HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EZETIMIBE TABLETS safely and effectively. See full prescribing information for EZETIMIBE TABLETS.

EZETIMIBE tablets, for oral use
Initial U.S. Approval: 2002

----RECENT MAJOR CHANGES----

Indications and Usage (1)	7/2023
Dosage and Administration (2)	7/2023
Contraindications (4)	7/2023
Warnings and Precautions (5.1, 5.2, 5.3)	7/2023

----INDICATIONS AND USAGE----

Ezetimibe tablets are indicated (1):

- In combination with a statin, or alone when additional low density lipoprotein cholesterol (LDL-C) lowering therapy is not possible, as an adjunct to diet to reduce elevated LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).
- In combination with a statin as an adjunct to diet to reduce elevated LDL-C in pediatric patients 10 years of age and older with HeFH.
- In combination with fenofibrate as an adjunct to diet to reduce elevated LDL-C in adults with mixed hyperlipidemia.
- In combination with a statin, and other LDL-C lowering therapies, to reduce elevated LDL-C levels in adults and in pediatric patients 10 years of age and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the reduction of elevated sitosterol and campesterol levels in adults and in pediatric patients 9 years of age and older with homozygous familial sitosterolemia.

When ezetimibe tablets are used in combination with a statin, fenofibrate, or other LDL-C lowering therapies, refer to the Prescribing Information of these products for information on the safe and effective use (1).

----DOSAGE AND ADMINISTRATION----

- 10 mg orally once daily, with or without food (2)
- Administer ezetimibe tablets either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant. (2)
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating ezetimibe tablets. (2)

----DOSAGE FORMS AND STRENGTHS----

- Tablets: 10 mg (3)

----CONTRAINDICATIONS----

- Hypersensitivity to ezetimibe or any excipient of ezetimibe tablets. (4)
- When used in combination with a statin, fenofibrate, or other LDL-C lowering therapy, ezetimibe tablets are contraindicated in patients for whom a statin, fenofibrate, or other LDL-C lowering therapy are contraindicated. Refer to the Prescribing Information of these products for a list of their contraindications. (4)

----WARNINGS AND PRECAUTIONS----

- Risks Associated with Combination Treatment with a Statin, Fenofibrate, or Other LDL-C Lowering Therapies: Refer to the Prescribing Information of these products for a description of their risks including, but not limited to, the warnings and precautions. (5.1)
- Liver Enzyme Abnormalities and Monitoring: Increases in serum transaminases have been reported with use of ezetimibe. Perform liver enzyme testing as clinically indicated and consider withdrawal of ezetimibe if increases in ALT or AST ≥3 X ULN persist. (5.2)
- Skeletal Muscle Effects (e.g., Myopathy and Rhabdomyolysis): Ezetimibe may cause myopathy and rhabdomyolysis. In post-marketing reports, most patients who developed rhabdomyolysis were taking a statin or other agents known to be associated with an increased risk of rhabdomyolysis, such as fibrates. If myopathy is suspected, discontinue ezetimibe and other concomitant medications, as appropriate. (5.3)

----ADVERSE REACTIONS----

- Common adverse reactions in clinical trials:
  - o Ezetimibe administered alone (incidence ≥2% and greater than placebo): upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity, fatigue, and influenza. (6.1)
  - o Ezetimibe coadministered with a statin (incidence ≥2% and greater than statin alone): nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea, back pain, influenza, pain in extremity, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----DRUG INTERACTIONS----

- Cyclosporine: Combination increases exposure of ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients taking ezetimibe concomitantly. (7)
- Fibrates: Coadministration of ezetimibe with fibrates other than fenofibrate is not recommended until use in patients is adequately studied. If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder studies are indicated, and alternative lipid-lowering therapy should be considered. (7)
- Bile Acid Sequestrants: Cholestyramine combination decreases exposure of ezetimibe. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ezetimibe tablets are indicated:

- In combination with a statin, or alone when additional low-density lipoprotein cholesterol (LDL-C) lowering therapy is not possible, as an adjunct to diet to reduce elevated LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).
- In combination with a statin as an adjunct to diet to reduce elevated LDL-C in pediatric patients 10 years of age and older with HeFH.
- In combination with fenofibrate as an adjunct to diet to reduce elevated LDL-C in adults with mixed hyperlipidemia.
- In combination with a statin, and other LDL-C lowering therapies, to reduce elevated LDL-C levels in adults and in pediatric patients 10 years of age and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the reduction of elevated sitosterol and campesterol levels in adults and in pediatric patients 9 years of age and older with homozygous familial sitosterolemia.

When ezetimibe tablets are used in combination with a statin, fenofibrate, or other LDL-C lowering therapies, refer to the Prescribing Information of these products for information on the safe and effective use.

2 DOSAGE AND ADMINISTRATION

- The recommended dose of ezetimibe tablets is 10 mg orally once daily, administered with or without food.
- If as dose is missed, take the missed dose as soon as possible. Do not double the next dose.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating ezetimibe tablets.
- Administer ezetimibe tablets at least 2 hours before or 4 hours after administration of a bile acid sequestrant *[see Drug Interactions (7)]*.

3 DOSAGE FORMS AND STRENGTHS

Ezetimibe tablets USP, 10 mg are white to off-white, capsule shaped, flat faced bevel edged tablets debossed with 'I' on one side and '83' on the other side.

4 CONTRAINDICATIONS

Ezetimibe tablets are contraindicated in patients with a known hypersensitivity to ezetimibe or any of the excipients in ezetimibe tablets. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria have been reported *[see Adverse Reactions (6.2)]*.

When used in combination with a statin, fenofibrate, or other LDL-C lowering therapy, ezetimibe tablets are contraindicated in patients for whom a statin, fenofibrate, or other LDL-C lowering therapy are contraindicated. Refer to the Prescribing Information of these products for a list of their contraindications *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risks Associated with Combination Treatment with a Statin, Fenofibrate, or Other LDL-C Lowering Therapies

If ezetimibe is administered with a statin, fenofibrate, or other LDL-C lowering therapies, refer to the Prescribing Information of these products for a description of their risks including, but not limited to, the warnings and precautions *[see Contraindications (4)]*.

5.2 Liver Enzymes

Increases in serum transaminases have been reported with use of ezetimibe *[see Adverse Reactions (6.1)]*. In controlled clinical combination studies of ezetimibe initiated concurrently with a statin, the incidence of consecutive elevations (≥3 X ULN) in hepatic transaminase levels was 1.3% for patients treated with ezetimibe administered with statins and 0.4% for patients treated with statins alone. Perform liver enzyme testing as clinically indicated and consider withdrawal of ezetimibe if increases in ALT or AST ≥3 X ULN persist.

5.3 Myopathy/Rhabdomyolysis

Ezetimibe may cause myopathy [muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK)] and rhabdomyolysis *[see Adverse Reactions (6.1)]*. In post-marketing reports, most patients who developed rhabdomyolysis were taking a statin or other agents known to be associated with an increased risk of rhabdomyolysis, such as fibrates. If myopathy is suspected, discontinue ezetimibe and other concomitant medications, as appropriate.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Liver enzyme abnormalities *[see Warnings and Precautions (5.2)]*
- Rhabdomyolysis and myopathy *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Monotherapy
In 10 double-blind, placebo-controlled clinical trials, 2,396 patients with primary hyperlipidemia (age range 9 to 86 years; 50% female, 90% White, 5% Black or African American, 2% Asian, 3% other races; 3% identified as Hispanic or Latino ethnicity) and elevated LDL-C were treated with ezetimibe 10 mg daily for a median treatment duration of 12 weeks (range 0 to 39 weeks).

Adverse reactions reported in ≥2% of patients treated with ezetimibe and at an incidence greater than placebo in placebo-controlled studies of ezetimibe are shown in Table 1.

TABLE 1: Adverse Reactions Occurring ≥2% and Greater than Placebo in Ezetimibe -treated Patients

Adverse Reaction	Placebo (%) n = 1,159	Ezetimibe 10 mg (%) n = 2,396
Upper respiratory tract infection	2.5	4.3
Diarrhea	3.7	4.1
Arthralgia	2.2	3
Sinusitis	2.2	2.8
Pain in extremity	2.5	2.7
Fatigue	1.5	2.4
Influenza	1.5	2

Combination with a Statin
In 28 double-blind, controlled (placebo or active-controlled) clinical trials, 11,308 patients with primary hyperlipidemia (age range 10 to 93 years, 48% female, 85% White, 7% Black or African American, 3% Asian, 5% other races; 4% identified as Hispanic or Latino ethnicity) and elevated LDL-C were treated with ezetimibe 10 mg/day concurrently with or added to on-going statin therapy for a median treatment duration of 8 weeks (range 0 to 112 weeks).

The incidence of consecutive increased transaminases (≥3 X ULN) was higher in patients receiving ezetimibe administered with statins (1.3%) than in patients treated with statins alone (0.4%).

Adverse reactions reported in ≥2% of patients treated with ezetimibe + statin and at an incidence greater than statin are shown in Table 2.

TABLE 2: Adverse Reactions Occurring ≥2% in Ezetimibe-treated Patients Coadministered with a Statin and at an Incidence Greater than Statin

Adverse Reaction	All Statins* (%) n = 9,361	Ezetimibe + All Statins* (%) n = 11,308
Nasopharyngitis	3.3	3.7
Myalgia	2.7	3.2
Upper respiratory tract infection	2.8	2.9
Arthralgia	2.4	2.6
Diarrhea	2.2	2.5
Back pain	2.3	2.4
Influenza	2.1	2.2
Pain in extremity	1.9	2.1
Fatigue	1.6	2

* All Statins = all doses of all statins

Combination with Fenofibrate
This clinical trial involving 625 patients with mixed dyslipidemia (age range 20 to 76 years; 44% female, 79% White, 1% Black or African American, 20% other races; 11% identified as Hispanic or Latino ethnicity) treated for up to 12 weeks and 576 patients treated for up to an additional 48 weeks evaluated coadministration of ezetimibe and fenofibrate. Incidence rates for clinically important elevations (≥3 X ULN, consecutive) in hepatic transaminase levels were 4.5% and 2.7% for fenofibrate monotherapy (n=188) and ezetimibe coadministered with fenofibrate (n=183), respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% and 1.7% for fenofibrate monotherapy and ezetimibe coadministered with fenofibrate, respectively *[see Drug Interactions (7)]*.

6.2 Post-Marketing Experience

Because the reactions below are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval use of ezetimibe:

Blood Disorders: thrombocytopenia

Gastrointestinal Disorders: abdominal pain; pancreatitis; nausea

Hepatobiliary Disorders: elevations in liver transaminases, including elevations more than 5 X ULN; hepatitis; cholelithiasis; cholecystitis

Immune System Disorders: Hypersensitivity reactions including: anaphylaxis, angioedema, rash, and urticaria

Musculoskeletal Disorders: elevated creatine phosphokinase; myopathy/rhabdomyolysis

Nervous System Disorders: dizziness; paresthesia; depression; headache

Skin and Subcutaneous Tissue Disorders: erythema multiforme

7 DRUG INTERACTIONS

Table 3 includes a list of drugs with clinically important drug interactions when administered concomitantly with ezetimibe and instructions for preventing or managing them.

Table 3: Clinically Important Drug Interactions with Ezetimibe

Cyclosporine	
Clinical Impact:	Concomitant use of ezetimibe and cyclosporine increases ezetimibe and cyclosporine concentrations. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor cyclosporine concentrations in patients receiving ezetimibe and cyclosporine. In patients treated with cyclosporine, weigh the potential effects of the increased exposure to ezetimibe from concomitant use against the benefits of alterations in lipid levels provided by ezetimibe.
Fibrates	
Clinical Impact:	Both fenofibrate and ezetimibe may increase cholesterol excretion into the bile, leading to cholelithiasis. Co-administration of ezetimibe with fibrates other than fenofibrate is not recommended *[see Adverse Reactions (6.1)]*.
Intervention:	If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder studies are indicated, and alternative lipid-lowering therapy should be considered.
Bile Acid Sequestrants	
Clinical Impact:	Concomitant cholestyramine administration decreased the mean exposure of total ezetimibe. This may result in a reduction of efficacy *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking a bile acid sequestrant, administer ezetimibe at least 2 hours before or 4 hours after the bile acid sequestrant *[see Dosage and Administration (2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are insufficient data on ezetimibe use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits orally administered ezetimibe during the period of organogenesis at doses that resulted in up to 10 and 150 times, respectively, the human exposure at the MRHD, based on AUC *(see Data)*. Ezetimibe should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When ezetimibe is administered with a statin, refer to the Prescribing Information for the statin.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data
In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats (gestation days 6-15) and rabbits (gestation days 7-19), there was no evidence of maternal toxicity or embryolethal effects at the doses tested (250, 500, 1,000 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 1,000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1,000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). The animal-to-human exposure multiple for total ezetimibe at the no-observed effect level was 6 times for rat and 134 times for rabbit. Fetal exposure to ezetimibe (conjugated and unconjugated) was confirmed in subsequent placental transfer studies conducted using a maternal dose of 1,000 mg/kg/day. The fetal maternal plasma exposure ratio (total ezetimibe) was 1.5 for rats on gestation day 20 and 0.03 for rabbits on gestation day 22.

The effect of ezetimibe on prenatal and postnatal development and maternal function was evaluated in pregnant rats at doses of 100, 300 or 1,000 mg/kg/day from gestation day 6 through lactation day 21. No maternal toxicity or adverse developmental outcomes were observed up to and including the highest dose tested (17 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe).

Multiple-dose studies of ezetimibe given in combination with statins in rats and rabbits during organogenesis resulted in higher ezetimibe and statin exposures. Reproductive findings occurred at lower doses in combination therapy compared to monotherapy.

8.2 Lactation

Risk Summary
There is no information about the presence of ezetimibe in human milk. Ezetimibe is present in rat milk *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There is no information about the effects of ezetimibe on the breastfed infant or the effects of ezetimibe on milk production. Ezetimibe should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Data
Ezetimibe was present in the milk of lactating rats. The pup to maternal plasma ratio for total ezetimibe was 0.5 on lactation day 12.

8.4 Pediatric Use

The safety and effectiveness of ezetimibe in combination with a statin as an adjunct to diet to reduce LDL-C have been established in pediatric patients 10 years of age and older with HeFH. Use of ezetimibe for this indication is based on a double-blind, placebo-controlled clinical trial in 248 pediatric patients (142 males and 106 postmenarchal females) 10 years of age and older with HeFH *[see Clinical Studies (14)]*. In this limited controlled trial, there was no significant effect on growth or sexual maturation in the adolescent males or females, or on menstrual cycle length in females.

The safety and effectiveness of ezetimibe in combination with a statin, and other LDL-C lowering therapies, to reduce LDL-C have been established in pediatric patients 10 years of age and older with HoFH. Use of ezetimibe for this indication is based on a 12-week double-blind, placebo-controlled clinical trial followed by an uncontrolled extension period in 7 pediatric patients 11 years of age and older with HoFH *[see Clinical Studies (14)]*.

The safety and effectiveness of ezetimibe as an adjunct to diet for the reduction of elevated sitosterol and campesterol levels have been established in adults and pediatric patients 9 years of age and older with homozygous familial sitosterolemia. Use of ezetimibe for this indication is based on an 8-week double-blind, placebo-controlled clinical trial in 4 patients 9 years of age and older with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) *[see Clinical Studies (14)]*.

The safety and effectiveness of ezetimibe have not been established in pediatric patients younger than 10 years of age with HeFH or HoFH, in pediatric patients younger than 9 years of age with homozygous familial sitosterolemia, or in pediatric patients with other types of hyperlipidemia.

8.5 Geriatric Use

Of the 2,396 patients who received ezetimibe in clinical trials, 669 (28%) were 65 years of age and older, and 111 (5%) were 75 years of age and older. Of the 11,308 patients who received ezetimibe in combination with a statin in clinical trials, 3587 (32%) were 65 years of age and older, and 924 (8%) were 75 years of age and older *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness of ezetimibe have been observed between patients 65 years of age and older and younger patients. No clinically meaningful differences in the pharmacokinetics of ezetimibe were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dosage adjustment of ezetimibe is necessary in patients with renal impairment.

8.7 Hepatic Impairment

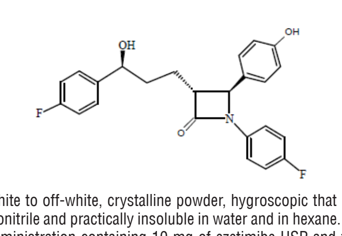
Ezetimibe is not recommended for use in patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to the unknown effects of the increased exposure to ezetimibe *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

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 (3*R*, 4S)-1-(ρ-Fluorophenyl)-3-[(3*S*)-3-(ρ-fluorophenyl)-3-hydroxypropyl]-4-(ρ-hydroxyphenyl)-2-azetidinone. The molecular formula is $C_{24}H_{21}F_2NO_3$. Its relative molecular mass is 409.43 and its structural formula is:



Ezetimibe USP is a white to off-white, crystalline powder, hygroscopic that is soluble in absolute alcohol (99.5%), acetonitrile and practically insoluble in water and in hexane. Ezetimibe is available as a tablet for oral administration containing 10 mg of ezetimibe USP and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.

The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes 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 LDL receptors, resulting in clearance of cholesterol from the blood.

12.2 Pharmacodynamics

Ezetimibe reduces total cholesterol (total-C), LDL-C, apolipoprotein (Apo) B, and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with hyperlipidemia.

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

12.3 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 ezetimibe 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.

Effect of Food
Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ezetimibe 10 mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals.

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

Elimination

Metabolism
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 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.

Excretion
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.

Specific Populations

Geriatric Patients
In a multiple-dose trial 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. However, the difference in plasma concentrations is not clinically meaningful.

Gender
In a multiple-dose trial with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in females than in males.

Race
Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Black and White subjects. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe were similar to those seen in White subjects.

Renal Impairment
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).

Hepatic Impairment
After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (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 trial (10 mg daily) in patients with moderate hepatic impairment, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects *[see Use in Specific Populations (8.7)]*.

Drug Interactions
Ezetimibe 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" trial 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.

TABLE 4: Effect of Coadministered Drugs on Total Ezetimibe

Coadministered Drug and Dosing Regimen	Total Ezetimibe* Change in AUC	Total Ezetimibe* Change in C_{max}
Cyclosporine-stable dose required (75 to 150 mg BID)†, ‡	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days‡	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days‡	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days‡	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose§	↓4%	↓30%
Cimetidine, 400 mg BID, 7 days	↑6%	↑22%
Glipizide, 10 mg, single dose	↑4%	↓8%
Statins		
Lovastatin 20 mg QD, 7 days	↑9%	↑3%
Pravastatin 20 mg QD, 14 days	↑7%	↑23%
Atorvastatin 10 mg QD, 14 days	↓2%	↑12%
Rosuvastatin 10 mg QD, 14 days	↑13%	↑18%
Fluvastatin 20 mg QD, 14 days	↓19%	↑7%

* Based on 10 mg dose of ezetimibe.
† Post-renal transplant patients with mild impaired or normal renal function. In a different trial, 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.
‡ See Drug Interactions (7).
§ Supralox, 20 mL.

TABLE 5: Effect of Ezetimibe Coadministration on Systemic Exposure to Other Drugs

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

* See Drug Interactions (7).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1,500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 X the human exposure at 10 mg daily based on AUC_{0-24hr} 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 X the human exposure at 10 mg daily based on AUC_{0-24hr} 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 1,000 mg/kg/day in male or female rats (~7 X the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe).

14 CLINICAL STUDIES

Primary Hyperlipidemia in Adults
Ezetimibe reduces total-C, LDL-C, Apo B, and non-HDL-C in patients with hyperlipidemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

Monotherapy
In two multicenter, double-blind, placebo-controlled, 12-week trials in 1719 patients (age range 18 to 86 years, 52% females; 91% White, 5% Black or African American, 1% Asian, 3% other races mostly identified as Hispanic or Latino ethnicity) with primary hyperlipidemia, ezetimibe significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to placebo (see **Table 6**). Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

TABLE 6: Response to Ezetimibe in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline*)

	Treatment Group	N	Total-C	LDL-C	Apo B	Non-HDL-C
Trial 1†	Placebo	205	+1	+1	-1	+1
	Ezetimibe	622	-12	-18	-15	-16
Trial 2†	Placebo	226	+1	+1	-1	+2
	Ezetimibe	666	-12	-18	-16	-16
Pooled Data† (Trials 1 & 2)	Placebo	431	0	+1	-2	+1
	Ezetimibe	1288	-13	-18	-16	-16

* Baseline - on no lipid-lowering drug.
† Ezetimibe significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to placebo.

Combination with Statins: Ezetimibe Added to On-going Statin Therapy
In a multicenter, double-blind, placebo-controlled, 8-week trial, 769 patients (age range 22 to 85 years, 42% females; 90% White, 6% Black or African American, 1% Asian, 3% other races; and 2% identified as Hispanic or Latino ethnicity) with primary hyperlipidemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving statin monotherapy but who had not met their NCEP ATP II target LDL-C goal, were randomized to receive either ezetimibe or placebo in addition to their on-going statin.

Ezetimibe, added to on-going statin therapy, significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared with a statin administered alone (see **Table 7**). LDL-C reductions induced by ezetimibe were generally consistent across all statins.

TABLE 7: Response to Addition of Ezetimibe to On-Going Statin Therapy* in Patients with Hyperlipidemia (Mean % Change from Treated Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
On-going Statin + Placebo ‡	390	-2	-4	-3	-3
On-going Statin + Ezetimibe ‡	379	-17	-25	-19	-23

* Patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin).
† Baseline - on a statin alone.
‡ Ezetimibe + statin significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to statin alone.

Combination with Statins: Ezetimibe Initiated Concurrently with a Statin
In four multicenter, double-blind, placebo-controlled, 12-week trials, in 2,382 patients (age range 18 to 87 years, 57% female; 88% White, 5% Black or African American, 2% Asian, 5% other races mostly identified as Hispanic or Latino) with hyperlipidemia, ezetimibe or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin.

When all patients receiving ezetimibe with a statin were compared to all those receiving the corresponding statin alone, ezetimibe significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to the statin administered alone. LDL-C reductions induced by ezetimibe were generally consistent across all statins. (See footnote†, **Tables 8** to **11**.)

TABLE 8: Response to Ezetimibe and Atorvastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline*)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	60	+4	+4	+3	+4
Ezetimibe	65	-14	-20	-15	-18
Atorvastatin 10 mg	60	-26	-37	-28	-34
Ezetimibe + Atorvastatin 10 mg	65	-38	-53	-43	-49
Atorvastatin 20 mg	60	-30	-42	-34	-39
Ezetimibe + Atorvastatin 20 mg	62	-39	-54	-44	-50
Atorvastatin 40 mg	66	-32	-45	-37	-41

Ezetimibe + Atorvastatin 40 mg	65	-42	-56	-45	-52
Atorvastatin 80 mg	62	-40	-54	-46	-51
Ezetimibe + Atorvastatin 80 mg	63	-46	-61	-50	-58
Pooled data (All Atorvastatin Doses)†	248	-32	-44	-36	-41
Pooled data (All Ezetimibe + Atorvastatin Doses)†	255	-41	-56	-45	-52

* Baseline - on no lipid-lowering drug.
† Ezetimibe + all doses of atorvastatin pooled (10 to 80 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of atorvastatin pooled (10 to 80 mg).

TABLE 9: Response to Ezetimibe and Simvastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline*)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	70	-1	-1	0	-1
Ezetimibe	61	-13	-19	-14	-17
Simvastatin 10 mg	70	-18	-27	-21	-25
Ezetimibe + Simvastatin 10 mg	67	-32	-46	-35	-42
Simvastatin 20 mg	61	-26	-36	-29	-33
Ezetimibe + Simvastatin 20 mg	69	-33	-46	-36	-42
Simvastatin 40 mg	65	-27	-38	-32	-35
Ezetimibe + Simvastatin 40 mg	73	-40	-56	-45	-51
Simvastatin 80 mg	67	-32	-45	-37	-41
Ezetimibe + Simvastatin 80 mg	65	-41	-58	-47	-53
Pooled data (All Simvastatin Doses)†	263	-26	-36	-30	-34
Pooled data (All Ezetimibe + Simvastatin Doses)†	274	-37	-51	-41	-47

* Baseline - on no lipid-lowering drug.
† Ezetimibe + all doses of simvastatin pooled (10 to 80 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of simvastatin pooled (10 to 80 mg).

TABLE 10: Response to Ezetimibe and Pravastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline*)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	65	0	-1	-2	0
Ezetimibe	64	-13	-20	-15	-17
Pravastatin 10 mg	66	-15	-21	-16	-20
Ezetimibe + Pravastatin 10 mg	71	-24	-34	-27	-32
Pravastatin 20 mg	69	-15	-23	-18	-20
Ezetimibe + Pravastatin 20 mg	66	-27	-40	-31	-36
Pravastatin 40 mg	70	-22	-31	-26	-28
Ezetimibe + Pravastatin 40 mg	67	-30	-42	-32	-39
Pooled data (All Pravastatin Doses)†	205	-17	-25	-20	-23
Pooled data (All Ezetimibe + Pravastatin Doses)†	204	-27	-39	-30	-36

* Baseline - on no lipid-lowering drug.
† Ezetimibe + all doses of pravastatin pooled (10 to 40 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of pravastatin pooled (10 to 40 mg).

TABLE 11: Response to Ezetimibe and Lovastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline*)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	64	+1	0	+1	+1
Ezetimibe	72	-13	-19	-14	-16
Lovastatin 10 mg	73	-15	-20	-17	-19
Ezetimibe + Lovastatin 10 mg	65	-24	-34	-27	-31
Lovastatin 20 mg	74	-19	-26	-21	-24
Ezetimibe + Lovastatin 20 mg	62	-29	-41	-34	-39
Lovastatin 40 mg	73	-21	-30	-25	-27
Ezetimibe + Lovastatin 40 mg	65	-33	-46	-38	-43
Pooled data (All Lovastatin Doses)†	220	-18	-25	-21	-23
Pooled data (All Ezetimibe + Lovastatin Doses)†	192	-29	-40	-33	-38

* Baseline - on no lipid-lowering drug.
† Ezetimibe + all doses of lovastatin pooled (10 to 40 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of lovastatin pooled (10 to 40 mg).

Combination with Fenofibrate
In a multicenter, double-blind, placebo-controlled, clinical trial in patients with mixed hyperlipidemia, 625 patients (age range 20 to 76 years, 44% female; 79% White, 1% Black or African American, 20% other races; and 11% identified as Hispanic or Latino ethnicity) were treated for up to 12 weeks and 576 for up to an additional 48 weeks. Patients were randomized to receive placebo, ezetimibe alone, 160 mg fenofibrate alone, or ezetimibe and 160 mg fenofibrate in the 12-week trial. After completing the 12-week trial, eligible patients were assigned to ezetimibe coadministered with fenofibrate or fenofibrate monotherapy for an additional 48 weeks.

Ezetimibe coadministered with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate administered alone (see **Table 12**).

TABLE 12: Response to Ezetimibe and Fenofibrate Initiated Concurrently in Patients with Mixed Hyperlipidemia (Mean % Change from Untreated Baseline* at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	63	0	0	-1	0
Ezetimibe	185	-12	-13	-11	-15
Fenofibrate 160 mg	188	-11	-6	-15	-16
Ezetimibe + Fenofibrate 160 mg	183	-22	-20	-26	-30

* Baseline - on no lipid-lowering drug.

The changes in lipid endpoints after an additional 48 weeks of treatment with ezetimibe coadministered with fenofibrate or with fenofibrate alone were consistent with the 12-week data displayed above.

HeFH in Pediatric Patients
The effects of ezetimibe coadministered with simvastatin (n=126) compared to simvastatin monotherapy (n=122) have been evaluated in males and females with HeFH. In a multicenter, double-blind, controlled trial followed by an open-label phase, 142 males and 106 postmenarchal females, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% White, 4% Asian, 2% Black or African American, 13% multi-racial; 14% identified as Hispanic or Latino ethnicity) with HeFH were randomized to receive either ezetimibe coadministered with simvastatin or simvastatin monotherapy. Inclusion in the trial required 1) a baseline LDL-C level between 160 and 400 mg/dL and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 225 mg/dL (range: 161 to 351 mg/dL) in the ezetimibe coadministered with simvastatin group compared to 219 mg/dL (range: 149 to 336 mg/dL) in the simvastatin monotherapy group. The patients received coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, coadministered ezetimibe and 40 mg simvastatin or 40 mg simvastatin monotherapy for the next 27 weeks, and open-label coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

The results of the trial at Week 6 are summarized in **Table 13**. Results at Week 33 were consistent with those at Week 6.

TABLE 13: Mean Percent Difference at Week 6 Between the Pooled Ezetimibe Coadministered with Simvastatin Group and the Pooled Simvastatin Monotherapy Group in Adolescent Patients with HeFH

	Total-C	LDL-C	Apo B	Non-HDL-C
Mean percent difference between treatment groups	-12%	-15%	-12%	-14%
95% Confidence Interval	(-15%, -9%)	(-18%, -12%)	(-15%, -9%)	(-17%, -11%)

HoFH in Adults and Pediatric Patients
A trial was conducted to assess the efficacy of ezetimibe in the treatment of HoFH. This double-blind, randomized, 12-week trial enrolled 50 patients (age range 11 to 74 years, 58% female; 90% White, 2% Black or African American, 8% other races identified as Hispanic or Latino) 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), ezetimibe administered with atorvastatin or simvastatin (40 mg), or ezetimibe administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine *[see Drug Interactions (7)]*, 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 ezetimibe plus atorvastatin 40 or 80 mg or simvastatin 40 or 80 mg. Ezetimibe, 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 ezetimibe plus 80 mg atorvastatin or with ezetimibe plus 80 mg simvastatin, LDL-C was reduced by 27%.

Homozygous Sitosterolemia (Phytosterolemia) in Adults and Pediatric Patients
A trial was conducted to assess the efficacy of ezetimibe in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients (age range 9 to 72 years, 65% females; 89% White, 3% Asian, 8% other races identified as Hispanic or Latino) with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) on their current therapeutic regimen (diet, bile-acid-binding resins, statins, ileal bypass surgery and/or LDL apheresis), were randomized to receive ezetimibe (n=30) or placebo (n=7). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine *[see Drug Interactions (7)]*, ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered. Excluding the one subject receiving LDL apheresis, ezetimibe 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 ezetimibe, mean plasma levels of plant sterols were reduced progressively over the course of the trial. Reductions in sitosterol and campesterol were consistent between patients taking ezetimibe concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

16 HOW SUPPLIED/STORAGE AND HANDLING
Ezetimibe tablets USP, 10 mg are white to off-white, capsule shaped, flat faced bevel edged tablets debossed with 'I' on one side and '83' on the other side. They are supplied as follows:

Bottle of 30 tablets	NDC 31722-628-30
Bottle of 90 tablets	NDC 31722-628-90
Bottle of 100 tablets	NDC 31722-628-01
Carton of 100 (10x10) unit-dose tablets (Clear PVC/Aclar-Alu)	NDC 31722-628-31
Carton of 100 (10x10) unit-dose tablets (Alu-Alu)	NDC 31722-628-34
Bottle of 500 tablets	NDC 31722-628-05
Bottle of 1000 tablets	NDC 31722-628-10

Storage
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-Approved Patient Labeling (Patient Information).

Inform patients that ezetimibe tablets may cause liver enzyme elevations *[see Warnings and Precautions (5.2)]*.

Muscle Pain
Advise patients that ezetimibe tablets may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.3), and Drug Interactions (7)]*.

Pregnancy
Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if ezetimibe tablets should be discontinued *[see Use in Specific Populations (8.1)]*.

Breastfeeding
Advise patients who have a lipid disorder and are breastfeeding to discuss the options with their healthcare provider *[see Use in Specific Populations (8.2)]*.

Missed Dose
Instruct patients to take ezetimibe tablets only as prescribed. If a dose is missed, it should be taken as soon as possible. Advise patients not to double their next dose.

CAMBER PHARMACEUTICALS, INC.

Manufactured for:
Camber Pharmaceuticals, Inc.
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PATIENT INFORMATION
Ezetimibe (e zet' i mibe) tablets, for oral use

Read this information carefully before you start taking ezetimibe tablets and each time you get more ezetimibe tablets. 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 ezetimibe tablets, ask your doctor. Only your doctor can determine if ezetimibe tablets are right for you.

What are ezetimibe tablets?
Ezetimibe tablets are a medicine used with a cholesterol lowering diet:
- and with other cholesterol medicines called a statin, or alone (when additional cholesterol lowering treatments are not possible), to lower elevated low-density lipoprotein cholesterol (LDL-C) or bad cholesterol in adults with primary hyperlipidemia (too many fats in your blood), including heterozygous familial hypercholesterolemia (HeFH). HeFH is an inherited condition that causes high levels of bad cholesterol.
- and with a statin to lower LDL-C in adults and children 10 years of age and older with HeFH.
- and with a medicine called fenofibrate to lower elevated LDL-C in adults with mixed hyperlipidemia.
- to lower elevated sitosterol and campesterol levels in adults and in children 9 years of age and older with homozygous familial sitosterolemia (a rare inherited condition that prevents the body from getting rid of cholesterol from plants).

Ezetimibe tablets are also used:
- with a statin and other cholesterol lowering treatments to lower elevated LDL-C levels in adults and patients 10 years of age and older with homozygous familial hypercholesterolemia (HoFH). HoFH is an inherited condition that causes high levels of bad cholesterol.

The safety and effectiveness of ezetimibe tablets has not been established in children:
- younger than 10 years of age with HeFH or HoFH.
- younger than 9 years of age with homozygous familial sitosterolemia.
- with other types of hyperlipemia.

Do not take ezetimibe tablets:
- if you are allergic to ezetimibe or any of the ingredients in ezetimibe tablets. See the end of this Patient Information leaflet for a complete list of ingredients in ezetimibe tablets. Stop using ezetimibe tablets and get medical help right away if you have symptoms of a serious allergic reaction including:
  - o swelling of the face, tongue, or throat
  - o difficulty breathing or swallowing
  - o fainting or feeling dizzy
  - o very fast heartbeat
  - o severe skin rash, hives, and itching
  - o flu-like symptoms including fever, sore throat, cough, tiredness, and joint pain
- with certain statins, fenofibrate, or other LDL-C lowering medicines if your healthcare provider has told you not to take them.

Before you take ezetimibe tablets, tell your healthcare provider about all your medical conditions, including if you:
- have liver problems. Ezetimibe tablets may not be right for you.
- are pregnant or plan to become pregnant. It is not known if ezetimibe tablets will harm your unborn baby. You and your healthcare provider should decide if you will take ezetimibe tablets while you are pregnant.
- are breastfeeding. It is not known if ezetimibe passes into your breast milk. You and your healthcare provider should decide the best way to feed your baby if you take ezetimibe tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Talk to your healthcare provider before you start taking any new medicines.

Taking ezetimibe tablets with certain other medicines may affect each other causing side effects. Ezetimibe tablets may affect the way other medicines work, and other medicines may affect how ezetimibe tablets work.

Especially tell your healthcare provider if you take:
- cyclosporine (a medicine for your immune system)
- fibrates (medicine for lowering cholesterol)
- bile acid sequestrants (medicine for lowering LDL-C)

Ask your healthcare provider or pharmacist for a list of medicines if you are not sure. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ezetimibe tablets?
- Take ezetimibe tablets 1-time each 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 healthcare provider if you can take them at the same time.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses of ezetimibe tablets at the same time.
- While taking ezetimibe tablets, continue to follow your cholesterol-lowering diet and to exercise as your healthcare provider told you to.
- If you take a medicine called a bile acid sequestrant, take ezetimibe tablets at least 2 hours before or 4 hours after you take the bile acid sequestrant.
- Your healthcare provider may do blood tests to check your LDL-C levels as early as 4 weeks after starting treatment with ezetimibe tablets.
- In case of an overdose, get medical help or contact a live Poison Center expert right away at 1-800-222-1222. Advice is also available online at poisonhelp.org.

What are the possible side effects of ezetimibe tablets?
Ezetimibe tablets may cause serious side effects including:
- **increased liver enzymes**. An increase in liver enzymes can happen in people taking ezetimibe tablets alone or with statins. Your healthcare provider may do blood tests to check your liver before and during treatment. Your healthcare provider may need to change or stop your treatment with ezetimibe tablets because of an increase in liver enzymes.
- **muscle pain, tenderness, and weakness (myopathy)**. Muscle problems, including muscle breakdown (rhabdomyolysis) can happen. Tell your healthcare provider right away if:
  - o you have unexplained muscle pain, tenderness, weakness, feel more tired than usual, or fever.
  - o you have muscle problems that do not go away even after your healthcare provider has advised you to stop taking ezetimibe tablets. Your healthcare provider may do further tests to diagnose the cause of your muscle problems.

Your chances of getting muscle problems are higher if you are also taking statins or fibrates.

The most common side effects of ezetimibe tablets taken alone include:
- upper respiratory tract infection
- joint pain
- pain in arms or legs
- flu-like symptoms
- diarrhea
- feeling tired
- inflammation of the sinuses

The most common side effects of ezetimibe tablets taken with a statin include:
- runny nose, sore throat
- flu-like symptoms
- diarrhea
- upper respiratory tract infection
- joint pain
- muscle aches and pains
- pain in arms or legs
- back pain
- feeling tired

Tell your healthcare provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of ezetimibe tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ezetimibe tablets?
- Store ezetimibe tablets at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Protect from moisture.

Keep ezetimibe tablets and all medicines out of the reach of children.

General information about safe and effective use of ezetimibe tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ezetimibe tablets for a condition for which it was not prescribed. Do not give ezetimibe tablets to other people, even if they have the same symptoms you have. They may harm them.

You can ask your pharmacist or healthcare provider for information about ezetimibe tablets that is written for health professionals.

What are the ingredients in ezetimibe tablets?
Active ingredient: ezetimibe.

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate.

CAMBER PHARMACEUTICALS, INC.

Manufactured for:
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Piscataway, NJ 08854

By: HETERO™
Hetero Labs Limited
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For more information, call 1-866-495-1995.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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