CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 21-445/S001, S003, S004

Trade Name: Zetia Tablets, 10mg

Generic Name: ezetimibe

Sponsor: MSP Singapore Co., LLC

Approval Date: July 23, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-445/S001/S003/S004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-445/S001/S003/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445/S-001, S-003, S-004

MSP Singapore Co., LLC
Schering Corporation, US Agent
Attention: Beth J. DiDomenico, PhD, Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. DiDomenico:

Please refer to the following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets, 10 mg:

Supplement -001, submitted April 3, 2003, provides for the addition of a Post-Marketing subsection to the ADVERSE REACTIONS section of the package insert (PI) to include hypersensitivity reactions, including angioedema and rash. The PPI was also revised to include this information.

Supplement -003, submitted April 24, 2003, provides for revisions to the CLINICAL PHARMACOLOGY (Drug Interactions subsection) and PRECAUTIONS (Cyclosporine subsection) sections of the PI to include information from a study of multiple dosing of cyclosporine on the PK of a single dose of ezetimibe.

Supplement -004, submitted May 5, 2004, provides for the following:
-addition of the terms pancreatitis and nausea to the Post-Marketing subsection of the ADVERSE REACTIONS section of the PI. This information has also been included in the Patient Package Insert (PPI) under the section "What are the possible side effects of ZETIA?"
-revision of the OVERDOSE section of the PI.

We completed our review of these supplemental new drug applications. They are approved, effective on the date of this letter, for use as recommended in the attached final printed labeling.
The approved package insert contains the identifier **25751841T, REV 03, Issued April 2004**. The approved patient package insert contains the identifier **25751744T, REV 03, Issued April 2004**.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
7/23/04 04:25:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-445/S001/S003/S004

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-445/S-001, S-003

Schering Corporation
Agent for the MSP Singapore Company, LLC
Attention: Mary Jane Nehring
Senior Director, Marketed Products Support and Training
2000 Galloping Hill Rd.
Kenilworth, NJ 07033

Dear Ms. Nehring:

Please refer to your supplemental new drug applications dated April 3, 2003, and April 24, 2003, received April 7, 2003, and April 25, 2003, for supplement-001 and -003 respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets.

We acknowledge receipt of your submissions for supplement-003, dated October 13 and December 17, 2003.

These "Changes Being Effected" supplemental new drug applications provides for:

- Supplement-001: Revision of the ADVERSE REACTIONS section of the package insert to include a Post-Marketing Experience subsection.

- Supplement-003: Revision of the PRECAUTIONS section, Cyclosporine subsection, to include information from a study of multiple dosing of cyclosporine on the PK of a single dose of ezetimibe.

We completed our review of these applications, as amended, and they are approvable. Before these applications may be approved, however, you must submit final printed labeling (FPL) for two sets of the package inserts (PI) and the patient package inserts (PPI); i.e., a set for the blister package and a set for the non-blister package, for the drug. The labeling should be identical in content to the submitted labeling (package insert submitted and patient package insert submitted December 17, 2003). To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – NDA's". Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
1/15/04 03:29:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

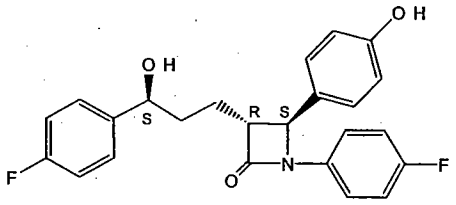
NDA 21-445/S001/S003/S004

LABELING

ZETIA®
(EZETIMIBE)
TABLETS

DESCRIPTION

ZETIA (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature. ZETIA is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Administration of ZETIA with an HMG-CoA reductase inhibitor is effective in improving serum total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone. The effects of ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been established.

Mode of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ZETIA inhibited intestinal cholesterol absorption by 54%, compared with placebo. ZETIA had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol content of the liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG-CoA reductase inhibitors, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols).

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

Pharmacokinetics

Absorption

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ZETIA to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 60% for AUC values.

Effect of Food on Oral Absorption

Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high fat meals. ZETIA can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism and Excretion

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Special Populations

Geriatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Pediatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit further pharmacokinetic comparisons.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients (see CONTRAINDICATIONS and PRECAUTIONS, *Hepatic Insufficiency*).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Drug Interactions (See also PRECAUTIONS, *Drug Interactions*)

ZETIA had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

Warfarin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males.

Digoxin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of twelve healthy adult males.

Gemfibrozil: In a study of twelve healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Oral Contraceptives: Co-administration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel in a study of eighteen healthy adult females.

Cimetidine: Multiple doses of cimetidine (400 mg twice daily) had no significant effect on the oral bioavailability of ezetimibe and total ezetimibe in a study of twelve healthy adults.

Antacids: In a study of twelve healthy adults, a single dose of antacid (Supralox™ 20 mL) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 30%.

Glipizide: In a study of twelve healthy adult males, steady-state levels of ezetimibe (10 mg once daily) had no significant effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

HMG-CoA Reductase Inhibitors: In studies of healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of either lovastatin, simvastatin, pravastatin, atorvastatin, or fluvastatin. No significant effect on the bioavailability of total ezetimibe and ezetimibe was demonstrated by either lovastatin (20 mg once daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), or fluvastatin (20 mg once daily).

Fenofibrate: In a study of thirty-two healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C_{max} and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Cholestyramine: In a study of forty healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Cyclosporine: In a study of eight post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), stable doses of cyclosporine (75 to 150 mg twice daily) increased the mean AUC and C_{max} values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold

(range 3.0- to 4.4-fold), respectively, compared to a historical healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects.

ANIMAL PHARMACOLOGY

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED_{50} value of 0.5 μg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED_{50} values in dogs, rats, and mice were 7, 30, and 700 μg/kg/day, respectively. These results are consistent with ZETIA being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (SCH 60663) was administered intraduodenally, the metabolite was as potent as the parent compound (SCH 58235) in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03-300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3-5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ZETIA for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of ^{14}C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

CLINICAL STUDIES

Primary Hypercholesterolemia

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

ZETIA is effective in patients with hypercholesterolemia, in men and women, in younger and older patients, alone or administered with an HMG-CoA reductase inhibitor. Experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with homozygous familial hypercholesterolemia (HoFH) or sitosterolemia.

Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETIA.

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Table 1
Response to ZETIA in Patients with Primary Hypercholesterolemia
(Mean[a] % Change from Untreated Baseline[b])

	Treatment group	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Study 1[c]	Placebo	205	+1	+1	-1	-1	-1
	Ezetimibe	622	-12	-18	-15	-7	+1
Study 2[c]	Placebo	226	+1	+1	-1	+2	-2
	Ezetimibe	666	-12	-18	-16	-9	+1
Pooled Data[c] (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	Ezetimibe	1288	-13	-18	-16	-8	+1

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo.

Combination with HMG-CoA Reductase Inhibitors
ZETIA Added to On-going HMG-CoA Reductase Inhibitor Therapy

In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with primary hypercholesterolemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving HMG-CoA reductase inhibitor monotherapy, but who had not met their NCEP ATP II target LDL-C goal were randomized to receive either ZETIA or placebo in addition to their on-going HMG-CoA reductase inhibitor therapy.

ZETIA, added to on-going HMG-CoA reductase inhibitor therapy, significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared with an HMG-CoA reductase inhibitor administered alone (see Table 2). LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors.

Table 2
Response to Addition of ZETIA to On-going HMG-CoA Reductase Inhibitor Therapy[a] in Patients with Hypercholesterolemia
(Mean[b] % Change from Treated Baseline[c])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[b]	HDL-C
On-going HMG-CoA reductase inhibitor +Placebo[d]	390	-2	-4	-3	-3	+1
On-going HMG-CoA reductase inhibitor +ZETIA[d]	379	-17	-25	-19	-14	+3

[a] Patients receiving each HMG-CoA reductase inhibitor: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)
[b] For triglycerides, median % change from baseline
[c] Baseline - on an HMG-CoA reductase inhibitor alone.
[d] ZETIA + HMG-CoA reductase inhibitor significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to HMG-CoA reductase inhibitor alone.

ZETIA Initiated Concurrently with an HMG-CoA Reductase Inhibitor

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 2382 hypercholesterolemic patients, ZETIA or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin.

When all patients receiving ZETIA with an HMG-CoA reductase inhibitor were compared to all those receiving the corresponding HMG-CoA reductase inhibitor alone, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and, with the exception of pravastatin, increased HDL-C compared to the HMG-CoA reductase inhibitor administered alone. LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors. (See footnote c, Tables 3 to 6.)

Table 3
Response to ZETIA and Atorvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	60	+4	+4	+3	-6	+4
ZETIA	65	-14	-20	-15	-5	+4
Atorvastatin 10 mg	60	-26	-37	-28	-21	+6
ZETIA + Atorvastatin 10 mg	65	-38	-53	-43	-31	+9
Atorvastatin 20 mg	60	-30	-42	-34	-23	+4
ZETIA + Atorvastatin 20 mg	62	-39	-54	-44	-30	+9
Atorvastatin 40 mg	66	-32	-45	-37	-24	+4
ZETIA + Atorvastatin 40 mg	65	-42	-56	-45	-34	+5
Atorvastatin 80 mg	62	-40	-54	-46	-31	+3
ZETIA + Atorvastatin 80 mg	63	-46	-61	-50	-40	+7
Pooled data (All Atorvastatin Doses)[c]	248	-32	-44	-36	-24	+4
Pooled data (All ZETIA + Atorvastatin Doses)[c]	255	-41	-56	-45	-33	+7

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of atorvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

Table 4
Response to ZETIA and Simvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	70	-1	-1	0	+2	+1
ZETIA	61	-13	-19	-14	-11	+5
Simvastatin 10 mg	70	-18	-27	-21	-14	+8
ZETIA + Simvastatin 10 mg	67	-32	-46	-35	-26	+9
Simvastatin 20 mg	61	-26	-36	-29	-18	+6
ZETIA + Simvastatin 20 mg	69	-33	-46	-36	-25	+9
Simvastatin 40 mg	65	-27	-38	-32	-24	+6
ZETIA + Simvastatin 40 mg	73	-40	-56	-45	-32	+11
Simvastatin 80 mg	67	-32	-45	-37	-23	+8
ZETIA + Simvastatin 80 mg	65	-41	-58	-47	-31	+8
Pooled data (All Simvastatin Doses)[c]	263	-26	-36	-30	-20	+7
Pooled data (All ZETIA + Simvastatin Doses)[c]	274	-37	-51	-41	-29	+9

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of simvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of simvastatin pooled (10-80 mg).

Table 5
Response to ZETIA and Pravastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	65	0	-1	-2	-1	+2
ZETIA	64	-13	-20	-15	-5	+4
Pravastatin 10 mg	66	-15	-21	-16	-14	+6
ZETIA + Pravastatin 10 mg	71	-24	-34	-27	-23	+8
Pravastatin 20 mg	69	-15	-23	-18	-8	+8
ZETIA + Pravastatin 20 mg	66	-27	-40	-31	-21	+8
Pravastatin 40 mg	70	-22	-31	-26	-19	+6
ZETIA + Pravastatin 40 mg	67	-30	-42	-32	-21	+8
Pooled data (All Pravastatin Doses)[c]	205	-17	-25	-20	-14	+7
Pooled data (All ZETIA + Pravastatin Doses)[c]	204	-27	-39	-30	-21	+8

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of pravastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG compared to all doses of pravastatin pooled (10-40 mg).

Table 6
Response to ZETIA and Lovastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	64	+1	0	+1	+6	0
ZETIA	72	-13	-19	-14	-5	+3
Lovastatin 10 mg	73	-15	-20	-17	-11	+5
ZETIA + Lovastatin 10 mg	65	-24	-34	-27	-19	+8
Lovastatin 20 mg	74	-19	-26	-21	-12	+3
ZETIA + Lovastatin 20 mg	62	-29	-41	-34	-27	+9
Lovastatin 40 mg	73	-21	-30	-25	-15	+5
ZETIA + Lovastatin 40 mg	65	-33	-46	-38	-27	+9
Pooled data (All Lovastatin Doses)[c]	220	-18	-25	-21	-12	+4
Pooled data (All ZETIA + Lovastatin Doses)[c]	192	-29	-40	-33	-25	+9

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of lovastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of lovastatin pooled (10-40 mg).

Homozygous Familial Hypercholesterolemia (HoFH)

A study was conducted to assess the efficacy of ZETIA in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), ZETIA

administered with atorvastatin or simvastatin (40 mg), or ZETIA administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 4 hours before or after administration of resins. Mean baseline LDL-C was 341 mg/dL in those patients randomized to atorvastatin 80 mg or simvastatin 80 mg alone and 316 mg/dL in the group randomized to ZETIA plus atorvastatin 40 or 80 mg or simvastatin 40 or 80 mg. ZETIA, administered with atorvastatin or simvastatin (40 and 80 mg statin groups, pooled), significantly reduced LDL-C (21%) compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg (7%). In those treated with ZETIA plus 80 mg atorvastatin or with ZETIA plus 80 mg simvastatin, LDL-C was reduced by 27%.

Homozygous Sitosterolemia (Phytosterolemia)

A study was conducted to assess the efficacy of ZETIA in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) on their current therapeutic regimen (diet, bile-acid-binding resins, HMG-CoA reductase inhibitors, ileal bypass surgery and/or LDL apheresis), were randomized to receive ZETIA (n=30) or placebo (n=7). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered. Excluding the one subject receiving LDL apheresis, ZETIA significantly lowered plasma sitosterol and campesterol, by 21% and 24% from baseline, respectively. In contrast, patients who received placebo had increases in sitosterol and campesterol of 4% and 3% from baseline, respectively. For patients treated with ZETIA, mean plasma levels of plant sterols were reduced progressively over the course of the study. The effects of reducing plasma sitosterol and campesterol on reducing the risks of cardiovascular morbidity and mortality have not been established.

Reductions in sitosterol and campesterol were consistent between patients taking ZETIA concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

INDICATIONS AND USAGE

Primary Hypercholesterolemia

Monotherapy

ZETIA, administered alone, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination therapy with HMG-CoA reductase inhibitors

ZETIA, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HoFH)

The combination of ZETIA and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia

ZETIA is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 7.)

Table 7
Summary of NCEP ATP III Guidelines

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes[a] (mg/dL)	LDL level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents[b] (10-year risk >20%)[c]	<100	≥100	≥130 (100-129: drug optional)[d]
2+ Risk factors[e] (10-year risk ≤20%)[c]	<130	≥130	10-year risk 10-20%: ≥130[c] 10-year risk <10%: ≥160[c]
0-1 Risk factor[f]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] Therapeutic lifestyle changes include: 1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d), 2) weight reduction, and 3) increased physical activity.

[b] CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10-year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).

[c] Risk assessment for determining the 10-year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486-2497, or the NCEP website (http://www.nhlbi.nih.gov) for more details.

[d] Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

[e] Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on anti-hypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years). HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

[f] Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Prior to initiating therapy with ZETIA, secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dL (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

The combination of ZETIA with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See PRECAUTIONS, *Pregnancy*.)

PRECAUTIONS

Concurrent administration of ZETIA with a specific HMG-CoA reductase inhibitor should be in accordance with the product labeling for that HMG-CoA reductase inhibitor.

Liver Enzymes

In controlled clinical monotherapy studies, the incidence of consecutive elevations (≥3 X the upper limit of normal [ULN]) in serum transaminases was similar between ZETIA (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ZETIA initiated concurrently with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations (≥3 X ULN) in serum transaminases was 1.3% for patients treated with ZETIA administered with HMG-CoA reductase inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ZETIA is co-administered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ZETIA compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for ZETIA vs 0.1% for placebo, and 0.1% for ZETIA co-administered with an HMG-CoA reductase inhibitor vs 0.4% for HMG-CoA reductase inhibitors alone.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients. (See CLINICAL PHARMACOLOGY, *Special Populations.*)

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions*)

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Co-administration of ZETIA with fibrates is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

HMG-CoA Reductase Inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Cyclosporine: Caution should be exercised when initiating ezetimibe in patients treated with cyclosporine due to increased exposure to ezetimibe. This exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine (see CLINICAL PHARMACOLOGY, *Drug Interactions*).

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

Pregnancy

Pregnancy Category: C

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple dose studies of ezetimibe given in combination with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See CONTRAINDICATIONS.)

Labor and Delivery

The effects of ZETIA on labor and delivery in pregnant women are unknown.

Nursing Mothers

In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk; therefore, ZETIA should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Pediatric Use

The pharmacokinetics of ZETIA in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ZETIA in the pediatric population is limited to 4 patients (9 to 17 years) in the sitosterolemia study and 5 patients (11 to 17 years) in the HoFH study. Treatment with ZETIA in children (<10 years) is not recommended. (See CLINICAL PHARMACOLOGY, *Special Populations.*)

Geriatric Use

Of the patients who received ZETIA in clinical studies, 948 were 65 and older (this included 206 who were 75 and older). The effectiveness and safety of ZETIA were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, *Special Populations*, and ADVERSE REACTIONS.)

ADVERSE REACTIONS

ZETIA has been evaluated for safety in more than 4700 patients in clinical trials. Clinical studies of ZETIA (administered alone or with an HMG-CoA reductase inhibitor) demonstrated that ZETIA was generally well tolerated. The overall incidence of adverse events reported with ZETIA was similar to that reported with placebo, and the discontinuation rate due to adverse events was also similar for ZETIA and placebo.

Monotherapy

Adverse experiences reported in ≥2% of patients treated with ZETIA and at an incidence greater than placebo in placebo-controlled studies of ZETIA, regardless of causality assessment, are shown in Table 8.

Table 8*
Clinical Adverse Events Occurring in ≥2% of Patients Treated with ZETIA and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Placebo (%) n = 795	ZETIA 10 mg (%) n = 1691
Body as a whole – general disorders		
Fatigue	1.8	2.2
Gastro-intestinal system disorders		
Abdominal pain	2.8	3.0
Diarrhea	3.0	3.7
Infection and infestations		
Infection viral	1.8	2.2
Pharyngitis	2.1	2.3
Sinusitis	2.8	3.6
Musculo-skeletal system disorders		
Arthralgia	3.4	3.8
Back pain	3.9	4.1
Respiratory system disorders		
Coughing	2.1	2.3

*Includes patients who received placebo or ZETIA alone reported in Table 9.

The frequency of less common adverse events was comparable between ZETIA and placebo.

Combination with an HMG-CoA Reductase Inhibitor

ZETIA has been evaluated for safety in combination studies in more than 2000 patients.

In general, adverse experiences were similar between ZETIA administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. However, the frequency of increased transaminases was slightly higher in patients receiving ZETIA administered with HMG-CoA reductase inhibitors than in patients treated with HMG-CoA reductase inhibitors alone. (See PRECAUTIONS, *Liver Enzymes.*)

Clinical adverse experiences reported in ≥2% of patients and at an incidence greater than placebo in four placebo-controlled trials where ZETIA was administered alone or initiated concurrently with various HMG-CoA reductase inhibitors, regardless of causality assessment, are shown in Table 9.

Table 9*
Clinical Adverse Events occurring in ≥2% of Patients and at an Incidence Greater than Placebo, Regardless of Causality, in ZETIA/Statin Combination Studies

Body System/Organ Class Adverse Event	Placebo (%) n=259	ZETIA 10 mg (%) n=262	All Statins** (%) n=936	ZETIA + All Statins** (%) n=925
Body as a whole – general disorders				
Chest pain	1.2	3.4	2.0	1.8
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.9	1.9	1.4	2.8
Headache	5.4	8.0	7.3	6.3
Gastro-intestinal system disorders				
Abdominal pain	2.3	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Infection and infestations				
Pharyngitis	1.9	3.1	2.5	2.3
Sinusitis	1.9	4.6	3.6	3.5
Upper respiratory tract infection	10.8	13.0	13.6	11.8
Musculo-skeletal system disorders				
Arthralgia	2.3	3.8	4.3	3.4
Back pain	3.5	3.4	3.7	4.3
Myalgia	4.6	5.0	4.1	4.5

*Includes four placebo-controlled combination studies in which ZETIA was initiated concurrently with an HMG-CoA reductase inhibitor.
**All Statins = all doses of all HMG-CoA reductase inhibitors.

Post-marketing Experience

The following adverse reactions have been reported in post-marketing experience:
Hypersensitivity reactions, including angioedema and rash; pancreatitis; nausea.

OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdosage with ZETIA have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZETIA and should continue on this diet during treatment with ZETIA.

The recommended dose of ZETIA is 10 mg once daily. ZETIA can be administered with or without food.

ZETIA may be administered with an HMG-CoA reductase inhibitor for incremental effect. For convenience, the daily dose of ZETIA may be taken at the same time as the HMG-CoA reductase inhibitor, according to the dosing recommendations for the HMG-CoA reductase inhibitor.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, *Hepatic Insufficiency*).

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, *Special Populations*).

Geriatric Patients

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, *Special Populations*).

Co-administration with Bile Acid Sequestrants

Dosing of ZETIA should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant (see PRECAUTIONS, *Drug Interactions*).

HOW SUPPLIED

No. 3861 - Tablets ZETIA, 10 mg, are white to off-white, capsule-shaped tablets debossed with "414" on one side. They are supplied as follows:
NDC 66582-414-31 bottles of 30
NDC 66582-414-54 bottles of 90
NDC 66582-414-74 bottles of 500
NDC 66582-414-28 unit dose packages of 100.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from moisture.

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Merck/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA
By:
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or
Merck & Co., Inc.
Whitehouse Station, NJ 08889, USA

ZETIA® (ezetimibe) Tablets

Patient Information about ZETIA (zĕt´-ē-ă)
Generic name: ezetimibe (ĕ-zĕt´-ĕ-mīb)

Read this information carefully before you start taking ZETIA and each time you get more ZETIA. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ZETIA, ask your doctor. Only your doctor can determine if ZETIA is right for you.

What is ZETIA?

ZETIA is a medicine used to lower levels of total cholesterol and LDL (bad) cholesterol in the blood. It is used for patients who cannot control their cholesterol levels by diet alone. It can be used by itself or with other medicines to treat high cholesterol. You should stay on a cholesterol-lowering diet while taking this medicine.

ZETIA works to reduce the amount of cholesterol your body absorbs. ZETIA does not help you lose weight.

For more information about cholesterol, see the "What should I know about high cholesterol?" section that follows.

Who should not take ZETIA?

- Do not take ZETIA if you are allergic to ezetimibe, the active ingredient in ZETIA, or to the inactive ingredients. For a list of inactive ingredients, see the "Inactive ingredients" section that follows.
- If you have active liver disease, do not take ZETIA while taking cholesterol-lowering medicines called statins.
- If you are pregnant or breast-feeding, do not take ZETIA while taking a statin.

What should I tell my doctor before and while taking ZETIA?

Tell your doctor about any prescription and non-prescription medicines you are taking or plan to take, including natural or herbal remedies.

Tell your doctor about all your medical conditions including allergies.

Tell your doctor if you:
- ever had liver problems. ZETIA may not be right for you.
- are pregnant or plan to become pregnant. Your doctor will decide if ZETIA is right for you.
- are breast-feeding. We do not know if ZETIA can pass to your baby through your milk. Your doctor will decide if ZETIA is right for you.
- experience unexplained muscle pain, tenderness, or weakness.

How should I take ZETIA?

- Take ZETIA once a day, with or without food. It may be easier to remember to take your dose if you do it at the same time every day, such as with breakfast, dinner, or at bedtime. If you also take another medicine to reduce your cholesterol, ask your doctor if you can take them at the same time.
- If you forget to take ZETIA, take it as soon as you remember. However, do not take more than one dose of ZETIA a day.
- Continue to follow a cholesterol-lowering diet while taking ZETIA. Ask your doctor if you need diet information.

- Keep taking ZETIA unless your doctor tells you to stop. It is important that you keep taking ZETIA even if you do not feel sick.

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor may do blood tests to check your liver before you start taking ZETIA with a statin and during treatment.

What are the possible side effects of ZETIA?

In clinical studies patients reported few side effects while taking ZETIA. These included stomach pain and feeling tired.

Additionally, the following side effects have been reported in general use: allergic reactions (which may require treatment right away) including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing, and rash; inflammation of the pancreas; and nausea.

Tell your doctor if you are having these or any other medical problems while on ZETIA. For a complete list of side effects, ask your doctor or pharmacist.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Your total cholesterol is made up of LDL and HDL cholesterol.

LDL cholesterol is called "bad" cholesterol because it can build up in the wall of your arteries and form plaque. Over time, plaque build-up can cause a narrowing of the arteries. This narrowing can slow or block blood flow to your heart, brain, and other organs. High LDL cholesterol is a major cause of heart disease and stroke.

HDL cholesterol is called "good" cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your blood.

General Information about ZETIA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ZETIA for a condition for which it was not prescribed. Do not give ZETIA to other people, even if they have the same condition you have. It may harm them.

This summarizes the most important information about ZETIA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ZETIA that is written for health professionals.

Inactive ingredients:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

Issued April 2004

Manufactured for:
Merck/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA
By:
Schering Corporation
Kenilworth, NJ 07033, USA
or

Merck & Co., Inc.
Whitehouse Station, NJ 08889, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-445/S001/S003/S004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-445/SLR-003	Submission Date(s): April 24th, 2003
Brand Name	ZETIA
Generic Name	ezetimibe
Relevant IND(s)	52,791
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Merck/Schering-Plough Pharmaceuticals
Submission Type	SLR
Formulation; Strength(s)	Tablet; 10 mg
Indication	Hypercholesterolemia when administered alone or with an HMG-CoA reductase inhibitor; hypercholesterolemia in patients with homozygous familial hypercholesterolemia; elevated sitosterol and campesterol in patients with homozygous sitosterolemia

1 Executive Summary

On April 24th, 2003, Merck/Schering-Plough Pharmaceuticals submitted a study report for protocol MK-0653-027, "An Open-Label, Single Period Study to Evaluate the Effects of Multiple Oral Dosing of Cyclosporine on the Pharmacokinetics of Singe Oral Dose Ezetimibe". Based on the study results, the sponsor proposed a labeling change to the Cyclosporine subsection of the PRECAUTIONS section and addition to the Drug Interactions subsection of the CLINICAL PHARMACOLOGY section.

Concomitant cyclosporine administration increased total ezetimibe (unconjugated ezetimibe plus ezetimibe-glucuronide) AUC0-last and Cmax values 3.41-fold (2.3- to 7.9-fold) and 3.91-fold (3.0- to 4.4-fold), respectively.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-445/SLR003 submitted on 24 April 2003 and finds it acceptable. Labeling comments should be conveyed to the sponsor as appropriate.

2 Table of Contents

3 Summary of CPB Findings

Coadministration with cyclosporine resulted in a 3.41-fold (2.3- to 7.9-fold) and 3.91-fold (3.0- to 4.4-fold) increase in total ezetimibe (unconjugated ezetimibe plus ezetimibe-glucuronide) AUC0-last and Cmax values, respectively. The unconjugated ezetimibe AUC0-last and Cmax values were increased by 1.6- and 2.71-fold, respectively. Cyclosporine had minimal effect on total ezetimibe Tmax values, but decreased unconjugated ezetimibe Tmax from 5.7 hour to 1.0 hour. This present study showed that in renal transplant patients with mild or normal renal function coadministered with cyclosporine, the exposure to ezetimibe-glucuronide is 26 fold greater than that to unconjugated ezetimibe.

4 QBR

4.1 Extrinsic Factors

How does steady-state cyclosporine (CsA) administration affect the pharmacokinetics of ezetimibe in renal transplant patients?

To evaluate the effect of steady-state cyclosporine administration on the single dose pharmacokinetics of ezetimibe, eight renal transplant patients with mild impaired or normal renal function (creatinine clearance >50 mL/min) were enrolled. Doses of cyclosporine ranged from 75 to 150 mg twice daily. Results were compared to historical data obtained from 17 healthy subjects in studies 00749 and 00215.

Coadministration with cyclosporine resulted in a 3.41-fold (2.3- to 7.9-fold) and 3.91-fold (3.0- to 4.4-fold) increase in total ezetimibe (unconjugated ezetimibe plus ezetimibe-glucuronide) AUC0-last and Cmax values, respectively. The unconjugated ezetimibe AUC0-last and Cmax values were increased by 1.6- and 2.71-fold, respectively (**Tables 1** and **2**). Cyclosporine had minimal effect on total ezetimibe Tmax values, but decreased unconjugated ezetimibe Tmax from 5.7 hour to 1.0 hour (**Table 3**). Previous study showed that in healthy control subjects, the exposure to ezetimibe-glucuronide was 12-fold higher than that to unconjugated ezetimibe. This present study showed that in renal transplant patients with mild or normal renal function coadministered with cyclosporine, the exposure to ezetimibe-glucuronide is 26 fold greater than that to unconjugated ezetimibe (**Table 4**).

Table 1. Summary statistics for AUC0-last (ng.hr/mL) of total ezetimibe and unconjugated ezetimibe following a single oral ezetimibe 10 mg dose with or without cyclosporine coadministration.

	Total Ezetimibe		Unconjugated Ezetimibe	
	Eze	Eze+ CsA	Eze	Eze + CsA
Geometric LS mean	840.5	2867.3	66.8	106.8
Geometric Mean Ratio (GMR)		**3.41**		**1.60**
90% CI for GMR		(2.55, 4.56)		(1.12, 2.27)
Median	852.0	2495.5	54.0	109.3
Range	538.0--1579.0	1895.1--6613.3	36.7--172.0	74.0--404.6

Table 2. Summary statistics for Cmax (ng/mL) of total ezetimibe and unconjugated ezetimibe following a single oral ezetimibe 10 mg dose with or without cyclosporine coadministration

	Total Ezetimibe		Unconjugated Ezetimibe	
	Eze	Eze+ CsA	Eze	Eze + CsA
Geometric LS mean	92.9	363.2	3.8	10.2
Geometric Mean Ratio (GMR)		**3.91**		**2.71**
90% CI for GMR		(3.13, 4.89)		(1.72, 4.25)
Median	101.0	360.2	3.1	10.8
Range	32.7--190.0	279.0--405.0	1.5--15.1	4.5--26.0

Table 3. Summary statistics for Tmax (hr) of total ezetimibe and unconjugated ezetimibe following a single oral ezetimibe 10 mg with or without cyclosporine coadministration

	Total Ezetimibe		Unconjugated Ezetimibe	
	Eze	Eze+ CsA	Eze	Eze + CsA
Mean	1.4	1.8	5.7	1.0
SD	1.24	0.60	3.48	0.46
Median	1.0	1.5	6.0	1.0
Range	0.5--6.0	1.0--3.0	0.5--16.0	0.5--2.0

Table 4. Mean (SD) AUC0-last (ng.hr/mL) of total ezetimibe, unconjugated ezetimibe and ezetimibe-glucuronide following a single oral ezetimibe 10 mg with or without cyclosporine co-administration

Treatment	Total Ezetimibe	Unconjugated Ezetimibe	Ezetimibe-Glucuronide
Ezetimibe + CsA	3009 (1504)	109 (139)	2870 (1522)
Ezetimibe	904 (334)	71 (40)	833 (332)

Reviewer's Comments:

(1). This study clearly showed that cyclosporine increased total ezetimibe exposure by 3.41-fold (2.3 fold-7.9 fold) in renal transplant patients with mild impaired or normal renal function relative to the mean exposure in historical healthy control subjects. The Cmax value of total ezetimibe was increased by 3.91-fold (3.0- to 4.4-fold) by cyclosporine coadministration. The effect on unconjugated ezetimibe was less pronounced: AUC0-last was increased by 1.6-fold and Cmax by 2.71-fold.

(2). The increases in exposure to both unconjugated ezetimibe and ezetimibe-glucuronide suggested that the bioavailability was increased by coadministration with cyclosporine. Ezetimibe

has been shown to be a P-glycoprotein (Pgp) substrate, while cyclosporine and the inactive ingredient in cyclosporine formulation, polyoxyl 35 castor oil or polyoxyl 40 hydrogenated castor oil were Pgp inhibitors. Thus, the underlying mechanism that may attribute to the increase in bioavailability of ezetimibe may include the inhibition of Pgp activity by cyclosporine and/or the inactive ingredient (polyoxyl 35 castor oil or polyoxyl 40 hydrogenated castor oil).

(3). It was also noticed that the extent of increase in exposure to ezetimibe-glucuronide was more than that for unconjugated ezetimibe, suggesting that the elimination of ezetimibe-glucuronide was decreased. Since Canalicular Multispecific Organic Anion Transporter (MRP2) plays an important role in the canalicular secretion of glucuronides and cyclosporine has been shown to be an inhibitor of MRP2, it suggested that cyclosporine may inhibit the elimination of ezetimibe-glucuronide and increase the exposure to ezetimibe-glucuronide via the inhibition of MRP2. Thus, drugs showing inhibition capacity on Pgp and MRP2 may cause an increase in exposure to unconjugated ezetimibe and ezetimibe-glucuronide.

(4). The reviewer also realized that this study was conducted with renal transplant patients with mild impaired or normal renal function. Previous study showed that renal transplant patients with severe renal insufficiency had 1.5 fold higher exposure on average compared to healthy control. In addition, one renal transplant patient with server renal dysfunction receiving multiple medications including cyclosporine had a 12-fold greater exposure to total ezetimibe compared to healthy subjects. Therefore, it can be expected that cyclosporine would cause more significant increase in exposure to ezetimibe in severe renal impaired patients.

5 Labeling

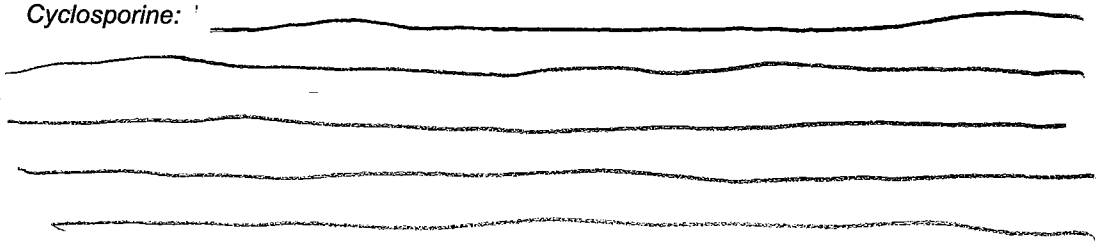
The reviewer recommends the following labeling changes:

Under ***CLINICAL PHARMACOLOGY*** Section **Drug Interactions** subsection

Cyclosporine: In a study of eight post-renal transplant patients with mild impaired or normal renal function (creatinine clearance of >50 mL/min), stable doses of cyclosporine (75 to 150-mg twice daily) increased the mean AUC and Cmax values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively, compared to a healthy control population (n=17). 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.

Under ***PRECAUTIONS*** Section

Cyclosporine:



14 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 21-445
S001/S003
S004

Summary

This document reports the results of the study: An Open-Label, Single Period Study to Evaluate the Effects of Multiple Oral Dosing of Cyclosporine on the Pharmacokinetics of Single Oral Dose Ezetimibe. This study (Protocol No. 027) was completed in the clinic [redacted]. The results of this study show that the mean total ezetimibe AUC in renal transplant patients with normal renal function receiving cyclosporine is approximately 3.4-fold increased over an historical healthy control population. An exposure of this magnitude is similar to the range of exposures in prior Phase I multiple dose pharmacokinetic studies.

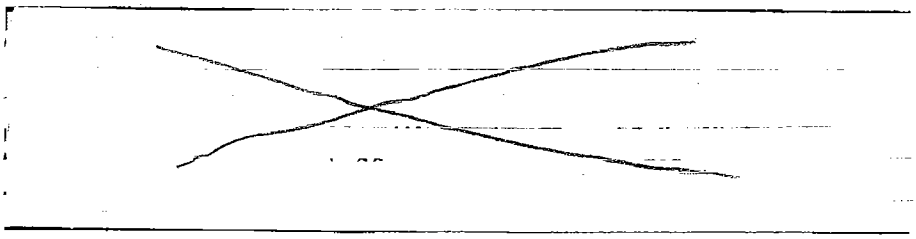
I. Background

This investigation was pursued due to the observation of an increased ezetimibe exposure in a single patient in an earlier study conducted in renal insufficiency patients. In the earlier study [redacted] the mean pharmacokinetic parameters of ezetimibe and ezetimibe-glucuronide were assessed in healthy subjects and patients with severe chronic renal insufficiency after a single oral dose of ezetimibe 10 mg. Whereas total ezetimibe exposure was increased by a mean 1.5-fold in the renal insufficiency group compared to a historical healthy control population, a single renal transplant patient in the severe renal dysfunction group was noted to have an approximately 12-fold greater exposure (AUC) to total ezetimibe.

This index case (Patient 16) was a 51 year old black male, post renal transplant patient with multiple but stable medical conditions including hypertension, asthma, gout, and coronary artery disease. He had severe renal dysfunction, with a creatinine clearance of 13.2 mL/min/1.73m2. He was taking cyclosporine [redacted] as part of his post transplant immunosuppressive regimen as well as multiple other medications to treat various medical conditions (Table 1). The cyclosporine dose was administered 4 hours after ezetimibe administration.

Table 1

Index Case (#16), [redacted], Concomitant Medications



The pharmacokinetic results for this patient indicated that the exposure (based on $AUC_{0-\infty}$) of total ezetimibe was approximately 12 times greater for this subject (11970 ng-hr/mL)

compared to exposure in healthy controls (mean $AUC_{0-\infty}$ 981 ng•hr/mL). The mean exposure in the severe renal insufficiency group was $AUC_{0-\infty}$ 1643 ng•hr/mL. Please see Figure 1 and Table 2 for $AUC_{0-\infty}$ and C_{max} data for Patient 16 in comparison with data from other chronic renal insufficiency patients and healthy subjects. There were no significant clinical findings during the study, and the subject did not report any adverse events.

Figure 1

Individual Plasma Concentration-Time Profiles of Total Ezetimibe Following Single Oral Administration of Ezetimibe 10 mg to Patients With Chronic Renal Insufficiency and Subjects With Normal Renal Function

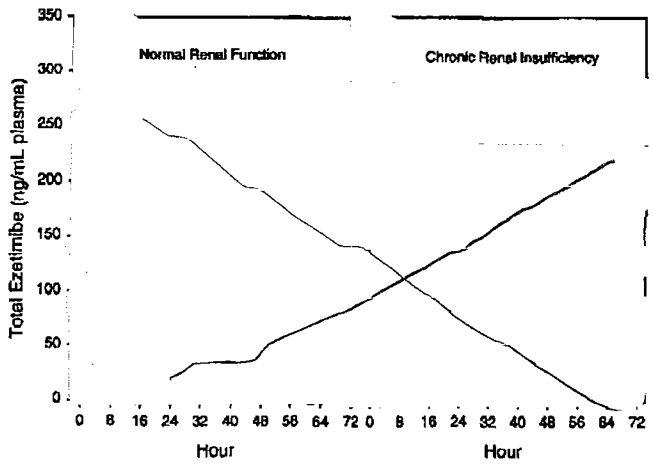


Table 2

Total Ezetimibe Concentrations Following Single Oral Administration of Ezetimibe 10 mg to Patients With Chronic Renal Insufficiency Excluding Patient 16, Separate Data for Patient 16, and Subjects With Normal Renal Function (Protocol 0749)

	Healthy Subjects			Chronic Renal Insufficiency Patients		
	N	Mean	% CV	N	Mean	% CV
C_{max} (ng/mL)	9	109	39	7	117	35
$AUC_{0-\infty}$ (ng•hr/mL)	9	981	32	7	1643	24

AUC = Area under the curve.
CV = Coefficient of variation.

It was speculated at that time that the excipients (e.g., alcohol, corn oil, castor oil) present in [redacted] intended to increase bioavailability of cyclosporine, may have enhanced the absorption of ezetimibe as well. There was no a priori reason to expect a pharmacokinetic interaction between the cyclosporine itself and ezetimibe, as the main pathway of ezetimibe metabolism is glucuronidation, which cyclosporine is not known to affect. Protocol No. 027 was therefore conducted to determine the effect of steady-state cyclosporine administration on the single-dose pharmacokinetics of ezetimibe in the setting of relatively normal renal function.

II. Study Design

In order to examine the effect of steady-state cyclosporine on ezetimibe exposure more precisely, particularly in the absence of renal dysfunction, an open-label, single-period pharmacokinetic drug interaction study (Study 027) was conducted. In this study, eight renal transplant patients (transplant > 6 months prior to study) with creatinine clearance >50 mL/min who had been on a stable dose of cyclosporine [redacted] for 3 months prior to start of study as well as prednisone and azathioprine as part of their immunosuppression regimen were enrolled. An important enrollment qualification was that patients had to have demonstrated a stable level of whole blood cyclosporine (morning fasting trough cyclosporine levels measured at 2 different times within 1 week prior to start of study within ±15%). For at least 1 week prior to study initiation, all patients continued taking their usual prescribed dosage of cyclosporine (ranging from 75 to 150-mg twice daily) but were instructed to take these doses on a more rigorously timed schedule, i.e., at precise 12-hour intervals (preferably at ~8 AM and ~8 PM). Concomitant medications were carefully restricted to avoid potential additional drug interactions. A single oral 10 mg dose of ezetimibe was coadministered with their morning prescribed dose of cyclosporine. Patients continued to receive their individualized doses of cyclosporine at the 12-hour scheduled intervals throughout the study. Plasma samples were collected for 120 hours post-dose. The pharmacokinetic parameters $AUC_{0\text{-last}}$ for (unconjugated) ezetimibe and total ezetimibe (ezetimibe + the active metabolite ezetimibe-glucuronide) were calculated and compared to pharmacokinetic parameters observed in healthy subjects pooled from two prior preidentified studies (00749 and 00215) following a 10-mg single oral dose of ezetimibe.

Blood was also collected for serial cyclosporine trough levels at 12, 24, 36, 48, 60, 72, and 120 hours post ezetimibe administration. This study was not designed to evaluate the effect of ezetimibe on cyclosporine pharmacokinetics since only a single dose of ezetimibe was administered. Cyclosporine trough levels were drawn only for safety monitoring within the study. Safety information was evaluated by tabulating adverse experiences and by clinical assessment of laboratory data.

The primary hypothesis for this study was: The geometric mean ratio (GMR) of the plasma area under the curve $(AUC)_{0\text{-last}}$ of total ezetimibe concentrations after a single oral dose of ezetimibe 10 mg in the setting of steady-state cyclosporine dosing will be comparable to the plasma $AUC_{0\text{-last}}$ of total ezetimibe concentrations without cyclosporine coadministration, i.e., the 90% confidence interval of the GMR of the plasma $AUC_{0\text{-last}}$ of total ezetimibe concentrations in postrenal transplant patients on a

stable dose of cyclosporine (for 3 months prior to start of study) versus total ezetimibe concentrations in the reference database (from healthy subjects with similar ages and weights) will be contained within the interval (0.50, 2.00) (Days 1 to 6 versus historical data).

III Statistical Methods

The $AUC_{0\text{-last}}$, C_{max} and $t_{1/2}$ of ezetimibe concentrations after a single 10 mg dose of ezetimibe following multiple oral doses of cyclosporine were compared to the data from a historical control population using an Analysis of Covariance (ANCOVA) model. The ANCOVA model contained the following factors: treatment group, age, weight, and height. Gender and race were not included in the final model since they were not appropriately represented in the sample patient population. A log transformation was applied to $AUC_{0\text{-last}}$ and C_{max} data (inverse transformation for $t_{1/2}$ data) to normalize their distributions. The Back-transformation from the log scale (inverse scale for $t_{1/2}$) was applied to present the results in the original scale. Ninety percent confidence intervals (CIs), based on the t-distribution, were computed on the least-squares means ratio between postrenal transplant patients after the oral dose of ezetimibe 10 mg and the historical control population for $AUC_{0\text{-last}}$, C_{max}, and $t_{1/2}$. If the 90% lower confidence limit for total ezetimibe $AUC_{0\text{-last}}$ was > 0.50 and the 90% upper confidence limit was <2.00, then no clinically important difference between the above two groups was to be concluded. The analysis of T_{max} was performed on ranks of T_{max} values. Summary statistics of cyclosporine trough concentration were also provided.

In addition to the above analyses and to show the spread relative to the historical control group, a scatter plot of the z-scores based on the residuals of the ANCOVA model were determined as follows:

$$z_i = (x_i - \bar{w}) / s_w$$

where x_i represents the residuals of the individual observation in the ANCOVA model without the treatment term.

$\bar{w}$ represents the mean of the residuals in the historical control group for each pharmacokinetic (PK) parameter.

s_w represents the standard deviation of the residuals in the historical control group for each PK parameter.

The z-score thus represents the adjusted number of standard deviations (SD) from the mean that the individual data point lies. Note that under the normal distribution and assuming that all observations come from the same distribution, ~ 95% of the observations should be contained within a z-score of (-2, 2). These scatter plots were used to present the above z-score distributions for $AUC_{0\text{-last}}$, C_{max} and $t_{1/2}$, $AUC_{0\text{-last}}$ and C_{max} using the log-transformation and for $t_{1/2}$ the inverse-transformation.

Jackknife method was used to estimate the standard deviation associated with the back inverse-transformed Ls mean of 1/half-life values. The principle of this method is to

estimate the variability of half-life values by dropping one data point at a time from the data set and estimating the parameter of interest and repeating this method across the entire data set.

IV. Results

Summary

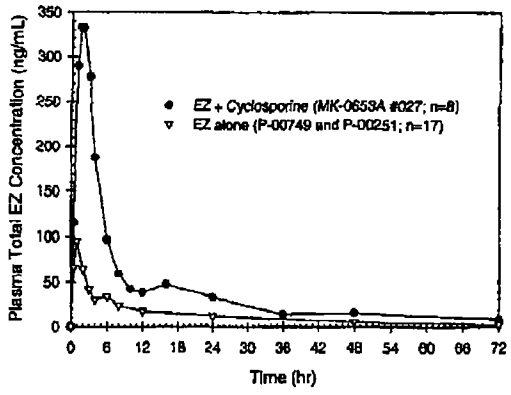
The results of this study indicate an approximate 3.4-fold higher $AUC_{0\text{-last}}$ for total ezetimibe in renal transplant patients taking cyclosporine as compared to a pooled historical healthy control population. Of note, a 3.9-fold increase in C_{max} was also observed in the cyclosporine group, suggesting that this effect appears to be a result of an increase in bioavailability. Data for the prespecified primary end point, total ezetimibe, are presented. Parallel data for ezetimibe, presented for completeness, have been included in Appendix II.

Total Ezetimibe

Mean plasma-concentration time profiles of total ezetimibe following a single oral 10 mg dose of ezetimibe with or without cyclosporine are depicted in Figure 2. Mean plasma concentrations were higher in renal transplant patients that were coadministered cyclosporine than the healthy control subjects.

Figure 2

Mean Total Ezetimibe Plasma Concentration-Time Profiles Following a 10-mg Single Oral Dose Ezetimibe With or Without Cyclosporine Coadministration.
(Preliminary Data Protocol No. 027)



Total Ezetimibe $AUC_{0\text{-last}}$

Total ezetimibe plasma $AUC_{0\text{-last}}$ was the primary pharmacokinetic endpoint in this study. Individual total ezetimibe $AUC_{0\text{-last}}$ values for renal transplant patients on cyclosporine

evaluated in this study as well as healthy control subjects are shown in Figure 3 and are listed in Appendix I, Table 1. Summary statistics, derived from an ANCOVA model, are presented in Table 3. The geometric least-squares mean $AUC_{0\text{-last}}$ of total ezetimibe following a single oral dose of ezetimibe 10 mg was 2867.3 ng•hr/mL in renal transplant patients on steady-state cyclosporine treatment and 840.5 ng•hr/mL in healthy control subjects. The least-squares mean ratio of total ezetimibe $AUC_{0\text{-last}}$ (patients on cyclosporine/historical control subjects) was 3.41 with a 90% confidence interval (CI) of (2.55, 4.56). This CI exceeded the pre-specified bounds of (0.50, 2.00). The between-treatment-group p-value ($p \leq 0.001$), was highly statistically significant. In Appendix I, Figure 1 almost all the adjusted Z-scores of postrenal transplant patients who had a single oral dose of ezetimibe 10 mg in the setting of steady-state cyclosporine dosing were above 2. This additional information also supports that the mean $AUC_{0\text{-last}}$ value for the group of postrenal transplant patients who had a single oral dose of ezetimibe 10 mg in the setting of steady-state cyclosporine dosing was higher than the mean $AUC_{0\text{-last}}$ value for the historical control group.

Table 3

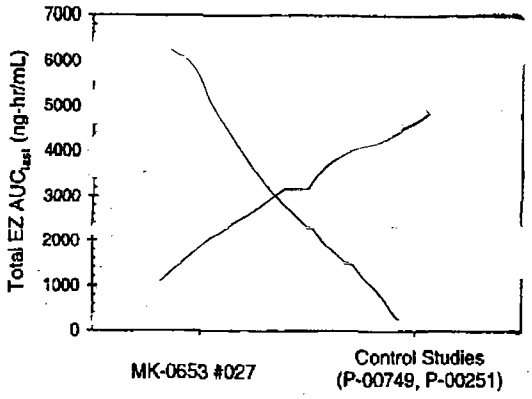
Summary Statistics for $AUC_{0\text{-last}}$ Total Ezetimibe (ng•hr/mL)
Following a Single Oral Ezetimibe 10 mg Dose With or
Without Cyclosporine Coadministration.
(Preliminary Data Protocol No. 027)

Treatment	N	Geometric LS Mean†	Median	Min	Max	SD‡	GMR‡	90% CI for GMR	p-Value
Ezetimibe + cyclosporine	8	2867.3	2495.5	1895.1	6613.3	1240.6	3.41	(2.55, 4.56)	<0.001
Ezetimibe	17	840.5	852.0	538.0	1579.0	356.31			

† Back-transformed from log scale.
‡ Least-squares mean ratio.
GMR = Geometric mean ratio.
SD = Standard deviation.

Figure 3

Individual (and Arithmetic Mean) Plasma Total Ezetimibe $AUC_{0\text{-last}}$ Values Following Administration of a Single Oral Ezetimibe 10 mg Dose With or Without Cyclosporine (Preliminary Data Protocol No. 027)



Total Ezetimibe C_{max}

Individual total ezetimibe C_{max} values for renal transplant patients on cyclosporine evaluated in this study as well as healthy control subjects are in Figure 4 and listed in Appendix I, Table 2. Summary statistics for C_{max} of total ezetimibe are provided in Table 4. The geometric least-squares mean C_{max} of total ezetimibe following a single oral dose of ezetimibe 10 mg was 363.2 ng/mL in the setting of steady-state cyclosporine dosing and 92.9 ng/mL without cyclosporine pretreatment. Consistent with the $AUC_{0\text{-last}}$ results, the least-squares mean ratio of total ezetimibe C_{max} (patients on cyclosporine)/historical control subjects) was 3.91 with a 90% confidence interval (CI) of (3.13, 4.89). The difference between treatment groups was significant ($p \leq 0.001$). Most of the adjusted Z-scores of postrenal transplant patients who had a single oral dose of ezetimibe 10 mg in the setting of steady-state cyclosporine dosing were also above 2.00 (Appendix I, Figure 2). This additional information also supports that the mean C_{max} value for the group of postrenal transplant patients who had a single oral dose of ezetimibe 10 mg in the setting of steady-state cyclosporine dosing was higher than the mean C_{max} value for the historical control group.

Table 4

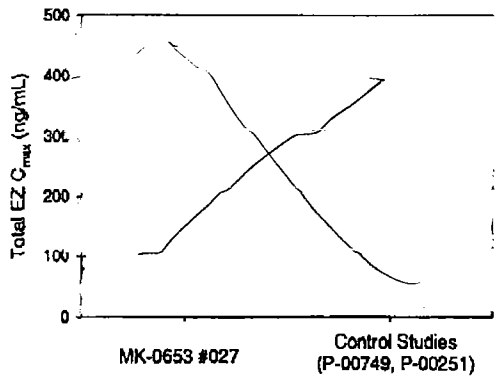
Summary Statistics for C_{max} Total Ezetimibe (ng/mL)
Following a Single Oral Ezetimibe 10 mg Dose With
or Without Cyclosporine Coadministration.
(Preliminary Data Protocol No. 027)

Treatment	N	Geometric LS Mean[†]	Median	Min	Max	SD	GMR[‡]	90% CI for GMR	p-Value
Ezetimibe + cyclosporine	8	363.2	360.2	279.0	405.0	54.36	3.91	(3.13, 4.89)	<0.001
Ezetimibe	17	92.9	101.0	32.7	190.0	53.53			

[†] Back-transformed from log scale.
[‡] Least-squares mean ratio.
GMR = Geometric mean ratio.
SD = Standard deviation.

Figure 4

Individual (and Arithmetic Mean) Plasma Total Ezetimibe C_{max} Values Following
Administration of a Single Oral Ezetimibe 10 mg Dose With or Without Cyclosporine
(Preliminary Data Protocol No. 027)



Total Ezetimibe T_{max}

Summary statistics of T_{max} for total ezetimibe are in Table 5 and individual T_{max} values are listed in Appendix I, Table 3. The median T_{max} values (with minimum and maximum) of total ezetimibe following a single oral dose of ezetimibe 10 mg were 1.5 (1.0, 3.0) hr in the setting of steady-state cyclosporine dosing and 1.0 (0.5, 6.0) hr without cyclosporine pretreatment. The very small difference in T_{max} between the 2 treatment groups was significantly different ($p = 0.010$).

Table 5

Summary Statistics for T_{max} Total Ezetimibe (hr)
Following a Single Oral Ezetimibe 10 mg Dose With or
Without Cyclosporine Coadministration (Preliminary Data Protocol No. 027)

Treatment	N	Mean	Median	Min	Max	SD[†]	Between Group p-Value[‡]
Ezetimibe + cyclosporine	8	1.8	1.5	1.0	3.0	0.60	0.010
Ezetimibe	17	1.4	1.0	0.5	6.0	1.24	

[†] Between-subject standard deviation.
[‡] p-Value based on rank transformation.

Ezetimibe and Ezetimibe-Glucuronide Apparent Elimination $t_{1/2}$

Individual total ezetimibe apparent elimination $t_{1/2}$ was not directly determined because total ezetimibe is comprised of 2 species (ezetimibe and ezetimibe glucuronide) that may have different plasma elimination kinetics. For this reason, apparent elimination $t_{1/2}$ values were determined for ezetimibe and ezetimibe glucuronide, and not for total ezetimibe directly. Individual ezetimibe and ezetimibe glucuronide summary statistics are presented in Tables 6 and 7 and apparent $t_{1/2}$ values are listed in Appendix I, Tables 4 and 5 respectively.

The least-squares mean $t_{1/2}$ values of ezetimibe following a single oral dose of ezetimibe 10 mg were 22.2 hr and 19.9 hr with and without cyclosporine pretreatment respectively. The difference between treatment groups was not significant ($p = 0.508$).

The least-squares mean $t_{1/2}$ values of ezetimibe glucuronide following a single oral dose of ezetimibe 10 mg were 24.0 hr and 19.2 hr with and without cyclosporine pretreatment respectively. The difference between treatment groups was not significant ($p = 0.187$). The lack of significant change between cyclosporine-treated and noncyclosporine-treated groups for $t_{1/2}$ of both active analytes supports the interpretation that coadministration of cyclosporine does not change the apparent elimination $t_{1/2}$ of ezetimibe.

In Appendix I, Figures 3 and 4, all of the adjusted Z-scores for apparent $t_{1/2}$ of ezetimibe and ezetimibe glucuronide of postrenal transplant patients who had a single oral dose of ezetimibe 10 mg in the setting of steady-state cyclosporine dosing were scattered around 0 and were contained within the bounds of (-2, 2).

Table 6

Summary Statistics for Apparent Elimination $t_{1/2}$ (hr) of Ezetimibe Following a Single Oral Ezetimibe 10 mg Dose With or Without Cyclosporine Coadministration (Preliminary Data Protocol No. 027)

Treatment	N	LS Mean[§]	Median	Min	Max	Jackknife SD[†]	Between Group p-Value[‡]
Ezetimibe + cyclosporine	8	22.2	23.9	14.5	36.4	7.54	0.508
Ezetimibe	16	19.9	21.1	12.3	49.9	6.41	

[†] Between-subject Standard Deviation
[‡] p-Value Based on Inverse Transformation
[§] Back -transformed from inverse scale

Table 7

Summary Statistics for Apparent Elimination $t_{1/2}$ (hr) of Ezetimibe Glucuronide Following a Single Oral Ezetimibe 10 mg Dose With or Without Cyclosporine Coadministration (Preliminary Data Protocol No. 027)

Treatment	N	LS Mean[§]	Median	Min	Max	Jackknife SD[†]	Between Group p-Value[‡]
Ezetimibe + cyclosporine	8	24.0	27.0	15.2	38.3	7.24	0.187
Ezetimibe	16	19.2	18.0	11.0	42.1	6.55	

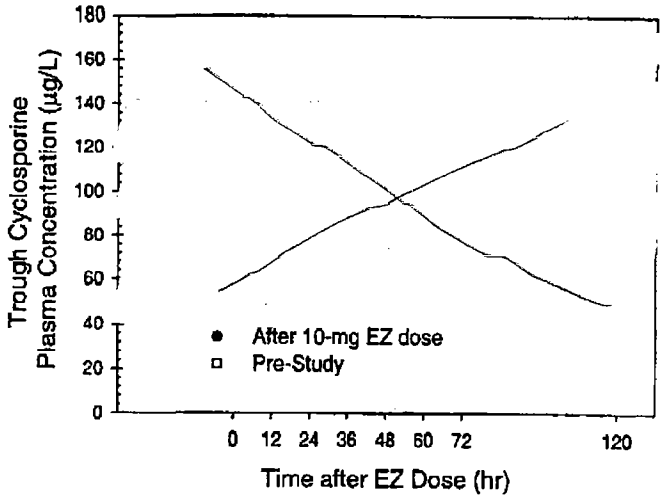
[†] SD = Between-subject standard deviation.
[‡] p-Value based on inverse transformation.
[§] Back -transformed from inverse scale.

Cyclosporine Trough Plasma Levels

The mean cyclosporine trough concentrations measured every 12 hours following a single 10-mg dose of ezetimibe remained stable for 120 hours following ezetimibe administration. Summary statistics for trough cyclosporine concentration from the time of the coadminstrations of ezetimibe 10 mg and cyclosporine to 120 hours later are depicted graphically in Figure 5 and shown in Appendix III, Table 1.

Figure 5

Trough Cyclosporine Plasma Concentrations With Continuous Administration of Cyclosporine Twice Daily Following a Single Oral Ezetimibe 10 mg Dose Mean (± SD) (Preliminary Data Protocol No. 027)



V. Safety Assessment

Coadministation of ezetimibe in the setting of steady-state cyclosporine dosing was well tolerated. There were no serious adverse experiences or laboratory adverse experiences recorded for this study. Table 1 of Appendix IV contains all of the clinical adverse events reported for Protocol No. 027. No patients were discontinued from the study due to adverse experiences.

VI. Discussion

The results of this study indicate that the mean total exposure of total ezetimibe in post-renal transplant patients on cyclosporine is approximately 3.4-fold higher than in the healthy pooled historical control population.

The implications of the increased exposures of ezetimibe in the setting of cyclosporine administration were reviewed in light of available animal and human clinical safety data. There were no animal toxicology findings in multiple dose studies at the highest exposures studied as ezetimibe monotherapy. The exposures in animals exceeds exposures achieved in humans at the 10-mg clinical dose and are approximately 3-fold

greater than in renal transplant patients on cyclosporine / ——— /

Additionally, the mean exposures in this study were similar to those observed in the phase I multiple-dose study (n = 9) in which 50-mg ezetimibe was administered daily for 14 days / ——— / and generally well tolerated. In an 8 week multiple dose safety and pharmacodynamic study in which rising doses of ezetimibe were administered for 8 weeks (up to 40 mg per day, n = 18), an analysis of ezetimibe trough levels for that study suggests similar mean ezetimibe exposures were attained to those in patients on chronic cyclosporine. The safety profile at the 40 mg ezetimibe dose was similar to that of the lower doses ——— In both studies, the highest exposures were well tolerated without higher incidence of total adverse experiences or evidence of dose-related toxicity.

VII Conclusions

In summary, the case of a single complex renal transplant patient with severe renal impairment, multiple concomitant medications, and cyclosporine coadministration, in which the 12-fold higher ezetimibe exposure was seen, may not be representative of the magnitude of interaction which would be expected with cyclosporine use in the typical transplant population, as evidenced by the mean approximately 3.4-fold higher total ezetimibe total exposure (2.3 to 7.9-fold relative to the mean exposure in healthy controls) observed in this study in renal transplant patients with relatively normal renal function.

Protocol No 027: Appendix V
Site: ———

Investigators: ———

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/s/

Wei Qiu
7/9/03 03:29:33 PM
BIOPHARMACEUTICS

Hae-Young Ahn
7/22/03 10:44:25 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-445/S001/S003/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Metabolic & Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-445/S-001, S-003, S-004

Name of Drug: Zetia (ezetimibe) Tablets, 10 mg.

Applicant: MSP Singapore Company, LLC

Material Reviewed:

Submission Date(s): July 13, 2004, Package insert (PI), patient package insert (PPI), final printed labeling (FPL)

Receipt Date(s): July 14, 2004

Background and Summary

Zetia was approved October 25, 2003 for the treatment of patients with primary hypercholesterolemia, homozygous familial hypercholesterolemia, and homozygous familial sitosterolemia.

The PI and the PPI are joined via perforation. The identifier and revision date will change ONLY if that piece of the labeling is revised (the revision of the PI will not AUTOMATICALLY cause the identifier and revision date of the PPI to be modified)

S-001, submitted 4/3/03, provides for the addition of a Post-Marketing subsection to the ADVERSE REACTIONS section of the PI to include hypersensitivity reactions, including angioedema and rash. The PPI was also revised to include this information.

S-003, submitted 4/24/03, provides revisions to the CLINICAL PHARMACOLOGY (Drug Interactions subsection) and PRECAUTIONS (Cyclosporine subsection) sections to include information from a study of multiple dosing of cyclosporine on the PK of a single dose of ezetimibe.

S-001 and S-003 were AE on January 14, 2004, pending FPL identical to that submitted on December 17, 2003. (See PM labeling review dated 1/9/04).

S-004 was submitted May 5, 2004, as a "Changes Being Effected" under 21 CFR 314.70 (c) and proposed the following revisions.

Package insert

-revision of the ADVERSE REACTIONS section to include pancreatitis and nausea.
-revision of the OVERDOSE section

Patient Package Insert
-revise the "What are the possible side effects of ZETIA" to include "inflammation of the pancreas, and nausea"

In addition, some minor editorial revision (such as replacing the "TM" symbol with "®") throughout the labeling have been made.

The revisions proposed for the PI and PPI in S-004 were found acceptable by the medical officer (Karen Murry Mahoney, MD) in her review dated 7/2/04.

Revised labeling for S-004 which included the labeling revisions that were AE for S-001 and S-003, as well as the labeling revision that SHOULD have been submitted with S-002 (approved 7/14/03, see 1/9/04 labeling review for S-001, S-002, and S-003) was submitted July 13, 2004.

Review

PI
The proposed FPL (**Identifier 25751841T, REV 03, Issued April 2004**) was compared to the labeling that was AE for S-001 and S-003, the FPL that was submitted for S-002.

Although not mentioned in the cover letter or highlighted in the marked-up version of the labeling, the firm made the following **BOLDED** revisions to the CLINICAL PHARMACOLOGY and PRECAUTIONS sections of the PI:

(CLINICAL PHARMACOLOGY) "Cyclosporine**:** In a study of eight post-renal transplant patients with mild **(mildly)** impaired or normal renal function…., compared to **(historical)** healthy control population (n=17).

(PRECAUTIONS, Cyclosporine subsection): Cyclosporine: Caution should be exercised when initiating ezetimibe in patients… In a pharmacokinetic study in post-renal transplant patients with mild **(mildly)** impaired or normal renal function….

According to Hae Young Ahn, PhD, Clinical Pharmacology Team Leader, these revisions are acceptable.

PPI

The proposed PPI (**Identifier 25751744T, REV 03, Issued April 2004**) was compared to the labeling that was AE for S-001 and S-003, the FPL that was submitted for S-002. No other revisions have been made other than those found acceptable by the medical officer.

Conclusions

The FPL submitted by the firm on July 13, 2004 is acceptable. An APPROVAL letter should be issued.

The currently approve PI and PPI for NDA 21-445 follows:
-PI- **Identifier 25751841T, REV 03, Issued April 2004**
-PPI-**Identifier 25751744T, REV 03, Issued April 2004**

Kati Johnson
Supervisor, Project Management Staff

DIVISION OF METABOLIC & ENDOCRINE DRUG PRODUCTS

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 21-445/S-001, S-002, S-003

Name of Drug: Zetia (ezetimibe) Tablets, 10 mg.

Applicant: MSP Singapore Company, LLC

Material Reviewed:
-SLR-001, submitted April 3, 2003, package insert (PI) and patient package insert (PPI)
-SLR-003, submitted April 24, 2003, PI
-amended October 13, 2003, PI
-amended December 16, 2003, PI and PPI
-SCM-002, Final printed labeling (FA) submitted October 6, 2003, PI and PPI

BACKGROUND AND SUMMARY

Zetia was approved October 25, 2001 for treatment of patients with primary hypercholesterolemia, homozygous familial hypercholesterolemia, and homozygous familial sitosterolemia.

The HOW SUPPLIED section of the PI lists the following presentations:
-bottles of 30
-bottles of 90
-bottles of 500
-unit dose package of 100

NOTE-The PI and PPI are attached via a perforation. According to Mr. Jack Scannelli (Regulatory Affairs, Schering Corporation) the identifier for the PI and the PPI will ONLY change if that piece of labeling is revised.

S-001 was submitted April 3, 2003, and proposed to revise the ADVERSE REACTIONS section of the PI to include a Post-Marketing Experience subsection containing the following text:

> "The following adverse reactions have been reported in post-marketing experience: Hypersensitivity reactions, including angioedema and rash"

The supplement also proposed to revise the PPI to include a more detailed response to the question **"What are the possible side effects of ZETIA?"**

Although the supplement was submitted as a "Special Supplement-Changes Being Effected", the application did not contain FPL, and the sponsor was notified in the Acknowledgement letter that it would be reviewed as a Prior Approval supplement.

S-002 was submitted April 17, 2003, and provided, among other things, for the addition of the Merck & Co., Inc., West Point, PA facility as a manufacturing and controls site for the drug product. In addition, it provided for the [redacted] The supplement was approved July 14, 2003.

When the supplement was submitted, it DID NOT contain revised labeling. It did contain a statement in the cover letter that the labeling would be revised to include the following underlined statement for those tablets manufactured at the West Point facility: "Manufactured for Merck/Schering-Plough Pharmaceuticals, North Wales, PA 19454, USA By Merck & Co., Inc., Whitehouse Station, NJ 08889, USA"

In a subsequent telephone conversation with Mr. Jack Scannelli at Schering Corporation, I was told that the sponsor was under the mistaken impression that FPL of the PI and PPI (which both contain the manufacturing site) could be submitted AFTER approval of the supplement. Mr. Scannelli was informed that labeling MUST be included with the supplemental application prior to approval. Otherwise, the proposed labeling is NOT approved.

S-003 was submitted April 24, 2003 and proposed to revise the PRECAUTIONS section, Cyclosporine subsection, to include information from a study of multiple dosing of cyclosporine on the PK of a single dose of ezetimibe.

The supplement also proposed to revise the CLINICAL PHARMACOLOGY section, Drug Interactions subsection with information from this study.

Following review by the Biopharmaceutics team, an FDA "counterproposal" for the cyclosporine text in the PI was faxed to the firm. In the October 13, 2003 response to the fax, the firm proposed some alternate language. This language was found acceptable (see review below). In response to my request, the firm submitted revised labeling for both the PI and PPI on December 17, 2003. This was the first submission of proposed PPI text in S-003 (see review below).

REVIEW

The PI in the amended S-003 submission dated October 13, 2003 contains all the revisions proposed in S-001.

The PI in the S-002 FPL is identical to the labeling contained in the October 13, 2003 amendment to S-003. The "Complimentary" carton is identical, with some minor formatting changes, to that approved with the original NDA except that the following statement has been added: [redacted]

In a December 16, 2003 conversation with Mr. Jack Scannelli (Regulatory Affairs, Schering Corporation, 908-740-5715) he stated that the PI contained in S-002 and S-003

This amendment was submitted December 17, 2003 and contained a PI and PPI

SINGLE PI and PPI for this product.

During the review of S-003, there were some negotiations on the proposed wording of the PI. The following wording was found acceptable by both the sponsor and the Agency (see October 28, 2003 MEMO to FILE from Wei Qiu, PhD, Clinical Pharmacology Reviewer):

CLINICAL PHARMACOLOGY section, Drug Interactions subsection:
"Cyclosporine: In a study of eight post-renal transplant patients with mild impaired or normal renal function (creatinine clearance of >50 mL/min), stable doses of cyclosporine (75 to 150-mg twice daily) increased the mean AUC and Cmax values of total ezetimibe 3.4-fold (range 2.3 – 7.9 fold) and 3.9-fold (range 3.0 to 4.4-fold), respectively, compared to a healthy control population (n=17). 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."

PRECAUTIONS:
"Cyclosporine: Caution should be exercised when initiating ezetimibe in patients treated with cyclosporine due to increased exposure with ezetimibe. This exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mild impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and Cmax of total ezetimibe 3.4-fold (range 2.3 – 7.9 fold) and 3.9-fold (range 3.0 to 4.4-fold), respectively. In a separate study, the total ezetimibe level **(exposure)** increased 12-fold in one renal transplant patient with severe renal function **(insufficiency)** receiving multiple medications, including cyclosporine (see CLINICAL PHARMACOLOGY, *Drug Interactions*).

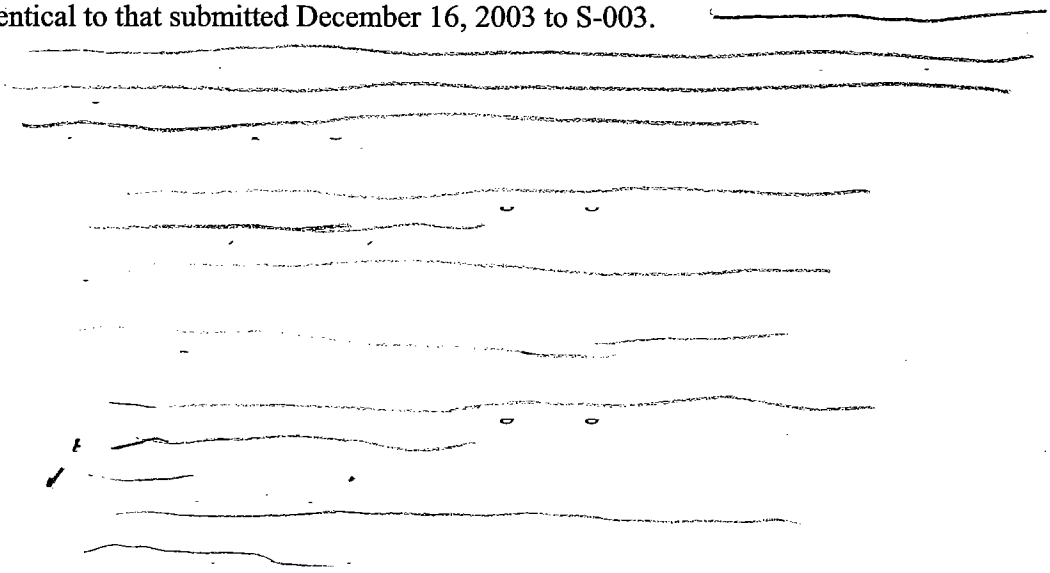
NOTE-The October 13, 2003 submission contained the identical wording that was found acceptable in the 10/28/03 Biopharm review EXCEPT that it contained the bolded words above was replaced with "exposure", and was

replaced with "insufficiency"). This revised text was found acceptable by Hae Young Ahn, PhD, Biopharmaceutics Team Leader on December 22, 2003).

There was no PPI labeling contained in the original submission of S-003. However, when the supplement was amended on December 17, 2003, that submission contained a PPI. The PPI is identical to what was submitted for S-002. The PPI also contains the revisions proposed in S-001.

Conclusion

An approval letter should be issued for S-001 and S-003, requesting FPL (PI and PPI) identical to that submitted December 16, 2003 to S-003.



An Acknowledge and Retain letter should be issued for the FPL submission to S-002 s only, as the PI and PPI are superceded by the labeling contained in S-003).

Labeling Reviewer: Kati Johnson, Chief, Project Management Staff, HFD-510

MEMO TO FILE

RE: NDA 21445 (ZETIA®, SCHERING CORPORATION) SPECIAL LABELING SUPPLEMENT- CHANGES BEING EFFECTED

Date of supplement letter: 5 May 04

Date of memo: 2 Jul 04

Medical Officer: Karen Murry Mahoney, MD, DMEDP

Due to postmarketing reports of pancreatitis, the Division of Metabolic and Endocrine Drug Products requested the addition of pancreatitis to the Zetia® product label. Please see my review from Feb 04 and the Supplement Request Letter from Mar 04, both in DFS. Schering submitted a Special Labeling Supplement for Changes Being Effected (CBE) on 5 May 04, which included new language for the label for pancreatitis, and additional information regarding nausea and overdose. After review by the medical officer, those changes were considered acceptable, and were permitted to go into effect. However, Schering now requests a formal approval letter; this memo is in support of that letter.

The proposed changes (with brief comments from the medical reviewer in *italics*) include:

1. In the ADVERSE REACTIONS section of product label, Postmarketing Experience subsection, the sponsor proposes to add "pancreatitis" and "nausea" to the list of events noted with postmarketing experience with Zetia®.

These additions are acceptable. DMEDP had previously requested the addition of pancreatitis to the label. Review of the sponsor's submission and the Adverse Event Reporting System support the addition of nausea to the Postmarketing Experience subsection also.

2. In the OVERDOSAGE section of the product label, the sponsor proposes the following changes (deletions are marked with a strikethrough line; additions are underlined):

~~Administration~~ In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdosage with ZETIA have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

The sponsor has received nine case reports of overdosage of Zetia®. Four cases involved adults ranging in age from 54-73 years old. All involved 20 mg/day instead of the recommended 10 mg/day, taken for 1-90 days. No adverse effects were reported, and no therapy for overdose was reported. Three children were reported to have taken Zetia® accidentally. One 18 month old female took a single dose of up to 150 mg (father was a Zetia® study subject); one 18 month old male took a single 10 mg dose; and one 3 year old male took a single dose of 20 mg. No adverse effects or therapy for overdose were reported. Two other males of unknown age also took doses of 20 mg/day; one for 49 days and one for an unknown amount of time. Neither received treatment for overdose. The latter male reported muscle pain lasting a few weeks, which resolved after the Zetia® was discontinued.

The sponsor's wording is reasonable.

3. In the Patient Package Insert, in the section entitled "What are the possible side effects of ZETIA?", the sponsor proposes to add "inflammation of the pancreas, and nausea".

As above, these changes are supported. The use of the term "inflammation of the pancreas" for pancreatitis is a reasonable descriptive term.

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/s/

Karen Mahoney
7/2/04 03:40:28 PM
MEDICAL OFFICER

MEMO TO FILE

22 APR 03

RE: N21445 ZETIA (EZETIMIBE, SCHERING/MERCK) LABELING CHANGE BEING EFFECTED REGARDING ANGIOEDEMA AND RASH

Document Date: 3 Apr 03; received 7 Apr 03

Document ID: SLR001

Reviewer: Karen Murry Mahoney, MD

The sponsor submits a special labeling supplement for changes being effected in their label for Zetia (ezetimibe). Since approval of the drug in Oct 02, the sponsor has received 6 reports of angioedema, and 36 reports of rash. The Agency has received an additional 3 case reports of angioedema which appear to be separate cases from those identified by the sponsor. The sponsor proposes the following addition to the "ADVERSE REACTIONS" section of the product label, under the subheading "Postmarketing Experience":

"The following adverse reactions have been reported in post-marketing experience: Hypersensitivity reactions, including angioedema and rash."

The sponsor also proposes the addition of the following to the Patient Product Information Sheet (PPIS), under the heading "What are the possible side effects of ZETIA?"

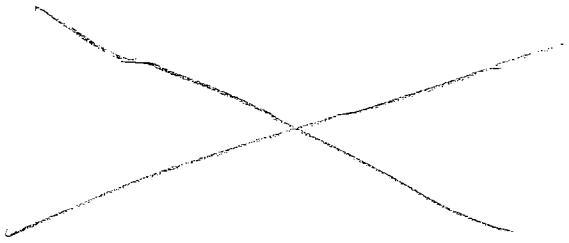
"Additionally, the following side effects have been reported in general use: allergic reactions (which may require treatment right away) including swelling of the face, lips, tongue and/or throat that may cause difficulty in breathing or swallowing, and rash.

Tell your doctor if you are having these or any other medical problems while on ZETIA. For a complete list of side effects, ask your doctor or pharmacist."

The above changes appear prudent and proactive on the sponsor's part. The reviewer has been aware of these reports, and plans to continue to follow incoming reports. Because angioedema can be associated with airway obstruction and/or anaphylaxis, emergence of significant numbers of cases of angioedema might necessitate stronger labeling changes. At this time, however, the number of reported cases is modest, and the sponsor's proposed inclusion of angioedema in the product label and PPIS appears appropriate.

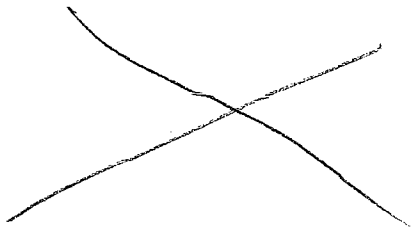
Karen Murry Mahoney MD

WAES case report numbers identified by sponsor in this submission, for angioedema:

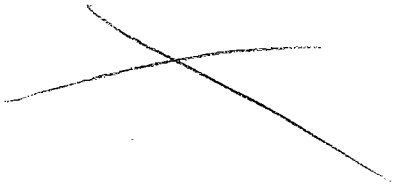


AERS cases of angioedema (discussed with Jennie Chang of FDA Office of Drug Safety; these appear to be additional reports):

Additional case reports regarding possible hypersensitivity from sponsor's periodic adverse event report 25 Oct 02-25 Jan 03:



Additional AERS reports regarding possible hypersensitivity:



Several cases of urticaria were reported both by the sponsor and in AERS, but are not listed in this memo.

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/s/

Karen Mahoney
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MEDICAL OFFICER

MEMO TO FILE

FROM: WEI QIU, Ph.D.
TO: NDA 21-445
DATE: October 13, 2003
SUBJECT: Response to Office of Clinical Pharmacology and Biopharmaceutical Review Report on Proposed Cyclosporine Labeling Changes

On October 13, 2003, MSP Singapore company LLC submitted a response to the Agency's labeling comments for the approved ZETIA™ (ezetimibe) regarding the Cyclosporine subsection of **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** sections of the package insert.

The following labeling recommendations were sent to the sponsor:

Under *Cyclosporine* subsection of **CLINICAL PHARMACOLOGY** section:

Cyclosporine: In a study of eight post-renal transplant patients with mild impaired or normal renal function (creatinine clearance of >50 mL/min) stable doses of cyclosporine (75 to 150-mg twice daily) increased the mean AUC and Cmax values of total ezetimibe, 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively compared to a healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects

Under *Cyclosporine* subsection of **PRECAUTIONS** section:

Cyclosporine

For **CLINICAL PHARMACOLOGY** section, the sponsor accepted the agency's recommendation with minor editorial revisions that are acceptable.

For **PRECAUTIONS** section, the sponsor proposed to replace the first sentence of the agency's recommendation with the following:

Caution should be exercised when initiating ezetimibe in patients treated with cyclosporine due to increased exposure to ezetimibe. This exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe.

This reviewer consulted with Dr. Mary Parks, Deputy Director of DMEDP. Dr. Parks agreed that the significant increase in exposure to ezetimibe might post safety concern for patients receiving cyclosporine especially in those with severe renal insufficiency. However, since the side effects of this product can be monitored, the sponsor's proposed labeling revision is acceptable. The sponsor accepted the remaining part of the agency's recommendation with minor editorial changes that are acceptable.

In summary, the proposed labeling revision provided by the sponsor is acceptable.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
10/21/03 12:26:21 PM
BIOPHARMACEUTICS

Hae-Young Ahn
10/28/03 10:08:15 AM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445/S-003

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products
U.S. Agent for MSP Singapore Co., LLC
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zetia (ezetimibe) 10 mg Tablets

NDA Number: 21-445

Supplement Number: S-003

Date of Supplement: April 24, 2003

Date of Receipt: April 25, 2003

This supplemental application was submitted as a "Changes Being Effected in 30 Days" supplement and proposes to add a "Cyclosporine" subsection to the Drug Interactions subsection of the CLINICAL PHARMACOLOGY section and to revise the "Cyclosporine" subsection of the PRECAUTIONS section of the package insert. However, the submission does not qualify because the Agency does not agree that the proposed changes increase the safe use of the drug. Also, the Agency must review the study before accepting the labeling changes. Therefore, this supplement will be reviewed as a prior approval supplement. Changes of this kind cannot be put into effect prior to approval of a supplement. An approved supplement is required for these proposed changes prior to distributing drug products made with these changes.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 24, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 25, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
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