Clinical Pharmacology Review

NDA	21-687 SE5 023
Submission Dates	December 19, 2007
Brand Name	VYTORIN™
Generic Name	Ezetimibe/simvastatin
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Sally Y. Choe, Ph.D.
OCP Division	Clinical Pharmacology 2 (HFD-870)
OND Division	Metabolism and Endocrinology Products (HFD-510)
Sponsor	Schering-Plough Pharmaceuticals/Merck
Formulation; Strengths	Oral immediate release tablet; (ezetimibe/simvastatin: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg)
Relevant IND	65,066
Submission Type; Code	Supplement; S
Indication	Treatment of (b) (4)

Background

NDA 21-687 SE5 023 does not contain new Clinical Pharmacology information. However, the sponsor submitted proposed labeling changes in PLR format for review.

Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) reviewed 21-687 SE5 023's proposed Clinical Pharmacology labeling changes.

The major recommended change was to replace the original text with the tables below for the "Drug Interactions" section in 12.3 Pharmacokinetics. Please see other recommendations in the approved labeling.

12.3 Pharmacokinetics

Drug Interactions [See also Drug Interactions (7)]

Ezetimibe

Table 4
Effect of Co-administered Drugs on Total Ezetimibe

Co-administered drug and dosing regimen	Total ezetimibe *	
	Change in AUC	Change in C_{max}
Cyclosporine- stable dose required (75-150 mg BID)†,**	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days†	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days†	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days†	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose§	↓4%	↓30%
Cimetidine 400 mg BID, 7 days	↑6%	↑22%
Glipizide 10 mg, single dose	↑4%	↓8%

Statins		
Lovastatin 20 mg QD, 7 days	↑9%	↑3%
Pravastatin 20 mg QD, 14 days	↑7%	↑23%
Atorvastatin 10 mg QD, 14 days	↓2%	↑12%
Rosuvastatin 10 mg QD, 14 days	↑13%	↑18%
Fluvastatin 20 mg QD, 14 days	↓19%	↑7%

* Based on 10 mg dose of ezetimibe

** Post-renal transplant patients with mild impaired or normal renal function. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects.

† See 7 Drug Interactions

§ Supralox®, 20 mL

Table 5
Effect of Ezetimibe Co-Administration on Systemic Exposure to Other Drugs

Co-administered Drug and its Dosage Regimen	Ezetimibe Dosage Regimen	Change in AUC of Co-administered Drug	Change in C_{max} of Co-administered Drug
Warfarin, 25 mg single dose on day 7	10 mg QD, 11 days	↓2%(R-warfarin) ↓4% (S-warfarin)	↑3% (R-warfarin) ↑1% (S-warfarin)
Digoxin, 0.5 mg single dose	10 mg QD, 8 days	↑2%	↓7%
Gemf brozil, 600mg BID, 7 days†	10 mg QD, 7 days	↓1%	↓11%
Ethinyl estradiol & Levonorgestrel QD, 21 days	10 mg QD, days 8-14 of 21d oral contraceptive cycle	Ethinyl estradiol 0% Levonorgestrel 0%	Ethinyl estradiol ↓9% Levonorgestrel ↓5%
Glipizide, 10 mg on days 1 and 9	10 mg QD, days 2-9	↓3%	↓5%
Fenof brate 200 mg QD, 14 days†	10 mg QD, 14 days	↑11%	↑7%
Cyclosporine 100 mg single dose day 7†	20 mg QD, 8 days	↑15%	↑10%
Statins			
Lovastatin 20 mg QD, 7 days	10 mg QD, 7 days	↑19%	↑3%
Pravastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓20%	↓24%
Atorvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↓4%	↑7%
Rosuvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↑19%	↑17%
Fluvastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓39%	↓27%

† See 7 Drug Interactions

Simvastatin

Table 6
Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Simvastatin	Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00		
				AUC	C_{max}
Avoid taking with VYTORIN *[see Warnings and Precautions (5.1)]*					
Telithromycin†	200 mg QD for 4 days	80 mg	simvastatin acid‡ simvastatin	12 8 9	15 5 3
Nelfinavir†	1250 mg BID for 14days	20 mg QD for 28 days	simvastatin acid‡ simvastatin	 6	 6 2
Itraconazole†	200 mg QD for 4 days	80 mg	simvastatin acid‡ simvastatin	 	13 1 13 1
Avoid >1 quart of grapefruit juice with VYTORIN *[see Warnings and Precautions (5.1)]*					
Grapefruit Juice§ (high dose)	200 mL of double-strength TID¶	60 mg single dose	simvastatin acid simvastatin	7 16	
Grapefruit Juice§ (low dose)	8 oz (about 237 mL) of single-strength#	20 mg single dose	simvastatin acid simvastatin	1.3 1.9	
Avoid taking with >10/20 mg VYTORIN, based on clinical and/or post-marketing simvastatin experience *[see Warnings and Precautions (5.1)]*					
Verapamil SR	240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	simvastatin acid simvastatin	2.3 2.5	2.4 2.1
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD X 14 days	80 mg QD on Days 8-14	simvastatin acid simvastatin	0.64 0.89	0 89 0 83
Niacin extended-release	2 g single dose	20 mg single dose	simvastatin acid simvastatin	1.6 1.4	1 84 1 08
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid simvastatin	2.69 3.10	2.69 2.88
Amlodipine	10 mg QD x 10 days	80 mg on Day 10	simvastatin acid simvastatin	1.58 1.77	1 56 1 47
Propranolol	80 mg single dose	80 mg single dose	total inhibitor active inhibitor	0.79 0.79	↓ from 33 6 to 21 1 ng eq/ml ↓ from 7 0 to 4 7 ng eq/mL

* Results based on a chemical assay except results with propranolol as indicated.
† Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.
‡ Simvastatin acid refers to the β-hydroxyacid of simvastatin.
§ The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.
¶ Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose simvastatin and 30 and 90 minutes following single dose simvasta in on Day 3.
# Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and simvastatin was administered in the evening on Day 3.

S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

FT signed by Sally Y. Choe, Ph.D., Team Leader 6/ /08

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

/s/

S.W. Johnny Lau
6/12/2008 08:13:28 AM
BIOPHARMACEUTICS

Sally Choe
6/12/2008 08:20:32 AM
BIOPHARMACEUTICS