EZOLETA TABLETS 10MG

1. NAME OF THE MEDICINAL PRODUCT

Ezoleta 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg ezetimibe.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to off white, capsule shaped tablets with bevelled edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolemia
Ezoleta, administered with an HMG-CoA reductase inhibitor (statin) or alone, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B) in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia.

Ezoleta, administered in combination with fenofibrate, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezoleta, administered with 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 (eg. LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia (Phytosterolemia)
Ezoleta is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

4.2 Posology and method of administration

Posology

The patient should be on an appropriate lipid lowering diet and should continue on this diet during treatment with Ezoleta.
The recommended dose is one Ezoleta 10 mg tablet daily. Ezoleta can be administered at any time of the day, with or without food.
When Ezoleta is added to a statin, either the indicated usual initial dose of that particular statin or the already established higher statin dose should be continued. In this setting, the dosage instructions for that particular statin should be consulted.

Patients with Renal Impairment
Monotherapy
In patients with renal impairment, no dosage adjustment of Ezoleta is necessary (see section 5.2, Special populations).

Combination Therapy with Simvastatin
In patients with mild renal impairment (estimated GFR ≥60 mL/min/1.73 m^2), no dosage adjustment of Ezoleta or simvastatin is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 m^2, the dose of Ezoleta is 10 mg and the dose of simvastatin is 20 mg once a day in the evening. In such patients, the use of higher doses of simvastatin should be closely monitored. (See section 5.2, Special populations and section 5.1)

Use in the Elderly
No dosage adjustment is required for elderly patients (see section 5.2, Special populations).

Use in Pediatric Patients
Children and adolescents ≥10 years: No dosage adjustment is required (see section 5.2, Special populations).

Children <10 years: Treatment with Ezoleta is not recommended.

Use in Hepatic Impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6).

Treatment with ezetimibe is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction. (See sections 4.4 and 5.2, Special populations)

Co-administration with bile acid sequestrants
Dosing of Ezoleta should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

4.3 Contraindications

Hypersensitivity to any component of this medication.

When Ezoleta is to be administered with a statin or with fenofibrate, please refer to the Package Insert for that particular medication.

The combination of Ezoleta with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All statins and fenofibrate are contraindicated in pregnant and nursing women. When Ezoleta is administered with a statin or with fenofibrate in a woman with childbearing potential, refer to the product labeling for that medication.

4.4 Special warnings and precautions for use

When Ezoleta is co-administered with a statin, please refer to the Package Insert for that particular medicinal product.

Liver enzymes
In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed. When Ezoleta is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin. (See section 4.8)

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. (See section 4.8)

In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomised to receive ezetimibe 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (>3 X ULN) was 0.7% for ezetimibe combined with simvastatin and 0.6% for placebo (See section 4.8).

Skeletal muscle
In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for ezetimibe vs 0.1% for placebo, and 0.1% for ezetimibe co-administered with a statin vs 0.4% for statins alone.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. All patients starting therapy with Ezoleta should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Ezoleta and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy.

In IMPROVE-IT, 18,144 patients with CHD were randomized to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 X ULN and <10 X ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. (See section 4.8)

In a clinical trial in which over 9000 patients with chronic kidney disease were randomized to receive ezetimibe 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median followup 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for ezetimibe combined with simvastatin and 0.1% for placebo. (See section 4.8)

Hepatic Insufficiency
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Ezoleta is not recommended in these patients (see section 5.2, Special populations).

Fibrates
The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of Ezoleta and fibrates (other than fenofibrate) is not recommended (see section 4.5).

Fenofibrate
If cholelithiasis is suspected in a patient receiving Ezoleta and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see section 4.8 and the Package Insert for fenofibrate).

Cyclosporine
Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving Ezoleta and cyclosporine. The degree of increase in ezetimibe 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 (see section 4.5).

Anticoagulants
If Ezoleta is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (See section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N- acetyltransferase.

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during coadministration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

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

Cyclosporine: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9- fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (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 concurrent controls.

In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see section 4.4).

Fibrates: The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see section 4.8 and 5.1, Co-administration with Fenofibrate); co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is

unknown, coadministration of Ezoleta with fibrates (other than fenofibrate) 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. This increase is not considered clinically significant.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

Statins: No clinically significant pharmacokinetic interactions were seen when ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Anticoagulants: 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. There have been post- marketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications (See section 4.4).

4.6 Fertility, pregnancy and lactation

No clinical data on exposed pregnancies are available. Animal studies of ezetimibe administered alone do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. However, note that all statins and fenofibrate are contraindicated in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

When ezetimibe was given with lovastatin, simvastatin, pravastatin or atorvastatin, no teratogenic effects were observed in embryo-fetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed.

When ezetimibe is to be administered with a statin, please refer to the Package Insert for that particular statin.

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, Ezoleta should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

4.8 Undesirable effects

The following serious adverse reactions are discussed in greater detail in other sections of the label:
- Liver enzyme abnormalities [see section 4.4, Liver Enzymes)]
- Rhabdomyolysis and myopathy [see section 4.4, Skeletal Muscle]

Monotherapy Studies:
In the ezetimibe controlled clinical trials database (placebo-controlled) of 2396 patients with a median treatment duration of 12 weeks (range 0 to 39 weeks), 3.3% of patients on ezetimibe and 2.9% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with ezetimibe that led to treatment discontinuation and occurred at a rate greater than placebo were:

- Arthralgia (0.3%)
- Dizziness (0.2%)
- Gamma-glutamyltransferase increased (0.2%)

The most commonly reported adverse reactions (incidence ≥2% and greater than placebo) in the ezetimibe monotherapy controlled clinical trial database of 2396 patients were: upper respiratory tract infection (4.3%), diarrhea (4.1%), arthralgia (3.0%), sinusitis (2.8%), and pain in extremity (2.7%).

Statin Co-Administration Studies:
In the ezetimibe + statin controlled clinical trials database of 11,308 patients with a median treatment duration of 8 weeks (range 0 to 112 weeks), 4.0% of patients on ezetimibe + statin and 3.3% of patients on statin alone discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with ezetimibe + statin that led to treatment discontinuation and occurred at a rate greater than statin alone were:

- Alanine aminotransferase increased (0.6%)
- Myalgia (0.5%)
- Fatigue, aspartate aminotransferase increased, headache, and pain in extremity (each at 0.2%)

The most commonly reported adverse reactions (incidence ≥2% and greater than statin alone) in the ezetimibe + statin controlled clinical trial database of 11,308 patients were: nasopharyngitis (3.7%), myalgia (3.2%), upper respiratory tract infection (2.9%), arthralgia (2.6%) and diarrhea (2.5%).

Clinical Trial 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, 2396 patients with primary hyperlipidemia (age range 9-86 years, 50% women, 90% Caucasians, 5% Blacks, 3% Hispanics, 2% Asians) and elevated LDL-C were treated with ezetimibe 10 mg/day 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, regardless of causality assessment, are shown in Table 1.

Table 1
Clinical Adverse Events Occurring in ≥2% of Patients Treated with ezetimibe and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Ezetimibe 10 mg (%) n = 2396	Placebo (%) n = 1159
Gastro-intestinal system disorders		
Diarrhea	4.1	3.7
General disorders and administration site conditions		
Fatigue	2.4	1.5
Infections and infestations		
Influenza	2.0	1.5
Sinusitis	2.8	2.2
Upper respiratory tract infection	4.3	2.5
Musculo-skeletal system disorders		
Arthralgia	3.0	2.2
Pain in extremity	2.7	2.5

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

Combination with a Statin:
In 28 double-blind, controlled (placebo or active-controlled) clinical trials, 11,308 patients with primary hyperlipidemia (age range 10-93 years, 48% women, 85% Caucasians, 7% Blacks, 4% Hispanics, 3% Asians) 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%). [See section 4.4, Liver enzymes]

Clinical adverse reactions reported in ≥2% of patients treated with ezetimibe + statin and at an incidence greater than statin, regardless of causality assessment, are shown in Table 2.

Table 2
Clinical Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe Co-administered with a Statin and at an Incidence Greater than Statin, Regardless of Causality

Body System/Organ Class Adverse Event	All Statins* (%) n=9361	Ezetimibe + All Statins* (%) n=11,308
Gastro-intestinal system disorders		
Diarrhea	2.2	2.5
General disorders and administration site conditions		
Fatigue	1.6	2.0
Infections and infestations		
Influenza	2.1	2.2
Nasopharyngitis	3.3	3.7
Upper respiratory tract infection	2.8	2.9
Musculoskeletal system and connective tissue disorders		
Arthralgia	2.4	2.6
Back pain	2.3	2.4
Myalgia	2.7	3.2
Pain in extremity	1.9	2.1

*All Statins = all doses of all statins

Combination with Fenofibrate:
This clinical study involving 625 patients with mixed dyslipidemia (age range 20-76 years, 44% women, 79% Caucasians, 0.1% Blacks, 11% Hispanics, 5% Asians) treated for up to 12 weeks and 576 patients treated for up to an additional 48 weeks evaluated co-administration of ezetimibe and fenofibrate. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (≥3 X ULN, consecutive) in hepatic transaminase levels were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy (n=188) and ezetimibe co-administered with fenofibrate (n=183), respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (95% CI: 0.0%, 3.1%) and 1.7% (95% CI: 0.6%, 4.0%) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively [see section 4.4, Fenofibrate]. The numbers of patients exposed to co-administration therapy as well as fenofibrate and ezetimibe monotherapy were inadequate to assess gallbladder disease risk. There were no CPK elevations >10 X ULN in any of the treatment groups.

<u>Patients with Coronary Heart Disease</u>

In the IMPROVE-IT study (see section 5.1), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n=9067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80

mg) or simvastatin 40 mg (n=9077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe/simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 times ULN and <10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin (see section 4.4.). Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalisations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

Patients with Chronic Kidney Disease

In the Study of Heart and Renal Protection (SHARP) (see section 5.1), involving over 9000 patients treated with a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg daily (n=4650) or placebo (n=4620), the safety profiles were comparable during a median follow-up period of 4.9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4% in patients treated with ezetimibe combined with simvastatin, 9.8% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2% in patients treated with ezetimibe combined with simvastatin and 0.1% in patients treated with placebo. Consecutive elevations of transaminases > 3X ULN) occurred in 0.7% of patients treated with ezetimibe combined with simvastatin compared with 0.6% of patients treated with placebo (see section 4.4). In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for ezetimibe combined with simvastatin, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

Laboratory values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between ezetimibe (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4.).

Clinically important elevations of CPK (≥10 X ULN) in patients treated with ezetimibe administered alone or co-administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

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: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria; erythema multiforme; arthralgia; myalgia; elevated creatine phosphokinase; myopathy/rhabdomyolysis (see section 4.4); elevations in liver transaminases; hepatitis; abdominal pain; thrombocytopenia; pancreatitis; nausea; dizziness; paresthesia; depression; headache; cholelithiasis; cholecystitis.

4.9 Overdose

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 hypercholesterolaemia for up to 56 days, and 40 mg/day to patients with homozygous sitosterolemia for 26 weeks, was generally well tolerated.

A few cases of overdose with ezetimibe 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents; ATC code: C10AX09.

Mechanism of action
Ezetimibe is orally active and potent, with a unique mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for 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 clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

Pharmacodynamic effects
In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54 %, compared with placebo. By inhibiting the absorption of intestinal cholesterol, ezetimibe reduces the delivery of cholesterol to the liver. Statins reduce cholesterol synthesis in the liver. Together these distinct mechanisms provide complementary cholesterol reduction. Ezetimibe, administered with a statin, is effective in improving serum total-C, LDL-C, Apo B, TG and HDL-C in patients with hypercholesterolemia, beyond either treatment alone. Administration of ezetimibe with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, TG, HDL-C, and non-HDL-C in patients with mixed hyperlipidemia.

Clinical studies demonstrate that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of 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-lowdensity lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

A series of preclinical studies was performed to determine the selectivity of ezetimibe 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, ethinyl estradiol, or the fat soluble vitamins A and D.

Clinical efficacy and safety

Primary hypercholesterolemia
Monotherapy
In two, double-blind, randomised placebo-controlled, 12-week studies in 1.719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo (see Table 3). Reduction in LDL-C was consistent across age, sex and baseline LDL-C. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ezetimibe. In addition, ezetimibe had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, had no effect on prothrombin time, and did not impair adrenocortical steroid hormone production.

Table 3
Mean Response to ezetimibe in Patients with Primary Hypercholesterolemia (Mean % Change from Baseline)

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

[a] Median % change from baseline

Co-Administration with a Statin
Ezetimibe Initiated Concurrently with a Statin

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 1187 patients with hypercholesterolemia, ezetimibe 10 mg was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin. In general, the incremental effect on LDL-C reduction was independent of the dose or specific statin used. In addition, LDL-C reduction for ezetimibe coadministered with the lowest tested dose (10 mg) of any of the statins was similar to or greater than the LDL-C reduction of the highest tested dose of the corresponding statin administered alone (Table 4).

Table 4
Mean % Change from Baseline in Plasma Concentration of Calculated LDL-C for ezetimibe Administered with Statins

	Atorvastatin Study	Simvastatin Study	Pravastatin Study	Lovastatin Study
Placebo	+4	-1	-1	0
Ezetimibe	-20	-19	-20	-19
10 mg statin	-37	-27	-21	-20
Ezetimibe + 10 mg statin	-53	-46	-34	-34
20 mg statin	-42	-36	-23	-26
Ezetimibe + 20 mg statin	-54	-46	-40	-41
40 mg statin	-45	-38	-31	-30
Ezetimibe + 40 mg statin	-56	-56	-42	-46
80 mg statin	-54	-45	-	-
Ezetimibe + 80 mg statin	-61	-58	-	-
Pooled data: All statin doses	-44	-36	-25	-25
Pooled data: All ezetimibe + statin doses	-56	-51	-39	-40

In a pooled analysis of all ezetimibe + statin doses, ezetimibe had a beneficial effect on total-C, Apo B, TG, and HDL-C (Table 5).

Table 5
Pooled Analysis of the Mean % Change from Baseline in Total-C, Apo B, TG, and HDL-C

	Total-C	Apo B	TG[a]	HDL-C
Ezetimibe + Atorvastatin	-41	-45	-33	+7
Atorvastatin alone	-32	-36	-24	+4
Ezetimibe + Simvastatin	-37	-41	-29	+9
Simvastatin alone	-26	-30	-20	+7
Ezetimibe + Pravastatin	-27	-30	-21	+8
Pravastatin alone	-17	-20	-14	+7
Ezetimibe + Lovastatin	-29	-33	-25	+9
Lovastatin alone	-18	-21	-12	+4

[a] median % change

Ezetimibe Added to On-going Statin Therapy
In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (100 to 160 mg/dl, depending on baseline characteristics) were randomized to receive either ezetimibe10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82 %), LDL-C goal at study endpoint was achieved by 72 % and 19 % of patients randomized to ezetimibe and placebo, respectively.

Ezetimibe, added to on-going statin therapy, significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C, compared with placebo (Table 6). LDL-C reductions were consistent across all statins.

Table 6
Mean Response to Addition of ezetimibe to On-going Statin Therapy[a] in Patients with Hypercholesterolemia (Mean % Change from Baseline)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[b]	HDL-C
On-going Statin +Placebo	390	-2	-4 (-6 mg/dl[c])	-3	-3	+1
On-going Statin +ezetimibe	379	-17	-25 (-36 mg/dl[c])	-19	-14	+3

[a] Percentages of patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)
[b] Median % change from baseline
[c] Change in LDL-C from baseline LDL-C (138 mg/dl and 139 mg/dl for statin + ezetimibe and statin + placebo, respectively)

Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10 % or 0 % from baseline, respectively.

In a multicenter, double-blind, 14 week study, 621 patients with hypercholesterolemia receiving atorvastatin 10 mg daily with an LDL-C >130 mg/dl were randomized to receive atorvastatin 20 mg or ezetimibe 10 mg added to atorvastatin 10 mg therapy. The atorvastatin dose could be titrated up to 80 mg in the atorvastatin arm and up to 40 mg in the ezetimibe plus atorvastatin co-administration arm, based on patients not attaining LDL-C goal (<100 mg/dl). The mean baseline LDL-C was 187 mg/dl and approximately 60 % of the patients had heterozygous familial hypercholesterolemia (HeFH). At study end, there was a significant difference in attainment of LDL-C goal between patients in the ezetimibe co-administration arm (22 %) and patients on atorvastatin monotherapy (7 %). At week 4,

there was a significant difference in LDL-C reductions between co-administration patients (24 %; ezetimibe + atorvastatin 10 mg) and monotherapy patients (9 %; atorvastatin 20 mg). In the sub-group of patients with HeFH, similar results for LDL-C goal attainment and LDL-C reductions were achieved.

In a similarly designed study in 100 patients with hypercholesterolemia receiving simvastatin 20 mg and not at LDL-C goal, the addition of ezetimibe 10 mg to simvastatin titration compared to titration of simvastatin alone produced similar advantages to those observed in the atorvastatin study described above. For example, significant differences in LDL-C goal attainment (27 % for ezetimibe + simvastatin vs. 3 % for simvastatin alone) and LDL-C reductions (24 % for ezetimibe + simvastatin vs. 11 % for simvastatin alone) were achieved.

Co-administration with Fenofibrate
In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients 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 study. After completing the 12-week study, eligible patients were assigned to ezetimibe coadministered with fenofibrate or fenofibrate monotherapy for an additional 48 weeks.

Ezetimibe co-administered with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate administered alone. The percent decrease in TG and percent increase in HDLC for EZETROL co-administered with fenofibrate were comparable to those for fenofibrate administered alone (see Table 7).

Table 7
Response to Ezetimibe and Fenofibrate Initiated Concurrently in Patients with Mixed Hyperlipidemia (Mean[a] % Change from Untreated Baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
Placebo	63	0	0	-1	-9	+3	0
Ezetimibe	185	-12	-13	-11	-11	+4	-15
Fenofibrate 160 mg	188	-11	-6	-15	-43	+19	-16
Ezetimibe + Fenofibrate 160 mg	183	-22	-20	-26	-44	+19	-30

[a] For triglycerides, median % change from baseline
[b] 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.

Homozygous Familial Hypercholesterolemia (HoFH)
A study was conducted to assess the efficacy of ezetimibe 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), ezetimibe 10 mg administered with atorvastatin or simvastatin (40 mg), or ezetimibe 10 mg administered with atorvastatin or simvastatin (80 mg). Results are shown in Table 8. Ezetimibe, administered with atorvastatin (40 or 80 mg) or simvastatin (40 or 80 mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg.

Table 8
Mean Response to ezetimibe in Patients with HoFH (Mean % Change from Baseline)

Treatment (Daily Dose)	N	LDL-C
Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-7
Ezetimibe + Atorvastatin (40, 80 mg) or Simvastatin (40, 80 mg)	33	-21
Sub-group analysis: Ezetimibe + Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-27

Prevention of Cardiovascular Events
The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicenter, randomised, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalisation for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤125 mg/dL (≤3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤100 mg/dL (≤2.6 mmol/L) if they had been receiving lipid-lowering therapy. All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n=9067) or simvastatin 40 mg (n=9077) and followed for a median of 6.0 years.

Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n=6390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid-lowering therapy (n=11594). Prior to the hospitalisation for the qualifying ACS event, 34% of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53.2 mg/dL (1.4 mmol/L) for the ezetimibe/simvastatin group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of cardiovascular death, major coronary events (MCE; defined as non-fatal myocardial infarction, documented unstable angina that required hospitalisation, or any coronary revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. The study demonstrated that treatment with ezetimibe when added to simvastatin resulted in relative risk reduction of 6.4% in terms of the reduction in the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with simvastatin alone (p=0.016). The primary endpoint occurred in 2572 of 9067 patients (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2742 of 9077 patients (7-year KM rate 34.67%) in the simvastatin alone group. (See Figure 1 and Table 9.)

The treatment effect of ezetimibe/simvastatin was generally consistent with the overall results across many subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, and hypertension (see Figure 2).

Figure 1: Effect of Ezetimibe/Simvastatin on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

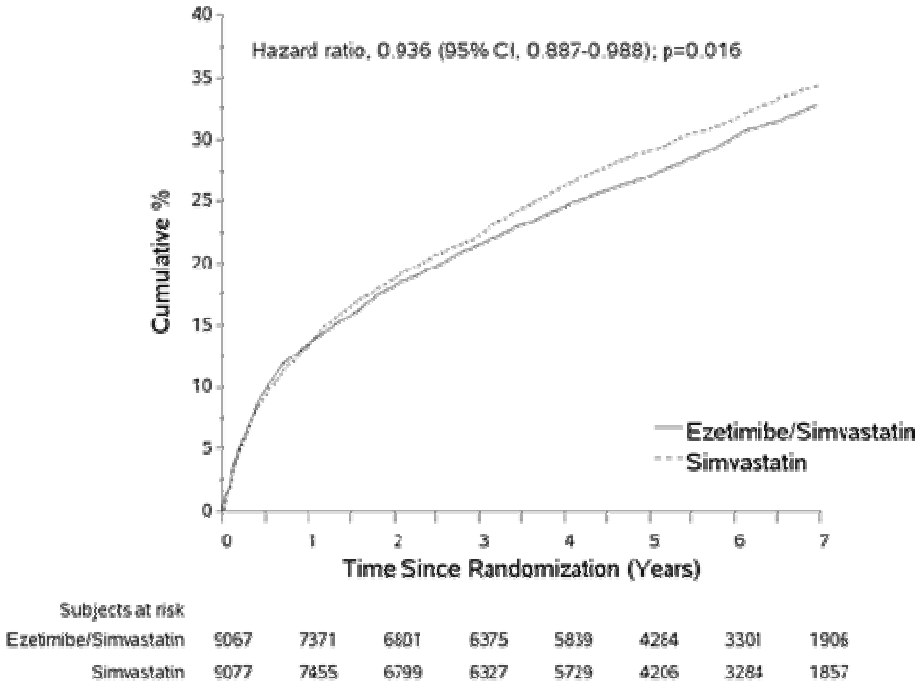


Figure 2
Subgroup Analysis of Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

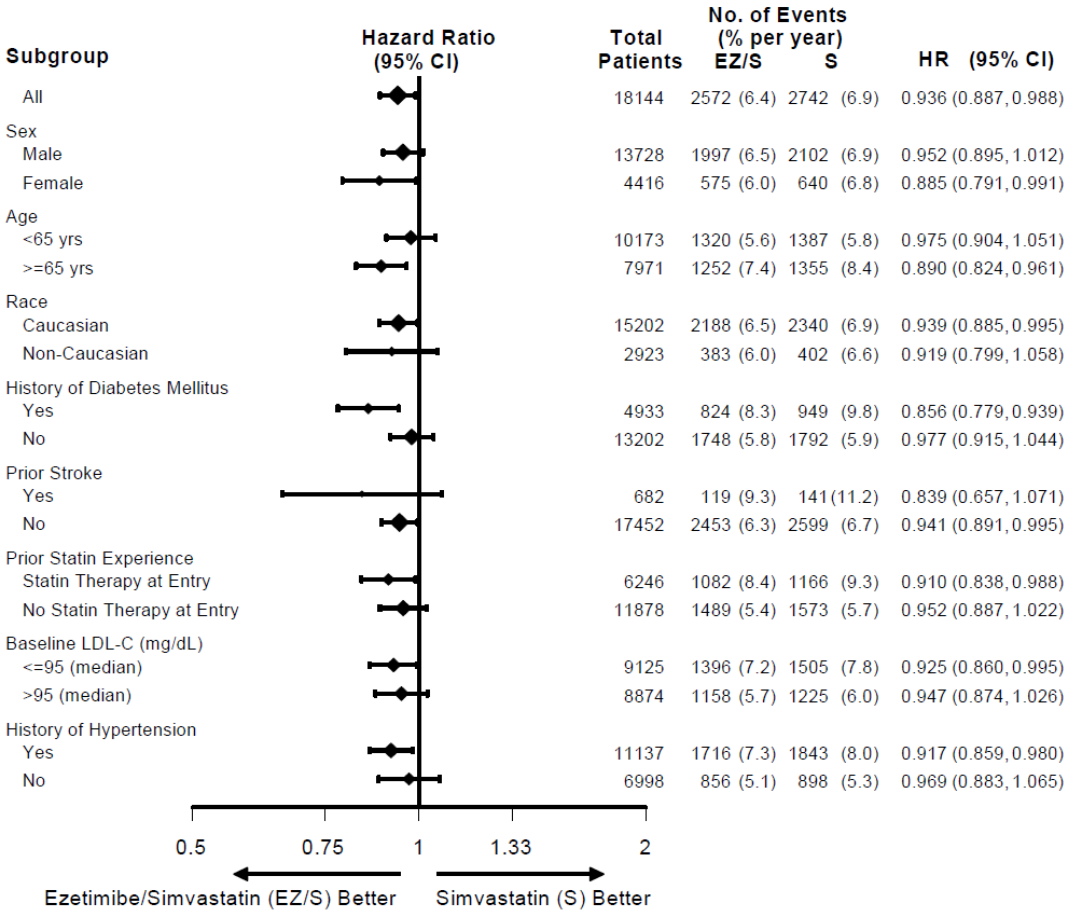


Table 9
Major Cardiovascular Events by Treatment Group in All Randomized Patients in IMPROVE-IT

Outcome	**Ezetimibe/Simvastatin 10/40 mg[a] (N=9067)**		**Simvastatin 40 mg[gb] (N=9077)**		**Hazard Ratio (95% CI)**	**p-value**
	n	K-M % [c]	n	K-M % c		
Primary Composite Efficacy Endpoint						
(CV death, Major Coronary Events and non-fatal stroke)	2572	32.72%	2742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, nonfatal MI, urgent coronary revascularization after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalization, any revascularization, non-fatal stroke	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalization	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularization after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-hemorrhagic stroke [d]	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Hemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1215	15.36%	1231	15.28%	0.989 (0.914,	0.782

					1.070)	

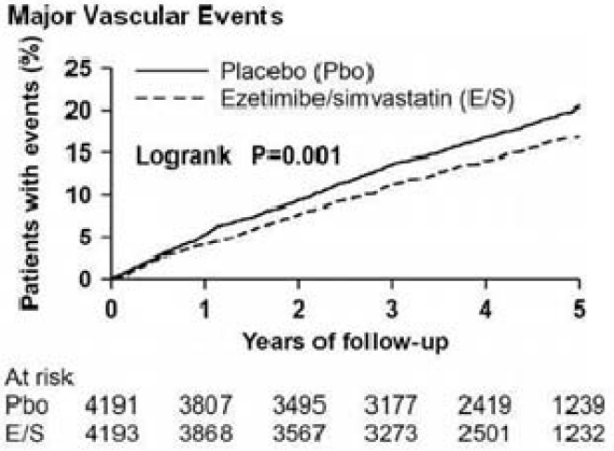
[a] 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.
[b] 27% were uptitrated to simvastatin 80 mg.
[c] Kaplan-Meier estimate at 7 years.
[d] includes ischemic stroke or stroke of undetermined type.

Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)
The Study of Heart and Renal Protection (SHARP) was a multi-national, randomized, placebo-controlled, double-blind study conducted in 9438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. For the first year, patients were randomized in a ratio of 4:4:1, respectively, to a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg, placebo, or simvastatin 20 mg daily. The 1-year simvastatin arm was included to enable the comparison of ezetimibe combined with simvastatin to simvastatin alone with regard to safety and lipids. At 1 year the simvastatin-only arm was re-randomized 1:1 to a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg or placebo. A total of 4650 patients were allocated to EZETROL 10 mg combined with simvastatin 20 mg and 4620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 and 63% were male, 72% Caucasian, 23% diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 108 mg/dL. As of the 1-year measurement, LDL-C was reduced 26% relative to placebo by simvastatin 20 mg alone and 38% for ezetimibe 10 mg combined with simvastatin 20 mg. At the midpoint of the study (2.5 years) mean LDL-C reduction in all randomized patients for ezetimibe combined with simvastatin relative to placebo was 32%. All lipid measurements included patients no longer taking study medication.

The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularization procedure) in only those patients initially randomized to the ezetimibe combined with simvastatin (n=4193) or placebo (n=4191) groups. Secondary analyses included the same composite analyzed for the full cohort randomized (at study baseline or at year 1) to ezetimibe combined with simvastatin (n=4650) or placebo (n=4620) as well as the components of this composite.

The primary endpoint analysis showed that ezetimibe combined with simvastatin significantly reduced the risk of major vascular events (749 patients with events in the placebo group vs. 639 in the ezetimibe combined with simvastatin group) with a relative risk reduction of 16% (p=0.001).

Figure 3
Effect of ezetimibe Combined with Simvastatin on the Primary Endpoint of Risk of Major Vascular Events



The individual components of MVE in all randomized patients are presented in Table 10. Ezetimibe combined with simvastatin significantly reduced the risk of stroke and any revascularization, with

non-significant numerical differences favouring ezetimibe combined with simvastatin for nonfatal MI and cardiac death.

Table 10
Major Vascular Events by Treatment Group in all randomized patients in SHARPa

Outcome	Ezetimibe 10 mg combined with simvastatin 20 mg (N=4650)	Placebo (N=4620)	Risk Ratio (95% CI)	P-value
Major Vascular Events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularization	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004
Major Atherosclerotic Events (MAE)b	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.002

[a]Intention-to-treat analysis on all SHARP patients randomized to ezetimibe combined with simvstatin or placebo either at baseline or year 1
[b] MAE; defined as the composite of nonfatal myocardial infarction, coronary death, non-hemorrhagic stroke, or any revascularization

Nevertheless, this study design did not allow for a separate contribution of the ezetimibe or simvastatin to efficacy to significantly reduce the risk of major vascular events in patients with CKD.

The absolute reduction in LDL cholesterol achieved with ezetimibe combined with simvastatin was lower among patients with a lower baseline LDL-C (<2.5 mmol/l) and patients on dialysis at baseline than the other patients, and the corresponding risk reductions in these two groups were attenuated.

Homozygous Familial Hypercholesterolaemia (HoFH)

A study 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 with homozygous sitosterolemia were randomized to receive ezetimibe 10 mg (n=30) or placebo (n=7). ezetimibe significantly lowered the two major plant sterols, 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, the reduction in plant sterols was progressive over the course of the study.

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).

5.2 Pharmacokinetic properties

Absorption
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically-active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10-mg tablets. Ezoleta can be administered with or without food.

Distribution
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Biotransformation
Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. 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 evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination
Following oral administration of ^{14}C ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

SPECIAL POPULATIONS
Paediatric population
The pharmacokinetics of ezetimibe are similar between children ≥6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Treatment with Ezoleta is not recommended for children less than 10 years old.

Geriatric Patients
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (more than 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with Ezoleta. Therefore, no dosage adjustment is necessary in the elderly.

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 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score >9) hepatic impairment, Ezoleta is not recommended in these patients (see section 4.4).

Renal impairment
After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl less than 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.
An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Gender
Plasma concentrations for total ezetimibe are slightly higher (< 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Race
Based on a meta-analysis of 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.

5.3 Preclinical safety data

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobilliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.
In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies.
Myopathy occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2.000 times the AUC level for the active metabolites).
In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.
Ezetimibe had no effect on the fertility of male or female rats, nor was it teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1.000 mg/kg/day. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium laurilsulfate
Povidone K30
Mannitol
Croscarmellose sodium
Cellulose, microcrystalline
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister: 30 tablets, in a box.

6.6 Special precautions for disposal

No special requirements.

MANUFACTURER

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DATE OF REVISION OF THE TEXT

August 2021