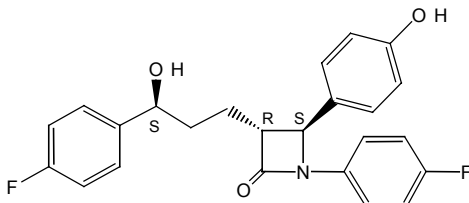


# ZETIA™ (EZETIMIBE) TABLETS

## 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<sub>24</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>3</sub>. 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 ( $\geq 65$  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 3-4 fold and 5-6 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  $\leq 30$  mL/min/1.73 m<sup>2</sup>), 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<sub>max</sub> 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  $\geq 130$  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  $\geq 130$  mg/dl) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C<sub>max</sub> 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  $\geq 130$  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.

## 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<sub>50</sub> value of 0.5 µg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED<sub>50</sub> 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 C14 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<sup>a</sup> % Change from Untreated Baseline<sup>b</sup>)

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

<sup>a</sup> For triglycerides, median % change from baseline

<sup>b</sup> Baseline - on no lipid-lowering drug

<sup>c</sup> 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<sup>a</sup> in Patients with Hypercholesterolemia**  
(Mean<sup>b</sup> % Change from Treated Baseline<sup>c</sup>)

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

<sup>a</sup> Patients receiving each HMG-CoA reductase inhibitor: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)

<sup>b</sup> For triglycerides, median % change from baseline

<sup>c</sup> Baseline - on an HMG-CoA reductase inhibitor alone.

<sup>d</sup> 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.)

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