1 PRODUCT NAME

EZETIMIBE SANDOZ 10 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg ezetimibe.

Contains Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ezetimibe Sandoz 10 mg is a white to almost white, oval tablet (7.4 mm x 4.1 mm) with debossing "10" on one side and "EZT" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

Ezetimibe Sandoz, 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), apolipoprotein B (Apo B), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) in adult and adolescent (10 to 17 years of age) patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

Ezetimibe Sandoz, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in adult and adolescent (10 to 17 years of age) patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

4.2 Dose and method of administration

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Ezetimibe Sandoz.

The recommended dose of Ezetimibe Sandoz is 10 mg once daily, used alone or with a statin. Ezetimibe Sandoz can be administered at any time of the day, with or without food.

Use in Renal Impairment/Chronic kidney Disease

Monotherapy

In patients with renal impairment, no dosage adjustment of Ezetimibe Sandoz is necessary (see Section 5.2, *Characteristics in Patients [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 Ezetimibe Sandoz 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 Ezetimibe Sandoz 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 4.4, and Section 5.2, *Characteristics in Patients [Special Populations]*) and Clinical Trials, Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)).

Use in the Elderly

No dosage adjustment is required for elderly patients (see Section 5.2, *Characteristics in Patients [Special Populations]).*

Use in Paediatric Patients

Children and adolescents ≥10 years: No dosage adjustment is required (see Section 5.2, *Characteristics in Patients [Special Populations]).*

Children <10 years: Treatment with Ezetimibe Sandoz 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 Section 4.4 and Section 5.2, *Characteristics in Patients [Special Populations].)*

Co-administration with bile acid sequestrants

Dosing of Ezetimibe Sandoz 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 Ezetimibe Sandoz is to be administered with a statin, please refer to the data sheet for that particular statin.

Ezetimibe in combination with fenofibrate is contraindicated in patients with gall bladder disease.

Therapy with ezetimibe in combination with a statin is contraindicated during pregnancy and lactation.

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

4.4 Special warnings and precautions for use

When Ezetimibe Sandoz is to be administered with a statin, please refer to the data sheet for that particular statin.

Liver Enzymes

There is sufficient evidence to suggest a causal association between ezetimibe monotherapy and drug-induced liver injury. 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 (See Section 4.8). When ezetimibe is administered alone or with

a statin, liver function tests should be performed at initiation of therapy and as indicated or according to the recommendations of the statin, and periodically thereafter. If an increase in ALT or AST ≥3 X the ULN persists the statin dose should be reduced or the statin withdrawn.

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 medicines. 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 regardless of causality. 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 agents known to be associated with increased risk of rhabdomyolysis. All patients starting therapy with Ezetimibe Sandoz should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Ezetimibe Sandoz 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 a clinical trial 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 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).

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established; therefore, co-administration of Ezetimibe Sandoz and fibrates is not recommended (see Section 4.5).

Fenofibrate

Fibrates may increase cholesterol excretion from the bile, and ezetimibe increased cholesterol in the gallbladder bile in a preclinical study in dogs. Given the potential for cholelithiasis, and the numerically higher incidence of cholecystectomies in patients administered ezetimibe and fenofibrate in a clinical study (see Sections 5.1, *Clinical trials* and 4.8), coadministration of ezetimibe and fenofibrate is contraindicated in patients with pre-existing gallbladder disease (see Section 4.3).

Ciclosporin

Caution should be exercised when initiating ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe Sandoz and ciclosporin (see Section 4.5).

Anticoagulants

If Ezetimibe Sandoz is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see Section 4.5).

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Ezetimibe Sandoz is not recommended in these patients (see Section 5.2, *Characteristics in Patients [Special Populations]).*

Paediatric Use

The use of ezetimibe co-administered with simvastatin in children and adolescent patients (10-17 years old) is recommended only for patients with Heterozygous Familial Hypercholesterolaemia (HeFH) or Homozygous Familial Hypercholesterolaemia (HoFH).

However, clinical efficacy/safety study experience in paediatric and adolescent patients (10-17 years old) has been mostly limited to patients with Heterozygous Familial Hypercholesterolaemia (see Section 5.1, *Clinical trials*). There are also no long-term (> 1 year) safety data in this population.

The clinical safety and efficacy of ezetimibe co-administered with simvastatin in children and adolescents (10-17 years old) with hypercholesterolaemia other than Heterozygous Familial Hypercholesterolaemia have not been studied.

Safety and effectiveness of ezetimibe co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least one year post-menarche. Doses greater than 10 mg ezetimibe with 40 mg simvastatin have not been studied in this population and are not recommended. In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a treatment period > 33 weeks on growth, sexual maturation, intellectual and psychosocial development have not been studied. (See Sections 4.2, 4.8 and 5.1, *Clinical trials, Clinical Studies in Paediatric Patients*). Adolescent females should be counselled on appropriate contraceptive methods while on co-administered ezetimibe and simvastatin therapy (see Sections 4.3, 4.4 and 4.6, *Use in pregnancy*).

The safety and efficacy of ezetimibe co-administered with simvastatin doses above 40 mg daily have not been studied in children and adolescents (10-17 years old) and are not recommended. The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Ezetimibe co-administered with simvastatin has not been studied in pre-menarchal girls or in pre-pubertal boys and is not recommended.

Excipient

Ezetimibe Sandoz contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 medicine metabolising enzymes. No clinically significant pharmacokinetic interactions have

been observed between ezetimibe and medicines known to be metabolised 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 co-administration. 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.

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

Therefore, dosing of ezetimibe and a bile acid binding sequestrant should take place several hours apart. However, efficacy of such combination has not been studied.

Ciclosporin: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of ciclosporin, 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) who had taken a single 10 mg dose of ezetimibe alone.

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 ciclosporin, 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 ciclosporin on Day 7 resulted in a mean 15% increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of ciclosporin alone (see Section 4.4).

Fibrates: Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5- and 1.7-fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of ezetimibe administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see Section 5.3, Animal Pharmacology). Although the relevance of this preclinical finding to humans is unknown, coadministration of Ezetimibe Sandoz with fibrates is not recommended until use in patients is studied.

Statins: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered 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 Normalised 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

Use in pregnancy

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/foetal development, parturition or postnatal development (see Section 5.3, Development). However, caution should be exercised when prescribing to pregnant women.

When ezetimibe was given with lovastatin, simvastatin, pravastatin or atorvastatin, no teratogenic effects were observed in embryo-foetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed (see Section 5.3, Development).

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

Use in lactation

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, Ezetimibe Sandoz 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 of the effects on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with Ezetimibe Sandoz may affect some patients' ability to drive or operate machinery. Individual responses to Ezetimibe Sandoz may vary. (See Section 4.8).

4.8 Undesirable effects

Clinical studies of 8 to 14 weeks duration in which ezetimibe 10 mg daily was administered alone, with a statin, or with fenofibrate in 3551 patients demonstrated: ezetimibe was generally well tolerated, adverse reactions were usually mild and transient, the overall incidence of side effects reported with ezetimibe was similar to that reported with placebo, and the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.

There were no drug-related adverse experiences reported occurring in ≥ 2% of patients taking ezetimibe alone (n = 1691).

The following drug-related adverse experiences were reported occurring in ≥ 2% in patients taking ezetimibe co-administered with a statin (n = 1675).

Table 1.

	All Statins (%) N=1676	Ezetimibe 10 mg Co-administered with a statin (%) N=1675
Musculoskeletal and connective tissue disorders		
Myalgia	2.4	3.2

In addition, the following common or uncommon drug-related adverse experiences were reported in clinical trials in patients taking ezetimibe alone and at a greater incidence than

placebo, or in patients taking ezetimibe co-administered with a statin and at a greater incidence than statin administered alone.

Ezetimibe administered alone:

Investigations:

Uncommon: ALT and/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: cough

Gastrointestinal Disorders:

Common: abdominal pain; diarrhoea; flatulence

Uncommon: dyspepsia; gastroesophageal reflux disease; nausea

Musculoskeletal and Connective Tissue Disorders

Uncommon: arthralgia; muscle spasms; neck pain

Metabolism and Nutrition Disorders:

Uncommon: decreased appetite

Vascular Disorders:

Uncommon: hot flush; hypertension

General Disorders and Administration Site Condition:

Common: fatigue

Uncommon: chest pain; pain

Ezetimibe co-administered with a statin:

Investigations:

Common: ALT and/or AST increased

Nervous System Disorders:

Common: headache

Uncommon: paresthesia

Gastrointestinal Disorders:

Uncommon: dry mouth; gastritis

Skin and Subcutaneous Tissue Disorders:

Uncommon: pruritus; rash; urticaria

Musculoskeletal and Connective Tissue Disorders:

Common: myalgia

Uncommon: back pain; muscular weakness; pain in extremity

General Disorders and Administration Site Condition:

Uncommon: asthenia; oedema peripheral

Ezetimibe co-administered with fenofibrate:

Gastrointestinal Disorders:

Common: abdominal pain

In a co-administration study with fenofibrate (see Section 5.1, Clinical trials), in which 292 patients were exposed for ≥ 24 weeks and 120 exposed for ≥ 52 weeks, the incidence rate of cholecystectomy in the coadministration group was 1.7% (95% CI 0.6, 4.0) per 100 patient years compared to 0 (95% CI 0, 9.2) per 100 PY for the ezetimibe group and 0.6% (95% CI 0, 3.1) per 100 PY for the fenofibrate group. Longer term safety outcomes have not been studied.

Patients with Chronic Kidney Disease

In the Study of Heart and Renal Protection (SHARP) (see Section 5.1, *Clinical Trials, Prevention of Major Vascular Events in Chronic Kidney Disease [CKD]*), 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. 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.

Paediatric Patients 10-17 Years of Age

In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥ 3x ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10x ULN). No cases of myopathy were reported (see Sections 4.4, *Paediatric Use*, and 5.1, *Clinical trials, Clinical Studies in Paediatric Patients*).

In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe co-administered with simvastatin for a treatment period > 33 weeks on growth, sexual maturation intellectual and psychosocial development have not been studied (see Sections 4.2; 4.4; and 5.1, *Clinical trials, Clinical Studies in Paediatric Patients*).

The study was not of sufficient duration to detect long term adverse effects.

Laboratory Test Findings

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.

In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of CPK (≥10 X ULN) occurred in two patients (2%) treated with ezetimibe plus simvastatin and in zero patients treated with simvastatin alone. No cases of myopathy were reported.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

Blood and lymphatic system disorders: thrombocytopaenia

Nervous system disorders: nausea; dizziness; paraesthesia

Gastrointestinal disorders: pancreatitis; constipation

Skin and subcutaneous tissue disorders: severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiforme

Musculoskeletal and connective tissue disorders: arthralgia; myalgia; myopathy/rhabdomyolysis (See Section 4.4)

General disorders and administration site conditions: asthenia

Immune system disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria

Hepatobiliary disorders: hepatitis; cholelithiasis; cholecystitis; drug-induced liver injury

Psychiatric disorders: depression

Investigations: increased CPK; elevations of liver transaminases

Reporting of suspected adverse reactions

Reporting suspected adverse reaction after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolaemia for 26 weeks, was generally well tolerated.

A few cases of over dosage 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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Ezetimibe Sandoz (ezetimibe) is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols.

Lipid modifying agents, Other lipid modifying agents, ATC code: C10A X09

Ezetimibe Sandoz 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 localises 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).

In a 2-week clinical study in 18 hypercholesterolaemic 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, reduces total-C, LDL-C, Apo B, and TG and increases HDL C in patients with hypercholesterolaemia, beyond either treatment alone.

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-low-density 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 TRIALS

Controlled clinical studies of varying designs were conducted with ezetimibe either as monotherapy or co-administration with a statin. Ezetimibe significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB) and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

A beneficial effect of ezetimibe on cardiovascular morbidity or mortality has not been established.

Primary Hypercholesterolemia

Monotherapy

In two, multicentre, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C compared to placebo (see Table 2). Reduction in LDL-C was consistent across age, sex, race, and baseline LDL-C. 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 2. Response to Ezetimibe in Patients with Primary Hypercholesterolaemia (Absolute and Percent Change from Baseline)

	Treatment group	N	Total-C Abs[a] (Pct[b])	LDL-C Abs[a] (Pct[b])	Apo B Abs[c] (Pct[b])	TG Abs[d] (Pct[e])	HDL-C Abs[a] (Pct[b])
Study 1	Placebo	205	+0.03 (+1%)	0.05 (+1%)	-0.03 (-1%)	-0.02 (-1%)	-0.02 (-1%)
	EZETIMIBE	622	-0.81 (-12%)	-0.79 (-18%)	-0.26 (-15%)	-0.12 (-7%)	0.01 (+1%)
Study 2	Placebo	226	0.06 (+1%)	0.05 (+1%)	-0.03 (-1%)	0.03 (+2%)	-0.03 (-2%)
	EZETIMIBE	666	-0.82 (-12%)	-0.77 (-18%)	-0.26 (-16%)	-0.15 (-9%)	0.01 (+1%)
Pooled Data (Studies 1 & 2)	Placebo	431	0.02 (0%)	0.04 (+1%)	-0.03 (-2%)	0.00 (0%)	-0.03 (-2%)
	EZETIMIBE	1288	-0.84 (-13%)	-0.79 (-18%)	-0.26 (-16%)	-0.14 (-8%)	0.01 (+1%)

[a] Mean absolute change from baseline, expressed as mmol/L

[b] Mean percent change from baseline

[c] Mean absolute change from baseline, expressed as g/L

[d] Median absolute change from baseline, expressed as mmol/L

[e] Median percent change from baseline

Co-Administration with a Statin

Ezetimibe Initiated Concurrently with a Statin

In four, multicentre, double-blind, placebo-controlled, 12-week trials, in 1187 patients with hypercholesterolaemia, ezetimibe 10 mg was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin. The greatest LDL-C reducing effect is seen with the lowest dose of each statin, with only a further 2-9% incremental reduction in LDL-C with each doubling of the dose. Comparatively, adding 10 mg of ezetimibe to a given dose of a statin is shown to achieve a greater reduction in LDL-C than that achieved with statin dose doubling.

Table 3. Mean Absolute and Percent Change from Baseline in Plasma Concentration of Calculated LDL-C for Ezetimibe Administered with Statins

	Atorvastatin Study Abs[a] (Pct[b])	Simvastatin Study Abs[a] (Pct)[b]	Pravastatin Study Abs[a] (Pct[b])	Lovastatin Study Abs[a] (Pct[b])
Placebo	0.20 (+4%)	-0.08 (-1%)	-0.03 (-1%)	0.00 (0%)
EZETIMIBE	-0.92 (-20%)	-0.92 (-19%)	-0.91 (-20%)	-0.86 (-19%)
10 mg statin	-1.76 (-37%)	-1.25 (-27%)	-0.96 (-21%)	-0.94 (-20%)
EZETIMIBE + 10 mg statin	-2.46 (-53%)	-2.10 (-46%)	-1.55 (-34%)	-1.56 (-34%)
20 mg statin	-1.91 (-42%)	-1.74 (-36%)	-1.10 (-23%)	-1.18 (-26%)

EZETIMIBE + 20 mg statin	-2.59 (-54%)	-2.16 (-46%)	-1.82 (-40%)	-1.87 (-41%)
40 mg statin	-2.09 (-45%)	-1.75 (-38%)	-1.43 (-31%)	-1.44 (-30%)
EZETIMIBE + 40 mg statin	-2.69 (-56%)	-2.55 (-56%)	-1.97 (-42%)	-2.15 (-46%)
80 mg statin	-2.57 (-54%)	-2.11 (-45%)	-	-
EZETIMIBE + 80 mg statin	-2.93 (-61%)	-2.64 (-58%)	-	-
Pooled data: All statin doses	-2.08 (-44%)	-1.71 (-36%)	-1.16 (-25%)	-1.19 (-25%)
Pooled data: All EZETIMIBE + statin doses	-2.67 (-56%)	-2.36 (-51%)	-1.78 (-39%)	-1.86 (-40%)

[a] Mean absolute change from baseline, expressed as mmol/L

[b] Mean percent change from baseline

In a pooled analysis of all Ezetimibe + statin doses, Ezetimibe had a beneficial effect on total-C, Apo B, TG, and HDL-C (Table 4).

Table 4. Pooled Analysis of Absolute and Percent Change from Baseline in Total-C, ApoB, TG, and HDL-C

	Total-C Abs[a] (Pct[b])	**Apo B Abs[c] (Pct[b])**	**TG Abs[d] (Pct[e])**	**HDL-C Abs[a](Pct[b])**
Ezemitibe + Atorvastatin	-2.86 (-41%)	-0.78 (-45%)	-0.55 (-33%)	0.09 (+7%)
Atorvastatin alone	-2.24 (-32%)	-0.61 (-36%)	-0.40 (-24%)	0.05 (+4%)
Ezemitibe + Simvastatin	-2.49 (-37%)	-0.69 (-41%)	-0.53 (-29%)	0.11 (+9%)
Simvastatin alone	-1.78 (-26%)	-0.51 (-30%)	-0.32 (-20%)	0.09 (+7%)
Ezemitibe + Pravastatin	-1.86 (-27%)	-0.51 (-30%)	-0.36 (-21%)	0.10 (+8%)
Pravastatin alone	-1.17 (-17%)	-0.35 (-20%)	-0.26 (-14%)	0.08 (+7%)
Ezemitibe + Lovastatin	-1.96 (-29%)	-0.57 (-33%)	-0.44 (-25%)	0.10 (+9%)
Lovastatin alone	-1.25 (-18%)	-0.36 (-21%)	-0.21 (-12%)	0.04 (+4%)

[a] Mean absolute change from baseline, expressed as mmol/L

[b] Mean percent change from baseline

[c] Mean absolute change from baseline, expressed as g/L

[d] Median absolute change from baseline, expressed as mmol/L

[e] Median percent change from baseline

Ezetimibe Added to On-going Statin Therapy

In a multicentre, double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.59 to 4.14 mmol/L, depending on baseline characteristics) were randomised to receive either ezetimibe 10 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 randomised 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 5). LDL-C reductions were consistent across all statins.

Table 5. Response to Addition of ezetimibe to On-going Statin Therapy[a] in Patients with Hypercholesterolaemia (Absolute and Percent Change from Baseline)

		Total-C	LDL-C	Apo B	TG	HDL-C
	N	Abs[b] (Pct[c])	Abs[b] (Pct[c])	Abs[d] (Pct[c])	Abs[e] (Pct[f])	Abs[b] (Pct[c])
On-going Statin +Placebo	390	-0.16 (-2%)	-0.16 (-4%)	-0.05 (-3%)	-0.05 (-3%)	0.00 (+1%)
On-going Statin +EZETIMIBE	379	-0.99 (-17%)	-0.92 (-25%)	-0.27 (-19%)	-0.19 (-14%)	0.03 (+3%)

[a] Percentages of patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)

[b] Mean absolute change from baseline, expressed as mmol/L

[c] Mean percent change from baseline

[d] Mean absolute change from baseline, expressed as g/L

[e] Median absolute change from baseline, expressed as mmol/L

[f] Median percent change from baseline

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

In a multicentre, double-blind, 14 week study, 621 patients with hypercholesterolaemia receiving atorvastatin 10 mg daily with an LDL-C > 3.36 mmol/L were randomised 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 (< 2.59 mmol/L). The mean baseline LDL-C was 4.84 mmol/L and approximately 60% of the patients had heterozygous familial hypercholesterolaemia (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 hypercholesterolaemia 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.

Other Studies

The use of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia demonstrated a numerically higher incidence of cholecystectomies in patients in the co- administration group compared with those in the monotherapy groups (see Sections 4.3 and 4.8). Each drug contributed to lowering LDL-C, but the effects on triglycerides and HDL-C were related to fenofibrate and were not enhanced by co-administration. Longer term clinical outcomes such as mortality and morbidity were not investigated.

Clinical Studies in Paediatric Patients

In a multicentre, double-blind, controlled study, 142 boys and 106 post-menarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% Multiracial) with heterozygous familial hypercholesterolaemia (HeFH) were randomised to receive either ezetimibe co-administered with simvastatin or simvastatin alone. Inclusion in this study required 1) a baseline LDL-C level between 4.1 and 10.4 mmol/L (160 and 400 mg/dL) and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 5.8 mmol/L (range: 4.2-9.1 mmol/L) in the ezetimibe co-administered with simvastatin group compared to 5.7 mmol/L (range: 3.9-8.7 mmol/L) in the simvastatin monotherapy group. The patients received co-administered ezetimibe and simvastatin (10 mg, 20 mg or 40 mg) or simvastatin alone (10 mg, 20 mg or 40 mg) for 6 weeks, co-administered ezetimibe and simvastatin 40 mg or 40 mg simvastatin alone for the next 27 weeks, and open-label co-administered ezetimibe and simvastatin (10 mg, 20 mg or 40 mg) for 20 weeks thereafter.

The primary hypothesis was that the percent change in LDL-C from baseline to Week 6 in the pooled ezetimibe and simvastatin groups would be greater than in the pooled simvastatin monotherapy groups. At Week 6, co-administered ezetimibe and simvastatin (all doses) lowered LDL-C significantly more than simvastatin (all doses) alone (49% vs 34% respectively). The results of the study at Week 6 are summarised in Table 6 and 6a1. Results at Week 33 were consistent with those at Week 6. At Week 53, the end of the open-label extension, the effects on lipid parameters were maintained.

Table 6. Response to ezetimibe Co-administered with Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolaemia

	Total- C	**LDL-C**	**Apo B**	**Non- HDL-C**	**TG†**	**HDL-C**
Mean absolute difference between treatment groups	-0.96	-0.93	-0.23	-0.95	-0.04	-0.01
95% Confidence Interval	-1.19, -0.73	-1.15, -0.72	-0.30, -0.17	-1.18, -0.72	-12, +0.04	-0.04, +0.03

*Mean (or median) absolute change from baseline (units are mmol/L for all parameters except Apo B, which is in g/L).

†For triglycerides, median absolute change from baseline.

Table 6a 1: Mean Percent Difference at Week 6 between Pooled ezetimibe and Simvastatin Group and Pooled Simvastatin Group in Adolescent Patients with Heterozygous Familial Hypercholesterolaemia

	Total- C	**LDL-C**	**Apo B**	**Non- HDL-C**	**TG***	**HDL-C**
Mean percent difference between treatment groups	**-12%**	**-15%**	**-12%**	**-14%**	**-2%**	**+0.1%**
95% Confidence Interval	**-15%, -9%**	**-18%, -12%**	**-15%, -9%**	**-17%, -11%**	**-9, +4**	**-3, +3**

*For triglycerides, median % change from baseline

From the start of the trial to the end of Week 33, discontinuations due to an adverse reaction occurred in 7 (6%) patients in the ezetimibe coadministered with simvastatin group and in 2 (2%) patients in the simvastatin monotherapy group.

The clinical safety and efficacy of ezetimibe co-administered with simvastatin in children and adolescents (10-17 years old) with hypercholesterolaemia other than Heterozygous Familial Hypercholesterolaemia have not been studied.

The safety and efficacy of ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in children and adolescents (10-17 years old) and are not recommended.

The long-term efficacy of therapy with ezetimibe in children and adolescents (10-17 years old) to reduce morbidity and mortality in adulthood has not been studied.

Homozygous Familial Hypercholesterolaemia (HoFH)

A study was conducted to assess the efficacy of ezetimibe in the treatment of HoFH. This double-blind, randomised, 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 randomised 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 7. 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 7. Mean Response to Ezetimibe in Patients with HoFH (Mean Absolute and Percent Change from Baseline)

Treatment (Daily Dose)	**N**	**LDL-C Abs[a] (Pct[b])**
Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-0.51 (-7%)
Ezetimibe + Atorvastatin (40, 80 mg) or Simvastatin (40, 80 mg)	33	-1.76 (-21%)
Subgroup analysis: **Ezetimibe + Atorvastatin (80 mg) or Simvastatin (80 mg)**	17	-2.00 (-27%)

[a] Mean absolute change from baseline, expressed as mmol/L

[b] Mean percent change from baseline

Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)

The Study of Heart and Renal Protection (SHARP) was a multinational, randomised, placebo-controlled, double-blind study conducted in 9,438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. Patients with a definite history of myocardial infarction (MI) or coronary revascularisation procedure, existing or planned renal transplant, recent acute uraemic emergency, evidence of active inflammatory muscle disease or creatine kinase (CK) >3xULN were excluded. For the first year, patients were randomised 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-randomised 1:1 to a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg or placebo. A total of 4,650 patients were allocated to ezetimibe 10 mg combined with simvastatin 20 mg and 4,620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 (ranging in age from 39 to 94.5 years old); 63% were male, 72% were Caucasian and 23% were diabetic; and, for those not on dialysis, the median serum creatinine was 0.22 mmol/L and the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 m^2, with 94% of patients having an eGFR < 45 mL/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 2.8 mmol/L. 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 randomised patients for ezetimibe combined with simvastatin relative to placebo was 32%. All lipid measurements included patients no longer taking study medication.

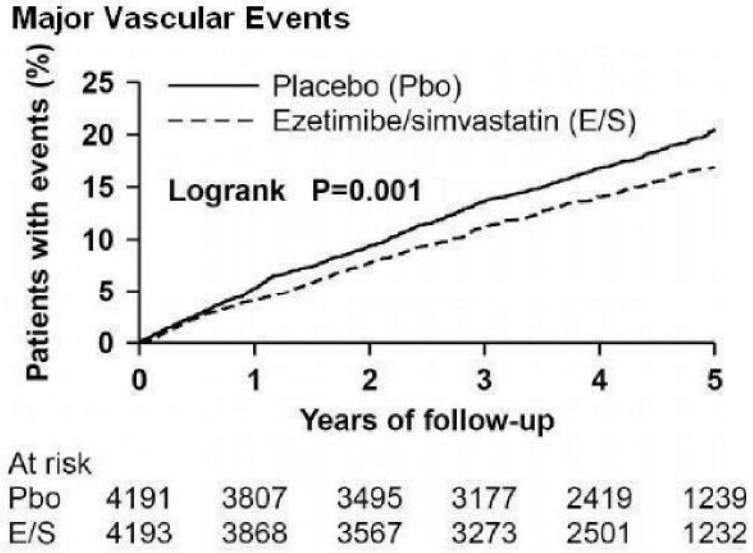
The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularisation procedure) in only those patients initially randomised to the ezetimibe combined with simvastatin (n=4,193) or placebo (n=4,191) groups. Secondary analyses included the same composite analysed for the full cohort randomised (at study baseline or at year 1) to ezetimibe combined with simvastatin (n=4,650) or placebo (n=4,620) as well as the components of this composite.

The primary endpoint analysis showed that ezetimibe combined with simvastatin significantly reduced the risk of MVE (749 patients with events in the placebo group vs. 639 in the ezetimibe combined with simvastatin group) with an absolute risk reduction of 2.3% (number needed to treat, 43) and a relative risk reduction of 16% (p=0.001) (see Figure 1). An analysis of major atherosclerotic events (MAE, a subset of the MVE composite that excluded non-coronary cardiac deaths and haemorrhagic stroke) showed that Ezetimibe combined with simvastatin significantly reduced the risk of MAE (526 (11.3%) of 4650 patients ever allocated to ezetimibe combined with simvastatin and 619 (13.4%) of 4620 patients ever allocated to placebo), corresponding to an absolute risk reduction of 2.1% (number needed to treat, 48) and a relative risk reduction of 17% (p=0.002).

The risk reduction for the MVE composite was directionally consistent (i.e., Ezetimibe combined with simvastatin numerically superior to placebo) with that of the entire cohort of patients for the following key baseline predefined subgroups: age, gender, dialysis vs. non-dialysis, eGFR, diabetes, pre-existing atherosclerotic disease, blood pressure, or tertiles of baseline LDL-C.

Compliance rates with placebo and study medication declined over the course of the study. For example, at 20-25 months of follow-up, 68% of patients allocated to ezetimibe/simvastatin and 67% of patients allocated to placebo were taking 80% or more of the study medication, while at 44-49 months, compliance had fallen to 60% and 56%, respectively.

Figure 1: Effect of ezetimibe Combined with Simvastatin on the Primary Endpoint of Risk of Major Vascular Events



The individual components of MVE in all randomised patients are presented in Table 8. ezetimibe combined with simvastatin significantly reduced the risk of stroke and any revascularisation, with non-significant numerical differences favouring ezetimibe combined with simvastatin for nonfatal MI and cardiac death.

Table 8. Major Vascular Events by Treatment Group in All Randomised Patients in SHARP[a]

Outcome	Ezetimibe 10 mg combined with simvastatin 20 mg (N=4,650)	Placebo (N=4,620)	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-haemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Haemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularisation	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 randomised to ezetimibe combined with simvastatin or placebo either at baseline or year 1.

[b] MAE defined as the composite of nonfatal myocardial infarction, coronary death, non-haemorrhagic stroke, or any revascularisation.

No significant treatment effect of ezetimibe combined with simvastatin on MVE was found in the subgroup of patients on dialysis at baseline compared with those not on dialysis at baseline.

Among 3023 patients on dialysis at baseline, ezetimibe combined with simvastatin reduced the risk of MVE by 6% (RR 0.94: 95% CI 0.80-1.09) compared with 22% (RR 0.78: 95% CI 0.69-0.89) among 6247 patients not on dialysis at baseline (interaction P=0.08).

Among patients not on dialysis at baseline, ezetimibe combined with simvastatin did not reduce the risk of progressing to end-stage renal disease compared with placebo.

There were no significant differences between the Ezetimibe Sandoz combined with simvastatin and placebo groups on all cause mortality, or on any specific cause of death.

The study design precluded drawing conclusions regarding the independent contribution of either ezetimibe or simvastatin to the observed effect, and was not able to provide evidence of efficacy for the combination of ezetimibe 10 mg with simvastatin 20 mg compared to either the lower dose combination (i.e. Ezetimibe 10 mg with simvastatin 10 mg) or to treatment with statin alone (i.e. simvastatin 20 mg).

The effect of ezetimibe taken in combination with other statins in patients with CKD has not been studied.

5.2 Pharmacokinetic properties

Ezetimibe Sandoz, ezetimibe is described chemically as 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4.

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature.

Pharmacokinetics

Absorption

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) 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. Ezetimibe Sandoz 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.

Metabolism

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 medicine-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine 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 patient considerations

Characteristics in Patients (Special Populations)

Paediatric Patients

The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population <10 years of age are not available.

Geriatric Patients

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

Hepatic Insufficiency

After a single 10 mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (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 insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, ezetimibe is not recommended in these patients (see Section 4.4).

Renal Insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73m^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.

5.3 Preclinical safety data

Animal Pharmacology

The hypocholesterolaemic effect of ezetimibe was evaluated in Rhesus monkeys, a model for the human metabolism of cholesterol, as well as in dogs. Rhesus monkeys were fed a cholesterol-containing diet that mimics a human Western diet. Ezetimibe was found to have an ED_{50} of 0.0005 mg/kg/day for inhibiting the rise in plasma cholesterol levels (ED_{100} = 0.003 Llmg/kg/day). The ED_{50} in dogs was found to be 0.007 mg/kg/day. These results are consistent with ezetimibe being an extremely potent cholesterol absorption inhibitor.

In dogs given ezetimibe (≥0.03 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 3-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a normal or cholesterol rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively. The relevance of these preclinical findings to humans is unknown.

Animal Toxicology

Acute Toxicity

In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

Chronic Toxicity

Ezetimibe was well tolerated by mice, rats and dogs. No target organs of toxicity were identified in chronic studies at daily doses up to 1500 (males) and 500 mg/kg (females) in rats, up to 500 mg/kg in mice, or up to 300 mg/kg in dogs.

The safety of concomitant administration of ezetimibe and statins was assessed in rats and dogs. When ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin or lovastatin, for three months, toxicologic findings were consistent with those seen with statins administered alone.

Carcinogenicity

In two-year studies conducted in mice and rats, ezetimibe was not carcinogenic.

Mutagenesis

Ezetimibe was not genotoxic in a series of *in vivo* and *in vitro* tests.

Combinations of ezetimibe with atorvastatin, simvastatin, pravastatin, or lovastatin were not genotoxic in a series of *in vitro* and *in vivo* assays.

Reproduction

Ezetimibe did not affect the fertility of male or female rats.

Development

Ezetimibe was not teratogenic in rats or rabbits and had no effect on prenatal or postnatal development.

Concomitant administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits, a low incidence of skeletal malformations (fused sternebrae, fused caudal vertebrae, reduced number of caudal vertebrae) was observed when ezetimibe (1000 mg/kg; ≥146 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe) was administered with lovastatin (2.5 and 25 mg/kg), simvastatin (5 and 10 mg/kg), pravastatin (25 and 50

mg/kg), or atorvastatin (5, 25, and 50 mg/kg). Exposure to the pharmacologically active form of the statin ranged from 1.4 (atorvastatin) to 547 (lovastatin) times the human exposure at 10 mg daily (simvastatin or atorvastatin) or 20 mg daily (lovastatin and pravastatin) based on $AUC_{0\text{-}24hr}$.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 10 mg tablet contains:

- lactose monohydrate
- hypromellose
- croscarmellose sodium
- microcrystalline cellulose
- sodium lauryl sulfate
- magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C. Protect from moisture. Store in the original package.

6.5 Nature and contents of container

Ezetimibe Sandoz 10 mg, tablets are available in packs of 30 tablets.

6.6 Special precautions for handling, reconstitution and disposal

Any unused medicine should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9 DATE OF FIRST APPROVAL

18 June 2015

10 DATE OF REVISION OF THE TEXT

8 April 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of Drug induced liver injury with ezetimibe monotherapy
4.8	Minor editorial change
4.9	Updated risk assessment wording