing niacin ER/simvastatin (1000/20 mg) active drugs and inactive excipients is shown below.

Component	Quality Standard	Function	Amount per Tablet (mg)
Niacin	USP	Drug substance	1000.0
Povidone	USP		
Hypromellose	USP		
[3] Stearic Acid			
Simvastatin	USP	Drug substance	20.0
Polyethylene Glycol	NF		
Butylated Hydroxyanisole (BHA)	NF		
Color Coat			
Opadry® II Blue, 32K-10858 [4]	Mfr's standard	Colorant	
Opadry® Clear,			
Total Tablet Weight			1349.6

Components of all three tablet formulations are described below:

Table 6. Composition for Niacin ER /Simvastatin Tablets

	Component/ Excipient	Function	Tablet Strength (mg/mg) Concentrations		
			500/20	750/20	1000/20
	Niacin, USP	Active component	500	750	1000
	Hypromellose, USP				
	Povidone, USP				
	Simvastatin USP	Active component	20	20	20
	Butylated Hydroxyanisole (BHA)				
	Hypromellose, USP				
	PEG NF				
Color Coating Layer	Blue Opadry II 32K-10858	Color coating			
	Total Tablet Weight (mg)		798.9	1086.6	1349.6

Route of administration: Oral.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Studies reviewed within this submission: Both niacin ER and simvastatin used in the current application have been reviewed before under two NDAs. These two drugs are combined here in a fixed dose formulation. Sponsor has provided one niacin pharmacokinetic study in dogs and three genotox studies with niacin (two in vitro plus one in vivo). For all other studies, sponsor has provided only the prior literature on these two drugs. The safety of current drug formulation is reviewed.

Studies not reviewed within this submission: None

2.6.1 INTRODUCTION AND DRUG HISTORY

Niacin is an effective approved drug (NDA 20-381) that has been used for lipid disorders for more than 50 years it has distinctive lipid altering properties when used at gram doses. It is the most potent agent available for increasing HDL cholesterol. It also lowers levels of apoprotein B (apo B), including LDL-cholesterol, VLDL-cholesterol, triglycerides and lipoprotein a (LP[a])

Simvastatin (zocor, Merck, NDA 19-766) is an approved cholesterol lowering drug. It is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in cholesterol biosynthesis.

The pharmacology and safety profile of both agents individually have been well characterized. Both drugs have been marketed extensively for many years for oral administration. Sponsor had originally submitted an IND 65,197 to study the fixed dose combination of these two drugs.

Sponsor states that the niacin and simvastatin have complementary mechanisms of action with differing relative impacts on atherogenic particles. The addition of niacin ER to a statin has been shown to incrementally reduce LDL-C levels by up to an additional 23% while increasing HDL-C by up to an additional 27% and decreasing TG by up to an additional 30%. The expected effect of the fixed combination would be to positively impact both atherogenic and anti-atherogenic particles with reductions in LDL-C, TG (and VLDL remnants) and Lp(a), and increases in HDL-C and other Apo-A-containing particles.

2.6.2 PHARMACOLOGY

The safety profile of simvastatin (zocor, an HMG-CoA reductase inhibitor by Merck & Co.) has been well characterized, and is available from the approved NDA 19-766. Similarly, Niacin is a B-complex vitamin, and an antihyperlipidemic agent, it is available in strengths of 500, 750 and 1000 mg tablets and is recommended at doses up to 2000 mg/day (NDA 20-381).

Most of the preclinical pharmacology/toxicity studies were submitted in the original application of simvastatin (NDA 19-766). In contrast, no pharmacology/toxicology studies were conducted under niacin extended release (niaspan, NDA 20-381) as there was an extensive human experience with this drug. Therefore, no new pharm/tox studies were submitted here to support the use of this combination drug product. Following brief summary on pharmacology of both drugs was provided by the sponsor.

NIACIN PHARMACOLOGY

Primary effects of niacin appears to be decreased production of VLDL-C which may be due in part to a transient inhibitory effect of nicotinic acid on lipolysis, a decreased delivery of FFA's to the liver and a decrease in TG synthesis and VLDL-TG transport. Enhanced clearance of VLDL-C may also occur, possibly related to enhanced lipoprotein lipase. The mechanism to raise HDL-C is not clear, but may be related to a decreased clearance of apo A-I and a decreased synthesis of apo A-II.
Niacin is metabolized differently in different species; there is no perfect animal model for humans. The rabbit appears to be the best model for studying antihyperlipidemic and anti-atherosclerotic effects.

SIMVASTATIN PHARMACOLOGY

Simvastatin blocks the synthesis of cholesterol in the liver by inhibition of HMG-CoA Reductase. This enzyme catalyzes the rate-limiting step in cholesterol biosynthesis, the formation of mevalonate. Simvastatin is administered in the inactive, lactone form. After absorption, the lactone ring is readily hydrolyzed *in vivo* to form the β-hydroxyacid metabolite, a potent inhibitor of HMG-CoA reductase. Other hydroxyacid metabolites are formed in smaller quantities and are also active. Simvastatin reduces both normal and elevated low density lipoprotein cholesterol (LDL-C) concentrations. Reduction of LDL-C is primarily due to a decrease in LDL-C particles mediated via up-regulation of the LDL-C receptor consequent to inhibition of cholesterol synthesis.

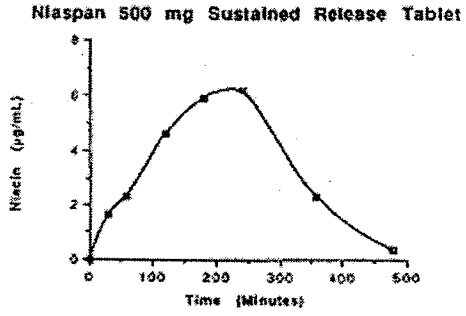
2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Niacin pharmacokinetics: The following pharmacokinetic study in dog s has been provided by the Kos Pharmaceuticals (the initial sponsor of this drug) in the current NDA.

Niacin pharmacokinetics were explored by Kos in a dog study. Nine healthy beagle dogs (7 male, 2 female) were dosed in a 3-way, single-dose crossover study.[15] In random order, the dogs received a single niacin ER tablet (500 mg Niaspan), a single-dose oral solution of niacin (500 mg niacin), and an intravenous (IV) infusion of niacin (187.4 mg infused over 3 hours). The dogs were fasted for 10 hours prior to dosing, and for 4 hours after treatment. Treatments were given approximately 1 week apart. Blood samples were collected at the same times for the tablet and solution treatments, and on a different schedule for the IV infusion. Plasma was harvested and stored frozen until analyzed for niacin and nicotinuric acid by validated methods.

Niacin plasma concentrations are shown in dogs below with the 500 mg niaspan tablet.

Niacin Plasma Concentration-Time Curves



The C_{max}, T_{max} and AUC values are shown below in dogs after administration by oral route or by iv infusions:

The mean maximum plasma concentration (C_{max}), time to peak concentration (T_{max}), and area under the concentration-time curve (AUC) values for niacin are shown in Table 1. Concentrations of nicotinuric acid were very low following the 3 formulations, and are not shown.

Table 1. Niacin Pharmacokinetics in Dog

Treatment	C_{max} (µg/mL) N=9	T_{max} (minutes) N=9	AUC (µg·mL/hr) N=9
Niacin ER tablets (500 mg niacin)	8.9	103	1639
Niacin oral solution (500 mg niacin)	86	37	10284
Niacin IV infusion (187.4 mg niacin)	86	103	691

Results are described below:

1. The extent of bioavailability of the slow release niacin formulation, Niaspan, is less than that of the reference formulations, oral solution and IV infusion. The average AUC for niacin following administration of 500 mg of Niaspan was about 16% of the AUC for the oral solution. However, the AUC of Niaspan, corrected for dose (500 mg Niaspan, 187.4 mg IV) was 89% of the AUC of the IV infusion (Table 7). There were very low levels of nicotinuric acid following the three formulations, and no conclusions based on the nicotinuric acid data are justified.

2. The comparison of the 500 mg Niaspan tablet with the niacin administered by intravenous infusion suggests that the sustained release formulation is highly bioavailable in dogs. The comparison of the Niaspan sustained release formulation with the oral solution leads to other conclusions. The absolute bioavaliability of the oral solution, based on comparison with the intravenous dose, is 568% ! This suggests that the first pass clearance of niacin is saturable, and dependent on the rate of release of the formulation. In the case of the oral solution, the liver was exposed to very high levels of niacin, whereas following administration of the intravenous infusion or the slow release formulation, the concentration presented to the liver at any time was low. This suggests that comparison of the sustained release preparation with a rapid release formulation will not be valid due to the nonlinear nature of the hepatic clearance.

These studies suggest that bioavailability of niacin ER in dogs is 89% as stated below:

Bioavailability of niacin from niacin ER tablets was 89%, whereas niacin bioavailability from oral solution was over 500%. The apparent "super" bioavailability of the niacin solution was likely due to saturation of niacin metabolism after the bolus oral solution dose, relative to the 3-hour IV infusion of a smaller dose. Results indicated that niacin is

Bioavailability of niacin from niacin ER tablets was 89%, whereas niacin bioavailability from oral solution was over 500%. The apparent "super" bioavailability of the niacin solution was likely due to saturation of niacin metabolism after the bolus oral solution dose, relative to the 3-hour IV infusion of a smaller dose. Results indicated that niacin is

completely absorbed from niacin ER tablets, and suggested significant first-pass metabolism. No conclusions could be made from the nicotinuric acid data.

2.6.6.3 Repeat-dose toxicity

Following is a brief summary of toxicity studies provided by the sponsor from the literature search or from niaspan label.

NIACIN TOXICOLOGY

Rat:

Daily feeding of 1 g/kg sodium nicotinate daily for 40 days to rats was without gross toxic effects, including body weight gain.[13] No histopathologic changes were observed in the heart, lungs, liver, spleen, kidney, gastrointestinal tract, bone marrow, or genitalia following sacrifice upon completion of the study.

In another study, in which rats were fed niacin 400 mg/kg diet for 3 months, food intake, growth rate, or liver weight did not change.[23] Plasma amino acid (methionine, homocysteine, and cysteine) and urinary methionine concentrations significantly increased, while plasma concentrations of vitamin B_{12} significantly decreased (folate concentrations were unchanged). In the same study, rats fed niacin 1000 mg/kg diet for 3 months exhibited a significant increase in body weight gain and liver weight, but not in daily food intake. Plasma and urinary concentrations of homocysteine and cysteine were further elevated in the rats by the higher dietary niacin content.

Dog:

In dogs, reports of toxic effects are inconsistent.[10] While some investigators report toxicity varying from weight loss to bloody feces, convulsions, gastric erosions, and death, others report no toxicity. In 2 dogs receiving 2 g niacin orally daily (in capsules, dose ~ 140 mg/kg), significant toxic effects leading to mortality were observed after 13 and 20 days.[22] However, 4 additional dogs given smaller doses by mouth (niacin 0.06 to 1 g/day, except on weekends) for 8 weeks appeared in good health other than minor abnormalities in urinalysis, and had gained weight. A separate study reported loss of body weight in dogs receiving niacin 100 mg/kg/day for 8 and 32 months.[10]

The no-observed-adverse-effect level (NOAEL) for dogs can be considered as >100 mg/kg, equivalent to 7g/day for a 70 kg human. The maximum recommended niacin dose is 2g/day for Niacin ER/simvastatin tablets.

Thus, primary information on niacin toxicity has relied on extensive experience in humans. Most studies are very old. 1 g/kg was well tolerated in mice; some animals died at 3 g/kg. Similar findings were found with I.V. administration of 1 g/kg in rats. In dogs, 2 g/kg were well tolerated.

LD_{50}:
~ 4500 mg/kg for mice
~3500 mg/kg in rats and guinea pigs.

Death was preceded by clonic convulsions at lethal or near-lethal doses. Animals either died or recovered without apparent lasting effects.

Few studies are available on multiple dose toxicity of niacin. There are some effects that are inconsistent. Some studies report 0.1-2% niacin administered in the diet produced fatty livers, while other experiments did not confirm this. In dogs, some studies report weight loss, bloody feces, convulsions and death with related gastrointestinal erosions and CNS effects; other studies show no toxicity. In one study, dogs administered 100 mg/kg/day for 8 and 32 months resulted in weight loss. However, none of the studies described were standard toxicology studies.

Following is a brief summary of toxicity studies provided by the sponsor from the literature search or from simvastatin (zocor) label.

SIMVASTATIN TOXICOLOGY

Rat

Administration of simvastatin 15 mg/kg/day in the diet to juvenile rats (3 weeks of age) caused abrupt onset of myopathy within 10 days and increased creatine kinase (CK) levels at the time of myopathy.[41] Muscle tissue with fast twitch type II fibers was more affected than muscle with slow twitch type I fibers. The simvastatin dose that caused damage was much lower for young rats than previously reported for adult rats.

A subsequent publication reported that myotoxicity in adult rats after simvastatin (80 mg/kg/day) via oral gavage occurred after approximately 9 to 12 days of dosing.[42] Higher doses did not appear to shorten the time to a histologic lesion. Type I muscle fibers were usually spared from necrosis, while type IIA, IID and IIB fibers were increasingly more sensitive to necrosis.

Evaluation of rat skeletal muscle fibers *in vivo* and *in vitro* suggested that muscle toxicity from HMG CoA-reductase inhibitors is due to an intracellular action mediated by the inhibition of muscle cholesterol synthesis.[43] The investigators postulated that because simvastatin is lipophilic, it is able to penetrate the muscle fiber via simple diffusion and may subsequently interfere with muscle cholesterol synthesis, eventually altering the lipid environment and the membrane microviscosity of striated fibers.

Liver and thyroid weights were increased by up to 66% and 83%, respectively, in female rats receiving simvastatin (30 to 180 mg/kg/day) for 14 weeks; lesser increases were seen in males.[44] To explore the mechanism of thyroid changes induced by simvastatin, female rats were treated with simvastatin, phenobarbital (positive control), or vehicle for 5 weeks. Simvastatin and phenobarbital (oral gavage, each at 50 mg/kg twice daily) significantly increased liver weight, while only phenobarbital significantly increased thyroid weight. Thyroid follicular cell hypertrophy was seen in most of the simvastatin-treated animals and in all phenobarbital-treated animals. Serum thyroid stimulating hormone (TSH) levels were elevated by both treatments, and thyroxine levels were decreased. The increased clearance of thyroxine in simvastatin-treated animals was not associated with enzyme induction, but may have been related to the observed increase in functional liver mass. The thyroid changes induced by simvastatin were likely the result of increased thyroxine clearance and the consequent stimulation of this gland from increased serum TSH.

Cataracts have been seen in female rats following 2 years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively).[30] Cataracts have also been observed in dogs after 3 months at 90 mg/kg/day (19 times the human AUC at 80 mg/day) and after 2 years at 50 mg/kg/day (5 times the human AUC at 80 mg/day).

Dog

Increases in transaminase levels were observed in dogs given simvastatin 30 mg/kg/day for 28 weeks and rats given 90 mg/kg/day for 3 months. However, the increases in transaminases occurred at doses comparable with 10 and 6 times the human dose, based on peak plasma levels.[31]

Optic nerve degeneration was seen in healthy dogs treated for 14 weeks at simvastatin 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean drug level in humans taking 80 mg/day.[30] A chemically similar drug in this class also produced optic nerve degeneration in dogs at 60 mg/kg/day.

Central nervous system vascular lesions with perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels have been seen in dogs treated with simvastatin at doses of 360 mg/kg/day.[30] This dose produced mean plasma drug levels that were approximately 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with other HMG-CoA reductase inhibitors.

2.6.6.4 Genetic toxicology

Genotox studies with niacin

The following genotox studies are provided by the Kos Pharmaceuticals (the initial sponsor of this drug) and was previously submitted to NDA 20-381 (Niaspan, annual report dated 9/22/2003).

Two *in vitro* studies and 1 *in vivo* study were performed by Kos to further assess the mutagenicity of niacin. All 3 studies were conducted in compliance with current GLP standards. These studies confirm no mutagenic potential for niacin, and are outlined below.

KOS STUDY NO. 001-02-03-NC

In a thymidine kinase (TK) +/- mouse lymphoma mutagenesis assay, niacin was evaluated at concentrations over the range of 39 to 5000 µg/mL with and without metabolic activation for 4 hours.[25] Cell cultures exposed to niacin at 313 to 5000 µg/mL were cloned and used for mutation selection. All responses were clearly negative, indicating no mutagenic response.

In a confirmatory assay, cultures were incubated for 24 hours without metabolic activation at niacin concentrations of 39 to 5000 µg/mL. The results were again negative.

KOS STUDY NO. 001-01-03-NC

Niacin was also tested *in vitro* in a *Salmonella typhimurium/Escherichia coli* plate incorporation preincubation mutation assay.[26] Niacin concentrations of 50 to 5000 µg/plate were tested by the incorporation method, with and without metabolic activation. The results were negative.

Since the definitive mutation assay was negative, a confirmatory mutation assay was conducted using the preincubation method. This test confirmed the results of the definitive assay.

The results of the Mutation Assays indicate that the test article did not induce any significant increase in the number of revertant colonies for any of the tester strains in the presence or absence of induced rat liver S-9. The positive and negative controls fulfilled the requirements of the test.

Summaries of the results of the definitive Mutation Assay are presented in Tables 3 & 4 (without and with activation)

TABLE 3
SALMONELLA TYPHIMURIUM/ESCHERICHIA COLI PLATE INCORPORATION MUTATION ASSAY
MUTATION ASSAY RESULTS - WITHOUT ACTIVATION

SPONSOR: Kos Pharmaceuticals, Inc.
EXPERIMENT NO.: B-1
TEST ARTICLE: Niacin
STUDY NO.: 0802-2140
SOLVENT: DMSO
CONC. IN: µg/plate

S. typhimurium		Average No. of Revertants Per Plate						
		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: TA98	REVERTANTS	591	23	33	24	24	20	23
DATE PLATED:	STD. DEV.	41	3	2	2	3	2	1
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.360E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA100	REVERTANTS	397	50	53	66	56	43	39
DATE PLATED:	STD. DEV.	13	9	11	13	12	3	3
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.140E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1535	REVERTANTS	338	18	16	20	17	17	17
DATE PLATED:	STD. DEV.	10	4	4	2	3	2	2
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 7.300E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1537	REVERTANTS	144	10	10	12	10	11	10
DATE PLATED:	STD. DEV.	24	3	5	2	2	3	1
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.040E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

E. coli		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: WP2 uvrA	REVERTANTS	466	10	16	16	13	11	16
DATE PLATED:	STD. DEV.	24	2	3	1	5	8	3
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 6.220E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

NL = Normal, healthy microcolony lawn. NP = No precipitate.

APPEARS THIS WAY
ON ORIGINAL

TABLE 4
SALMONELLA TYPHIMURIUM/ESCHERICHIA COLI PLATE INCORPORATION MUTATION ASSAY
MUTATION ASSAY RESULTS - WITH S-9 ACTIVATION

SPONSOR: Kos Pharmaceuticals, Inc. — STUDY NO.: 0802-2140
EXPERIMENT NO.: 8-1 SOLVENT: DMSO
TEST ARTICLE: Niacin CONC. IN: ug/plate

S. typhimurium		Average No. of Revertants Per Plate						
		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: TA98	REVERTANTS	507	37	36	30	33	34	31
DATE PLATED:	STD. DEV.	27	1	11	8	5	10	4
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.360E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA100	REVERTANTS	495	57	60	57	65	56	54
DATE PLATED:	STD. DEV.	42	6	10	5	2	5	9
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.140E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1535	REVERTANTS	119	16	14	15	15	15	16
DATE PLATED:	STD. DEV.	16	4	6	2	7	4	5
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 7.300E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1537	REVERTANTS	41	13	13	13	10	12	12
DATE PLATED:	STD. DEV.	3	1	3	3	1	3	5
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.040E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

E. coli		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: WP2 uvrA	REVERTANTS	104	16	13	15	17	17	13
DATE PLATED:	STD. DEV.	14	3	4	3	2	1	1
05/21/03	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 6.220E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

NL = Normal, healthy microcolony lawn. NP = No precipitate.

APPEARS THIS WAY
ON ORIGINAL

Summaries of the results of the confirmatory Mutation Assay (B-2) are presented in Tables 5 & 6 (without and with activation)

TABLE 5
SALMONELLA TYPHIMURIUM/ESCHERICHIA COLI PREINCUBATION MUTATION ASSAY
MUTATION ASSAY RESULTS - WITHOUT ACTIVATION

SPONSOR: Kos Pharmaceuticals, Inc.
EXPERIMENT NO.: B-2
TEST ARTICLE: Niacin
STUDY NO.: 0802-2140
SOLVENT: DMSO
CONC. IN: µg /plate

S. typhimurium		Average No. of Revertants Per Plate						
		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: TA98	REVERTANTS	429	25	24	23	10	14	22
DATE PLATED: 5/27/03	STD. DEV.	39	3	3	2	4	6	26
	LAWN	NL	NL	NL	NL	NL	SR	MR
CELLS SEEDED: 6.460E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA100	REVERTANTS	419	45	48	60	12	8	0
DATE PLATED: 5/27/03	STD. DEV.	4	7	11	5	1	1	0
	LAWN	NL	NL	NL	NL	NL	SR	AB
CELLS SEEDED: 5.380E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1535	REVERTANTS	295	9	14	9	14	10	4
DATE PLATED: 5/27/03	STD. DEV.	18	4	2	3	2	3	4
	LAWN	NL	NL	NL	NL	NL	SR	MR
CELLS SEEDED: 5.700E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1537	REVERTANTS	138	8	11	9	8	6	9
DATE PLATED: 5/27/03	STD. DEV.	6	2	4	2	1	2	16
	LAWN	NL	NL	NL	NL	NL	SR	MR
CELLS SEEDED: 5.860E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

E. coli		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: WP2 uvrA	REVERTANTS	464	15	12	17	21	20	0
DATE PLATED: 5/27/03	STD. DEV.	37	5	4	4	1	3	0
	LAWN	NL	NL	NL	NL	NL	NL	AB
CELLS SEEDED: 1.126E+08	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

NL = Normal, healthy microcolony lawn. NP = No precipitate. AB = Absence of microcolony lawn.
SR = Slight reduction of the microcolony lawn MR = Marked reduction of the microcolony lawn.

APPEARS THIS WAY
ON ORIGINAL

TABLE 6
SALMONELLA TYPHIMURIUM/ESCHERICHIA COLI PREINCUBATION MUTATION ASSAY
MUTATION ASSAY RESULTS - WITH S-9 ACTIVATION

SPONSOR: Kos Pharmaceuticals, Inc.
EXPERIMENT NO.: 6-2
TEST ARTICLE: Niacin
STUDY NO.: 0802-2140
SOLVENT: DMSO
CONC. IN: µg /plate

S. typhimurium		Average No. of Revertants Per Plate						
		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: TA98	REVERTANTS	464	22	27	32	25	24	31
DATE PLATED: 5/27/03	STD. DEV.	17	1	5	4	5	3	4
	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 6.460E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA100	REVERTANTS	375	48	49	54	55	62	48
DATE PLATED: 5/27/03	STD. DEV.	17	5	3	8	11	5	8
	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.380E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1535	REVERTANTS	57	10	12	13	10	10	8
DATE PLATED: 5/27/03	STD. DEV.	4	1	2	2	4	5	3
	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.700E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP
STRAIN: TA1537	REVERTANTS	31	10	12	10	10	13	13
DATE PLATED: 5/27/03	STD. DEV.	8	3	2	3	2	6	3
	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 5.860E+07	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

E. coli		Positive Control	Solvent Control	Concentration per plate 50	100	500	1000	5000
STRAIN: WP2 uvrA	REVERTANTS	124	17	16	17	15	19	16
DATE PLATED: 5/27/03	STD. DEV.	8	3	3	4	1	4	8
	LAWN	NL	NL	NL	NL	NL	NL	NL
CELLS SEEDED: 1.126E+08	PRECIPITATE	NP	NP	NP	NP	NP	NP	NP

NL = Normal, healthy microcolony lawn. NP = No precipitate.

Conclusions:

Under the conditions of this study, Niacin was negative in the *Salmonella typhimurium/Escherichia coli* Plate Incorporation/Preincubation Mutation Assay.

APPEARS THIS WAY
ON ORIGINAL

KOS STUDY NO. 001-03-03-NC

The micronucleus assay was performed *in vivo* to assess the potential for niacin to induce micronucleated polychromatic erythrocytes (MPCE) in the bone marrow cells of CD-1 mice.[27] Niacin or vehicle control was administered by oral gavage as a single dose. In the definitive test, mice received niacin at dose levels of 500 to 2000 mg/kg body weight. Niacin was negative in this test: there was no statistically significant increase in the number of MPCE in the niacin-treated groups of mice at any dose level or harvest time as compared with the concurrent vehicle control groups. Therefore, niacin is not considered to be a clastogenic agent.

Summary results are shown below in male and female mice:

Micronucleus assay in male mice

SUMMARY OF MICRONUCLEUS ASSAY RESULTS
Mean Percent PCE and Incidence of
MPCEs in Bone Marrow of Male Mice
Orally Administered Niacin

Study No.: 0802-1521 **Vehicle: 0.5% Methylcellulose (10 mL/kg)**

Time (hours)	Dose (mg/kg)	Cell Counts		PERCENT PCE	Change in %PCE***	MPCE for 2000 PCE
		PCE	NCE			
24	Vehicle	95	105	47.6	-	0.8
24	500	100	100	50.0	5.0 %	0.8
24	1000	105	95	52.3	9.9 %	0.2
24	2000	95	105	47.7	0.2 %	1.4
24	CP*	95	105	47.7	0.2 %	79.0 **
48	Vehicle	104	96	52.1	-	0.0
48	500	105	95	52.7	1.2 %	0.0
48	1000	104	96	52.1	0.0 %	0.0
48	2000	106	94	52.9	1.5 %	0.2

NOTE: Five animals were used per group.
* CP was used as positive control and was dosed at 80 mg/kg.
** These results are considered statistically significant because the p-value is less than or equal to 0.025.
*** Change of Percent PCE in comparison with concurrent vehicle, calculated by the following formula:

$$\frac{\text{Percent PCE for Test Dose} - \text{Percent PCE for vehicle}}{\text{Percent PCE for vehicle}} \times 100$$

APPEARS THIS WAY
ON ORIGINAL

Micronucleus assay in female mice

SUMMARY OF MICRONUCLEUS ASSAY RESULTS
Mean Percent PCE and Incidence of
MPCEs in Bone Marrow of Female Mice
Orally Administered Niacin

Study No.: 0802-1521 **Vehicle: 0.5% Methylcellulose (10 mL/kg)**

Time (hours)	Dose (mg/kg)	Cell Counts		PERCENT PCE	Change in %PCE***	MPCE for 2000 PCE
		PCE	NCE			
24	Vehicle	120	80	59.8	-	0.6
24	500	123	77	61.5	2.8 %	1.2
24	1000	119	81	59.4	-0.7 %	0.4
24	2000	119	81	59.5	-0.5 %	0.2
24	CP*	95	105	47.7	-20.2 %	82.6 **
48	Vehicle	120	80	60.2	-	0.4
48	500	120	80	60.2	0.0 %	0.4
48	1000	120	80	60.1	-0.2 %	0.4
48	2000	126	74	62.9	4.5 %	0.2

NOTE: Five animals were used per group.
* CP was used as positive control and was dosed at 80 mg/kg.
** These results are considered statistically significant because the p-value is less than or equal to 0.025.
*** Change of Percent PCE in comparison with concurrent vehicle, calculated by the following formula:

$$\frac{\text{Percent PCE for Test Dose} - \text{Percent PCE for vehicle}}{\text{Percent PCE for vehicle}} \times 100$$

Genotox studies with simvastatin: Simvastatin is not mutagenic (NDA 19-766).

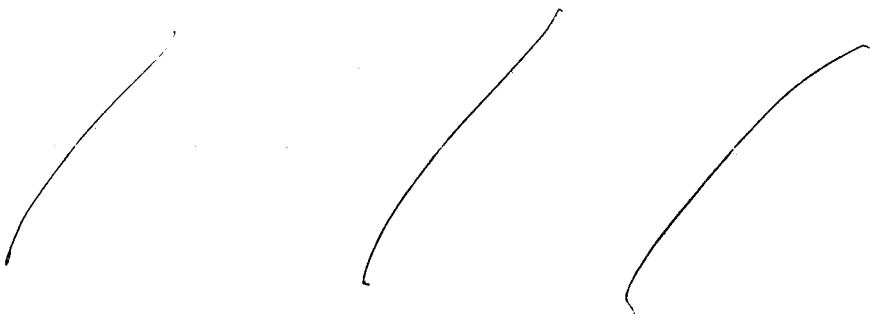
2.6.6.5 Carcinogenicity/2.6.6.6 Reproductive and developmental toxicology

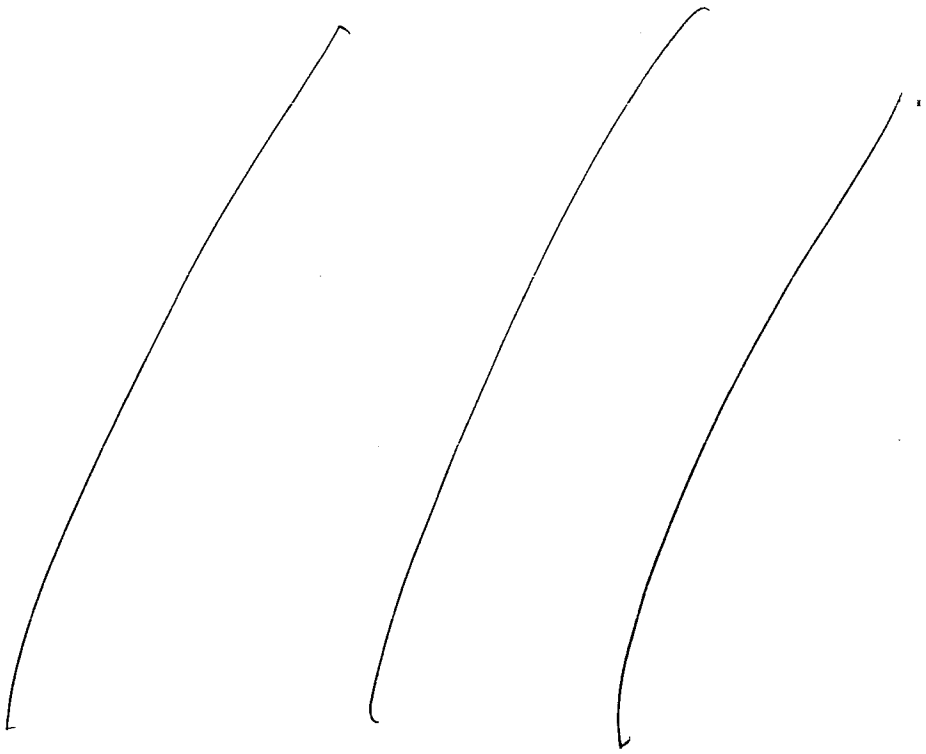
No studies regarding carcinogenicity, mutagenicity or impairment of fertility have been conducted with Simcor. The proposed labeling text

Niacin given to mice for a lifetime as 1% solution in drinking water (approximately 6-8 times the human dose of 3000 mg/day based on mg/m^2) was not carcinogenic. Niacin was negative in Ames test. No studies on impairment of fertility have been performed with Niacin. There is no information on reproductive or carcinogenicity studies with niacin. It is unknown whether niacin at doses used for lipid disorders can cause fetal harm when administered to pregnant women, or whether it affects reproductive capacity. However, carcinogenicity, mutagenicity or impairment of fertility and repro-tox studies have been conducted with Simvastatin. Simvastatin is indicated as pregnancy category X in the label and also in the Simcor label. Simvastatin carcinogenicity studies have indicated increased incidence of liver carcinomas and adenomas, pulmonary adenomas, and adenomas of the harderian gland, and thyroid follicular cell.

Fixed dose combination drug product formulation (Simcor)

As for excipients are concerned in the fixed dose combination of niacin ER +simvastatin (or Simcor), butylated hydroxyanisole (BHA) was a concern. Sponsor explains that BHA (chemically known as 3-tertiary-butyl-4-hydroxyanisole,





Butylated [redacted], the current fixed dose combination drug product (simcor) is present at doses of [redacted] tablet, and this amount has been used orally in other approved drug products in a tablet with [redacted] (from FDA's Inactive Ingredient Search on approved Drug Products).

OVERALL SUMMARY AND EVALUATION:

The drug Simcor is a combination of two drugs, niacin ER and simvastatin. Niacin is a B-complex vitamin. Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. It lowers elevated total and LDL cholesterol levels, reduces triglycerides, and increases HDL cholesterol. Simvastatin is a cholesterol-lowering drug; it is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme that catalyzes the rate-limiting step in cholesterol synthesis. Both drugs have been marketed extensively for many years, for oral administration. The proposed doses in combination have been approved for use as the individual agents. Simcor with its broad spectrum, has effects on all major lipoprotein classes (LDL-C, HDL-C, TG, Lipoprotein a). Simcor's indication is to lower lipids in individuals with primary hypercholesterolemia, mixed dyslipidemia, and hyper-triglyceridemia.

The Niaspan NDA (NDA 20-381) was approved in July 28, 1997. No preclinical pharmacology was required for the above NDA as there was extensive human experience prior to approval. Similarly simvastatin has been marketed since 1988 (NDA 19-766) and is approved at doses up to 80 mg/day. There is clinical experience with this drug in adults, major toxicities are known, and are associated with myopathy and liver dysfunction. Thus, proposed doses in the fixed dose combination in Simcor have been approved for use as the individual agents. Note that a niacin ER/lovastatin fixed dose combination drug product (Advicor) has been marketed since 2001 (NDA 21-249)

Niacin ER/simvastatin tablets are intended for oral use and are composed of a niacin ER [redacted] with an immediate release [redacted] simvastatin. The niacin ER [redacted] is unchanged from the existing marketed dosage form, which was originally approved in NDA 20-381 [redacted] is also used in the Advicor product (niacin ER /lovastatin), which was approved in NDA 21-249.

Safety Evaluation: The sponsor has provided the brief summary of available pharmacology and toxicity of both active agents. The combined use of niacin + simvastatin would supposedly provide a beneficial pharmacological effect for the treatment of dyslipidemia and has been studied in clinical studies.

In human pharmacokinetic studies, the bioavailability of niacin from the administration of 2x500/20 and 2x1000/20 niacin ER/simvastatin formulations were comparable to that from co-administration of the same doses of individual components (i.e. niacin ER and simvastatin alone). Similarly the bioavailability of niacin from 2x1000/20 niacin ER/simvastatin treatment was also comparable to 2x1000 mg niacin ER.

Internal comments: Since both are approved drugs, their safety profile has been individually well characterized, and is used at approved doses, the approval of this application is recommended.

External Recommendation: From the preclinical standpoint, approval of this application is recommended, pending labeling changes

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: NDA Arch
HFD-510/davisbruno/antonipillai/chowdhury/kati johnson
File name: nda22078 (fixed dose combination of niacin+simvastatin)

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

/s/

Indra Antonipillai
1/16/2008 12:32:09 PM
PHARMACOLOGIST

Pharmacology recommends approval of this application pending labeling chang

Approval of this application is recommended pendng labeling changes.

Karen Davis-Bruno
1/16/2008 01:14:01 PM
PHARMACOLOGIST

NDA 22-078/Filing

Signed off in DFS on 6/14/07

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 22-078: This NDA is a 505(b)(2) application.
Submission date: 4/17/2007
Sponsor: Abbott Laboratories, Abbott Park, L.
Drug: Simcor tablets which are niacin extended release (ER)/simvastatin combination tablets, in strengths of 500/20, 750/20, 1000/20 mg of niacin ER/simvastatin respectively.

Introduction: This tablet is a combination of two approved drug products, niacin ER (an antihyperlipidemic agent and vitamin) and simvastatin (an HMG-CoA reductase inhibitor). Niacin (NDA 20-381) and simvastatin (NDA 19-766, zocor, Merck) are both approved drugs. The combination product in the current NDA is proposed for patients with primary hypercholesterolemia requiring modification of lipid profiles including hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia.

Since both are approved drugs, no new toxicity studies are required with this combination. Sponsor has provided non-clinical studies based on literature or approved information on these drugs.

The niacin ER/simvastatin tablet is composed of a niacin ER with simvastatin. The niacin ER is unchanged from the existing marketed dosage form, which was originally approved in NDA 20-381. is also used in the Advicor product (niacin ER/lovastatin), which was approved on 5/22/2001 (NDA 21-249). However, simvastatin solubility in water was very low (1.4 µg/ml).

The niacin ER/simvastatin formulation uses standard pharmaceutical excipients, which are hypromellose, stearic acid, PEG, Opadry Blue, and BHA (chosen due to

Sponsor states that excipients/ingredients used in the combination tablet formulation have been commonly used in other drug products. The chemist on this review has no particular concerns about the excipients, impurities or degradants. However as indicated earlier simvastatin has low solubility (1.4 µg/ml in water).

ITEM: NDA 21-078	**YES**	**NO**	**COMMENT**
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		

2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	Yes		Both are approved drugs, and since most of the preclinical pharmacology/toxicity studies were conducted in the original application of niacin (NDA 20-381) and simvastatin, no new pharm/tox studies were submitted here. The sponsor has provided cross references to approved applications such as NDA 20-381 for Niaspan, and NDA 21-249 for Advicor (or fixed dose combination of niacin and simvastatin). The niacin — is equivalent to Niaspan approved in USA in 1997. Niacin is supposedly a most potent agent available for increasing HDL cholesterol and simvastatin is approved for reducing LDL cholesterol.
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	Yes		Have electronic files of the carcinogenicity studies been submitted for statistical review? No carcinogenicity or other preclinical studies have been conducted with Simcor, as both drugs in Simcor (niacin ER and simvastatin) are approved drug products.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (i.e., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			Yes. As indicated earlier, all non-clinical studies with niacin or simvastatin have been conducted under the approved NDAs for niacin (NDA 20-381 and NDA 21-249) or simvastatin (NDA 19-766), and these were adequately designed.

6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (i.e., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	Yes		Sponsor has used basically the same formulation in the current product, as used previously for approved niacin or Advicor (i.e. niacin + lovastatin fixed dose combination) 
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	Yes		In the previous approved applications the route of administration was oral, like in the current application
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	Yes		Yes, the draft labeling submitted in general is similar to the approved niacin or simvastatin label, and data express human dose multiples in mg/m^2 or AUC levels.

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	Yes		

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

/s/

Indra Antonipillai
6/14/2007 08:54:49 AM
PHARMACOLOGIST
From the pharm/tox point of view this NDA 22-078 is filable
The application is filable

Karen Davis-Bruno
6/14/2007 09:08:03 AM
PHARMACOLOGIST