CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-961

PHARMACOLOGY REVIEW

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:	**21-961**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**8/3/05**
PRODUCT:	**Simvastatin**
INTENDED CLINICAL POPULATION:	**treatment of hypercholesterolemia**
SPONSOR:	**Synthon**
DOCUMENTS REVIEWED:	**Vol. 32 (electronic)**
REVIEW DIVISION:	**Division of Metabolism & Endocrine Drugs**
PHARM/TOX REVIEWER:	**Davis-Bruno**
DIVISION DIRECTOR:	**Parks**
PROJECT MANAGER:	**Simoneau**

Date of review submission to Division File System (DFS): 2/14/06

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval (AP)

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: Sponsor's proposed labeling is acceptable

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: The nonclinical assessment of simvastatin relies on the FDA's previous determination of safety and effectiveness of Zocor (simvastatin) from the market application approved in 1991 (NDA 19-766) and supplement S028 approved in 1998 for the 80 mg dose. Synthon proposes bioequivalence to Zocor to support this application for an oral disintegrating tablet (ODT) formulation.

B. Pharmacologic activity: HMG CoA reductase inhibition.

C. Nonclinical safety issues relevant to clinical use: see product labeling

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-961
Review number: 1
Sequence number/date/type of submission: 000, 8/2/05
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Synthon Pharmaceuticals; Research Triangle Park, NC
Manufacturer for drug substance: [redacted] b(4)

Drug:

Trade name: Simvastatin ODT
Generic name: simvastatin
Chemical name:

[1*S*-[1α,3α,7β,8β(2*S**,4*S**),8aβ]]- [redacted]

2,2-dimethyl- [redacted] ,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4- hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenylester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),8aβ]]

CAS registry number: 79902-63-9
Molecular formula/molecular weight: 418.57 b(4)

Structure: [redacted]

Relevant INDs/NDAs/DMFs: IND 70,964; Zocor 19-766

Drug class: HMG CoA reductase inhibitor (statin)

Intended clinical population: treatment of hypercholesterolemia/hyperlipemia

Clinical formulation: 10, 20, 40, 80 mg disintegrating tablet

Table 6: Composition per Tablet Strength of Simvastatin 10 mg, 20 mg, 40 mg, and 80 mg Orally Disintegrating Tablets.

Ingredients	10 mg (mg)	20 mg (mg)	40 mg (mg)	80 mg (mg)
Simvastatin [1]	10.00	20.00	40.00	80.00
Butylated hydroxyanisole [2]				
Povidone				
Crospovidone				
Weight of				
hydroxypropylcellulose*				
Silicified microcrystalline cellulose [3]*				
Mint menthol*				
Sucralose				
Iron oxide yellow				
Iron oxide red				
Weight of blend				
Glyceryl behenate*				
Total mass per tablet				

* produced from a plant (vegetable) source.

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These excipients are listed in the CDER Inactive Ingredient guide and are present in the drug product at or below the levels listed for other approved products. Sucralose (acesulfame) is listed in Toxline as having an acceptable daily intake (ADI) 15 mg/kg as a food additive for human consumption.

Table 1: Synthon's Specifications for the Drug Substance, Simvastatin

Tests	Specifications
Appearance	White or almost white powder
IR spectrum	The same as the reference standard.
UV absorption (0.001% (m/V) in acetonitrile)	The same as the reference standard.
HPLC retention time	The same as the reference standard
Specific optical rotation (dry basis) $[\alpha]_{D,20}$ (0.5 % (m/V) in acetonitrile)	Between +285 ° and +298 °
Loss on drying (60°C, vacuum)	≤ 0.5 %
Residue on ignition	≤ 0.1 %
Heavy metals	≤ 0.002 %
Assay SVT (HPLC, dry basis)	
Residual solvents (GC):	
Impurities (HPLC):	
Lovastatin + Epilovastatin (LVS)	≤ 1.0 %
Largest unidentified impurity	
Total impurities (excl. LVS)	≤ 1.0 %
Antioxidant:	
Particle Size Distribution:	

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According to CMC the impurity profile is consistent with the USP monograph which is based on the innovator Zocor.

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-961 are owned by Synthon or are data for which Synthon has obtained a written right of reference. Any information or data necessary for approval of 21-961 that Synthon does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Synthon does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-961.

Studies reviewed within this submission: none submitted, 505(b)2 applicaton

Studies not reviewed within this submission: N/A
Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

Mechanism of action: competitive inhibitor of HMG CoA reductase. Simvastatin is a synthetic derivative of lovastatin, a fermentation product of *Aspergillus terreus*. Simvastatin is an inactive lactone prodrug that is converted to its hydroxyacid active form in order to elicit its mechanism of action as a HMG CoA reductase inhibitor. This microsomal enzyme is the rate limiting step in cholesterol synthesis which catalyzes the conversion of HMG-CoA to mevalonic acid.

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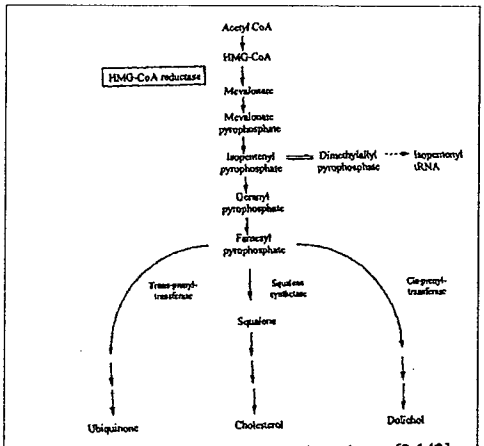

Figure 2.1: The cholesterol biosynthetic pathway [2,143].

Drug activity related to proposed indication: Competitive inhibition of reductase leads to 1) inhibition of sterol synthesis, 2) induction of HMG-CoA reductase protein and mRNA and 3) induction of LDL receptor transcription and activity. Enhanced clearance of LDL and precursors from the circulation is the primary mechanism of lowering cholesterol. However reduced hepatic production and secretion of lipoproteins may explain the observation of simvastatin lowering LDL in homozygous FH patients who lack functional LDL receptors.

The anti-atherosclerotic activity is attributable to inhibition of vascular smooth muscle and vascular endothelial cell proliferation (fibroblasts and myoblasts as well). In vascular smooth muscle cells, simvastatin is implicated in apoptosis as a result of increasing cytosolic free calcium by increasing intracellular calcium release. Simvastatin prevented atherosclerosis in cholesterol fed rabbits, but not in homozygous or heterozygous Watanabe Heritable Hyperlipidemic (WHHL) rabbits.

2.6.2.3 Secondary pharmacodynamics

Simvastatin has been shown to inhibit sterol synthesis in extrahepatic cells (i.e. eye lens, umbilical vascular endothelial cells, retinal pigment epithelium, corneal fibroblasts and granulose cells).

2.6.2.4 Safety pharmacology

Simvastatin or its active β-hydroxy acid form are well tolerated in the human cardiovascular, respiratory and GI systems in humans.

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Simvastatin is well absorbed in rats, dogs and humans, but the active form is poorly bioavailable. Protein binding is comparable in dog and man. There is a high hepatic extraction, extensive biliary excretion and relatively poor extrahepatic tissue penetration of the β-hydroxyacid. At least eight metabolites are identified across dog, rat and human species. CYP3A is the major enzyme responsible for simvastatin metabolism.

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic drug interactions

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

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2.6.4.10 Tables and figures to include comparative TK summary

Table 3.1: Pharmacokinetic parameters in mice, rats, dogs, monkeys and human subjects [42,84,126,143].

Species	Dose (mg/kg/day)	C_{max} (ng/ml)[1]	x human therap. dose[6]	AUC_{0-24h} (ng.h/ml)[1]	x human therap. dose[6]	T_{max} (h)	Protein binding (%)
Mouse	1			410 (M)			
	10			3700 (M)			
	25[2]	750	6	500	1		
	100[2]	2100	18	2300	6		
	400[2]	3000	25	5200	13		
Rat	25	2300					
		7800					
	50[2]	2000 (M)	17	4400	11	1	
		6000 (F)	50	14000	34		
	100[2]	2000 (M)	17	10000	24		
		4500 (F)	38	16000	39		
Dog	2[3]	70	0.6			40-60 min	97-99[7]
	10[3]	160	1	1100	3		
	50[3]	850	7	3300	8		
	90[3]	2200	18	12000	29		
	180[3]	2000	17	4000 (0-4h)			
	360[3]	2300	19	5400 (0-4h)			
Monkey	2[4]	3	0.03	3	0.01		
	10[4]	11	0.1	44	0.1		
	25[4]	25	0.2	93	0.2		
Human	40 mg	60		152			97-99[7]
	80 mg[5]	120		410			
	100 mg	120		600		2 (1.3-2.4)	

[1] Total inhibitory activity (concentration or AUC of both lactone and open acid).
[2] Dose was given for 8 days.
[3] Dose was given for 2 years.
[4] Dose was given for 12 weeks.
[5] Dose was given for 7 days.
[6] The human therapeutic dose was taken as 80 mg for one day.
[7] For the lactone form; for the acid form the values are 93-95%.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Liver vacuolization and necrosis and forestomach (nonglandular stomach) hyperplasia with discoloration and thickening are the target organs in rodents following acute oral simvastatin administration.

Subchronic/Chronic simvastatin dosing revealed the following target organ toxicity by test species:

Rat: increased hepatic and thyroid weight, forestomach acanthosis, edema, hyperkeratosis, inflammatory cell infiltration. Forestomach lesions have been associated with the mechanism of action of simvastatin. Periportal hepatocellular atypia was seen only in rats. Cataracts in females following two years treatment at ≥50 mg/kg/day (≥22-times the human AUC at 80 mg/day).

Hamster: Increased AST, ALT with hepatic lesions which were prevented by coadministration of mevalonic acid

Rabbit: liver necrosis, gallbladder necrosis, kidney tubular necrosis which were prevented by coadministration of mevalonic acid

Dog: Subcapsular lenticular opacity, degeneration of testes. Optic nerve degeneration was seen in dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, at 12-times mean plasma drug levels at the maximum human dose of 80 mg/day. Other drugs in the class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs dose dependently at 60 mg/kg/day, or 30-times higher than the human exposure (based on enzyme inhibitory activity) at the maximum human dose. Vestibulocochlear Wallerian-like degeneration and retinal gangion cell chromatolysis occurred in dogs treated for 14-weeks at 180 mg/kg/day. CNS vascular lesions (perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels) were seen in dogs treated at 360 mg/kg/day, at 14-times higher than mean plasma drug levels in humans given 80 mg/day. Cataracts were seen after three months treatment at 90 mg/kg/day (19-times human exposure) and at 50 mg/kg/day after two years treatment (5-times human exposure).

Myopathy is a class effect which was potentiated by coadministration of cyclosporine A, altering the clearance and increasing tissue exposure to simvastatin. Cholestasis associated with coadministration of cyclosporine A and HMG CoA reductase inhibitors is thought to result from decreased elimination and hence elevated systemic exposure.

2.6.6.4 Genetic toxicology no evidence of mutagenicity was observed in an Ames assay with or without rat S9, no evidence of damage to genetic material was noted in an in vitro alkaline elution assay with rat hepatocytes, a V-79 forward mutation study, and in vitro chromosome agerration study in CHO cells or an in vitro chromosomal aberration assay in bone marrow was negative.

2.6.6.5 CARCINOGENICITY

Lung and Harderian gland adenomas at 4-8 times human exposure in mice. In rats thyroid follicular cells tumors were observed and attributed to increased T4 clearance and consequent stimulation of the thyroid gland by increased serum TSH. Liver tumors seen in rats were observed with other HMG CoA reductase inhibitors. In a 72-week

carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid-and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.
In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

2.6.6.6 Reproductive and developmental toxicology
There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day).

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Studies in related statins and the β-hydroxyacid form of simvastatin, resulted in fetal skeletal malformations. In segment III studies the F1 generation had decreased weight at parturition and during lactation.

2.6.6.7 Local tolerance N/A

2.6.6.8 Special toxicology studies
Hemolysis of canine blood occurred after 30 min at 125 μg/ml β-hydroxy acid of simvastatin; this is a concentration 1000-times higher than the human Cmax at the MRHD.

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Simvastatin is an approved marketed drug. This proposed ODT (oral disintegrating tablet) formulation has been tested clinically. As a 505(b)2 application, the Agency relies on its previous determination of safety for the nonclinical portion of this simvastatin NDA submission.

Unresolved toxicology issues (if any): none

Recommendations: AP (approval)

Suggested labeling: The sponsor's proposed labeling is acceptable

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Karen Davis-Bruno
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PHARMACOLOGIST
AP, labeling is acceptable

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45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	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?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
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.)?	X		
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)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? Carcinogenicity studies were submitted with the NDA 19-766 approved in 1998. This sponsor is submitting a 505(b)2 application. No new nonclinical studies have been submitted.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			No studies were submitted, 505(b)2 application.
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 (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
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?	X		
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?	X		The sponsor claims to have demonstrated bioequivalence as part of the 505(b)2 submission.

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.	x		
10) Reasons for refusal to file: N/A			

Reviewing Pharmacologist: Karen Davis-Bruno; Supervisory Pharmacologist, HFD-510

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/s/

Karen Davis-Bruno
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NDA is fileable

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