AUSTRALIAN PRODUCT INFORMATION

EZETIMIBE VIATRIS

(ezetimibe) tablet

1 NAME OF THE MEDICINE

Ezetimibe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of EZETIMIBE VIATRIS for oral administration contains 10 mg ezetimibe.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

EZETIMIBE VIATRIS (ezetimibe) – 10 mg, white to off-white, capsule-shaped tablet, debossed with "10" on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults (≥ 18 Years)

Primary Hypercholesterolaemia

EZETIMIBE VIATRIS administered alone, or with an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

EZETIMIBE VIATRIS, administered with a statin, is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Homozygous Sitosterolaemia (Phytosterolaemia)

EZETIMIBE VIATRIS is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia.

Prevention of Cardiovascular Disease

EZETIMIBE VIATRIS is indicated for administration in combination with the maximum tolerated dose of a statin with proven cardiovascular benefit in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Children and Adolescents 10-17 Years

(pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche)

Heterozygous Familial Hypercholesterolaemia (HeFH)

EZETIMIBE VIATRIS co-administered with simvastatin (doses up to 40 mg) is indicated as an adjunctive therapy to diet in adolescent patients (10-17 years old) with heterozygous familial hypercholesterolaemia where use of a combination product is appropriate:

- Patients not appropriately controlled with a statin or ezetimibe alone

- Patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)

EZETIMIBE VIATRIS co-administered with simvastatin (doses up to 40 mg) is indicated in adolescent patients (10-17 years old) 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 VIATRIS.

Use in Patients with Primary Hypercholesterolemia

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

EZETIMIBE VIATRIS may be administered with a statin for incremental effect. For convenience, the daily dose of EZETIMIBE VIATRIS may be taken at the same time as the statin, according to the dosing recommendations for the statin.

Use in Patients with Coronary Heart Disease and a History of Acute Coronary Syndrome

Combination Therapy with a Statin

For incremental cardiovascular event reduction in patients with coronary heart disease, EZETIMIBE VIATRIS 10 mg may be administered with a statin with proven cardiovascular benefit.

Use in Patients with Renal Impairment/Chronic Kidney Disease

Monotherapy

In patients with renal impairment, no dosage adjustment of EZETIMIBE VIATRIS is necessary (see Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations)).

Combination Therapy with Simvastatin

In patients with mild renal insufficiency (estimated GFR ≥60 mL/min/1.73 m^2), no dosage adjustment of EZETIMIBE VIATRIS 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 VIATRIS is 10 mg and the dose of simvastatin is 20 mg once a day in the evening. Efficacy and safety at higher doses has not been evaluated in this CKD population (see Section 4.4 Special WARNINGS AND PRECAUTIONS FOR USE, Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations), and Section 5.1 PHARMACODYNAMIC PROPERTIES, 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 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations).

Paediatric Use

Initiation of treatment must be performed under review of a specialist.

Paediatric Patients 10-17 Years of Age

The use of EZETIMIBE VIATRIS 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).

There are no clinical safety and efficacy data on the use of EZETIMIBE VIATRIS co-administered with simvastatin in children and adolescent patients (10-17 years old) with non-familial hypercholesterolaemia, or mixed hyperlipidaemia.

Adolescents 10 to 17 years old (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche): No dosage adjustment is required (see Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations). The clinical experience in paediatric and adolescents patient (aged 10-17 years old) is however limited and mostly includes children and adolescents (10-17 years old) with Heterozygous Familial Hypercholesterolaemia. There are also no long-term (>1 year) safety data in this population.

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

When EZETIMIBE VIATRIS is administered with a statin, the dosage instructions for the statin in children should be followed.

Paediatric Patients < 10 Years of Age

Children < 10 years: EZETIMIBE VIATRIS is not recommended for use in children below 10 years of age. There are limited data on safety and efficacy in children 6-10 years of age. See Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Clinical studies in paediatric (6 to 17 years of age) patients; Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Paediatric (6 to 17 years of age) patients, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Paediatric (6 to 17 years of age) patients. There is no available data on use of EZETIMIBE VIATRIS in children < 6 years (see Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations)). The use of EZETIMIBE VIATRIS in combination with statins has not been studied in children < 10 years of age.

Hepatic Insufficiency

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 4.3 CONTRAINDICATIONS, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and see Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations)).

4.3 CONTRAINDICATIONS

EZETIMIBE VIATRIS is contraindicated in patients with hypersensitivity to any component of this medication.

When EZETIMIBE VIATRIS is to be administered with a statin, please refer to the Product Information for that particular statin.

EZETIMIBE VIATRIS in combination with fenofibrate is contraindicated in patients with gall bladder disease.

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

The combination of EZETIMIBE VIATRIS 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 VIATRIS is to be administered with a statin or fenofibrate, please refer to the Product Information for that particular product.

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×the upper limit of normal [ULN]) have been observed. 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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with CHD 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×ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In a controlled clinical study in which over 9,000 patients with chronic kidney disease were randomised to receive ezetimibe 10 mg with simvastatin 20 mg daily (n=4,650) or placebo (n=4,620) (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (>3×ULN) was 0.7% for ezetimibe combined with simvastatin and 0.6% for placebo (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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×ULN was 4 of 1674 (0.2%) patients administered ezetimibe alone vs. 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered ezetimibe and a statin vs. 4 of 929 (0.4%) patients administered a statin 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 should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Ezetimibe 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 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 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, pain or tenderness with a serum CK ≥10 times ULN with evidence of renal injury, ≥5×ULN and <10×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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In a clinical trial in which over 9,000 patients with chronic kidney disease were randomised to receive ezetimibe 10 mg combined with simvastatin 20 mg daily (n=4,650) or placebo (n=4,620) (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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Fibrates

The co-administration of ezetimibe with fibrates, other than fenofibrate, has not been studied and is therefore not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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 Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), coadministration of ezetimibe and fenofibrate is not recommended in patients with pre-existing gallbladder disease (see Section 4.3 CONTRAINDICATIONS).

Ciclosporin

Caution should be exercised when initiating ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving EZETIMIBE VIATRIS and ciclosporin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Anticoagulants

If EZETIMIBE VIATRIS is added to warfarin, another coumarin anticoagulant or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in Hepatic Impairment

Due to unknown effects of the increased exposure of ezetimibe in patients with moderate to severe hepatic insufficiency, EZETIMIBE VIATRIS is not recommended in these patients (see Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations)).

Use in Renal Impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Use in patients with renal impairment/chronic kidney disease and Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations), Renal insufficiency.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Use in the elderly and Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients (Special Populations), Geriatric patients.

Paediatric Use

Paediatric Patients 10 to 17 Years of Age

The use of EZETIMIBE VIATRIS 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 PHARMACODYNAMIC PROPERTIES, 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 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION; Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS); and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Clinical studies in paediatric (6 to 17 years of age) patients). Adolescent females should be counselled on appropriate contraceptive methods while on co- administered EZETIMIBE VIATRIS and simvastatin therapy (see Section

4.3 CONTRAINDICATIONS; Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy).

The safety and efficacy of EZETIMIBE VIATRIS 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 VIATRIS in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

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

Paediatric Patients < 10 Years of Age

EZETIMIBE VIATRIS is not recommended in children < 10 years of age.

Safety and effectiveness of ezetimibe in patients 6 to 10 years of age with heterozygous familial or non-familial hypercholesterolaemia have been evaluated in a 12-week controlled clinical trial. Children treated with ezetimibe had an adverse experience profile similar to that of adult patients treated with ezetimibe. In this study, there was generally no detectable effect on growth or sexual maturation in either boys or girls. However, the effects of ezetimibe for a treatment period greater than 12 weeks on growth, sexual maturation, intellectual and psychosocial development have not been studied. The use of EZETIMIBE VIATRIS in combination with statins has not been studied in children < 10 years of age. EZETIMIBE VIATRIS has not been studied in patients younger than 6 years of age (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION; Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS); and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Clinical studies in paediatric (6 to 17 years of age) patients).

Effects on Laboratory Tests

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Laboratory values.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs 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: The effect of ciclosporin on ezetimibe was studied in eight post-renal transplant patients with creatinine clearance of >50 mL/min who were 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 group of historical healthy volunteers (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 dose 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 4.3 CONTRAINDICATIONS and see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Anticoagulants: Concurrent administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability and prothrombin time in a study of twelve healthy adult males administered a single dose of warfarin. 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Ezetimibe had no effects on fertility in male and female rats at doses up to 1000 mg/kg/day by oral gavage, corresponding to exposures of approximately 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively.

Use in Pregnancy

[Pregnancy Category B3]

No clinical data on exposed pregnancies are available. Ezetimibe crossed the placenta in rats and rabbits. There was no evidence of foetal abnormalities in rats dosed with up to 1000 mg/kg/day of ezetimibe by oral gavage during organogenesis, corresponding to exposures of about 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively, based on AUC. There was an increase in the incidence of extra thoracic ribs in rabbits at doses of 250 to 1000 mg/kg/day, corresponding to exposures of 0.5 to 1 times and 100 to 150 times the adult human exposure for ezetimibe and total ezetimibe, respectively. The relevance of this finding to humans is not known. EZETIMIBE VIATRIS should be used in pregnancy only if the potential benefit exceeds the potential risk. When EZETIMIBE VIATRIS is to be administered with a statin, please refer to the Product Information for that particular statin.

Ezetimibe in combination with statins in rats and rabbits resulted in higher exposures to ezetimibe and/or statins than either drug administered alone. Skeletal malfunctions (hemivertebrae in rats and shortened /filamentous tail associated with fused and reduced number of caudal vertebrae in rabbits) and other less severe foetal abnormalities were observed in rats and rabbits dosed with ezetimibe/statin combinations during organogenesis. HMG-CoA reductase inhibitors (statins) are contraindicated during pregnancy, therefore, ezetimibe in combination with statins should not be used in pregnancy (see Section 4.3 CONTRAINDICATIONS).

Embryofoetal studies in rats showed no adverse foetal effects of oral ezetimibe/fenofibrate doses corresponding to 5 times (total ezetimibe) and 38 times (fenofibric acid) the anticipated human plasma exposure at the maximum recommended doses. In similar studies in rabbits, a No Effect Level for embryotoxicity was established at ca. 90 times (total ezetimibe) and 32 times (fenofibric acid) anticipated human exposure levels.

Use in Lactation

Studies in rats have shown that ezetimibe is excreted in milk. Ezetimibe had no effects on pup development in rats treated with up to 1000 mg/kg/day of ezetimibe during late pregnancy and lactation. Drug exposures (based on AUC) in pups were approximately 1.5% and 50% of maternal exposures for ezetimibe and total ezetimibe respectively. It is not known whether ezetimibe is excreted into human breast milk. EZETIMIBE VIATRIS 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 may affect some patients' ability to drive or operate machinery. Individual responses to ezetimibe may vary (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (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 gamma-glutamyltransferase increased; liver function test abnormal

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon cough

Gastrointestinal Disorders:

Common abdominal pain; diarrhoea; flatulence

Uncommon dyspepsia; gastro-oesophageal reflux disease

Musculoskeletal and Connective Tissue Disorders:

Uncommon 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

Gastrointestinal Disorders:

Uncommon dry mouth; gastritis

Skin and Subcutaneous Tissue Disorders:

Uncommon pruritus

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 PHARMACODYNAMIC PROPERTIES, 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 Coronary Heart Disease

In the IMPROVE-IT study (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials), 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, pain or tenderness with a serum CK ≥10 times ULN with evidence of renal injury, ≥5×ULN and <10×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×ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 PHARMACODYNAMIC PROPERTIES, Clinical trials, Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)), involving over 9,000 patients treated with a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg daily (n=4,650) or placebo (n=4,620), 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 (>3×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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 (6 to 17 Years of Age) Patients

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 (≥3×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 (≥10×ULN). No cases of myopathy were reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, (Paediatric (6 to 17 years of age) patients; Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Clinical studies in paediatric (6 to 17 years of age) 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION; Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE; and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Clinical studies in paediatric (6 to 17 years of age) patients).

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

Paediatric Patients < 10 Years of Age

In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n=138), the safety and tolerability profile of the group treated with ezetimibe was similar to that of adult patients treated with ezetimibe. Elevations of ALT and/or AST (≥3×ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥10×ULN). No cases of myopathy were observed. The duration of this study was 12 weeks and safety data from this study is therefore limited (see Section 4.4 SPECIAL WARNINGS AND

PRECAUTIONS FOR USE, (Paediatric (6 to 17 years of age) patients; Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Clinical studies in paediatric (6 to 17 years of age) patients).

EZETIMIBE VIATRIS is not recommended in children < 10 years of age.

Laboratory Values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3×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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clinically important elevations of CPK (≥10×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

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

Hypersensitivity reactions, including anaphylaxis, angioedema, rash and urticaria; 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; arthralgia; myalgia; increased CPK; elevations of liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; dizziness; paraesthesia; depression; cholelithiasis; cholecystitis; drug-induced liver injury; constipation; asthenia and, very rarely myopathy/rhabdomyolysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/safety/reporting-problems.

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 hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdosage 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

EZETIMIBE VIATRIS (ezetimibe) is in a class of lipid-modifying compounds that inhibit the intestinal absorption of cholesterol and related plant sterols.

Ezetimibe has a mechanism of action that differs from other classes of cholesterol reducing compounds (eg statins, bile acid sequestrants [resins], fibric acid derivatives, and plant sterols).

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 therefore 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 [14C]-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.

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	Simvastatin Study	Pravastatin Study	Lovastatin Study
	Abs[a] (Pct[b])	Abs[a] (Pct[b])	Abs[a] (Pct[b])	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	Apo B	TG	HDL-C
	Abs[a] (Pct[b])	Abs[c] (Pct[b])	Abs[d] (Pct[e])	Abs[a] (Pct[b])
Ezetimibe + 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%)
Ezetimibe + 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%)
Ezetimibe + 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%)
Ezetimibe + 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)

	N	Total-C Abs[b] (Pct[c])	LDL-C Abs[b] (Pct[c])	Apo B Abs[d] (Pct[c])	TG Abs[e] (Pct[f])	HDL-C 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 Section 4.3 CONTRAINDICATIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 (6 to 17 Years of Age) Patients

Paediatric Patients 10 to 17 Years of Age

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 coadministered 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 6a. 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 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.

Paediatric Patients < 10 Years of Age

In a multicentre, double-blind, controlled study, 138 patients [59 boys (51 Tanner stage I and 6 Tanner stage II) and 79 girls (52 Tanner stage I, 22 Tanner stage II and 1 Tanner stage III)], 6 to 10 years of age (mean age 8.3 years) with heterozygous familial or non-familial hypercholesterolaemia were randomised to either ezetimibe 10 mg or placebo for 12 weeks. Inclusion in the study required 1) a baseline LDL-C > 4.1 and < 10.4 mmol/L (>159 and < 400 mg/dL) and 2) a medical history and clinical presentation consistent with HeFH.

At week 12, ezetimibe significantly reduced total-C, LDL-C, Apo-B and non-HDL-C compared to placebo. Results for the two treatment groups were similar for TG and HDL-C.

Table 7 Response to ezetimibe in Paediatric Patients with Heterozygous Familial Hypercholesterolaemia

(Mean Absolute and Percent Change from Untreated Baseline[a])							
Treatment (Daily Dose)	**N**	**Total-C Abs[c] (Pct)[d]**	**LDL-C Abs (Pct)**	**Apo B Abs (Pct)**	**HDL-C Abs (Pct)**	**TG[b] Abs (Pct)**	**Non-HDL-C Abs (Pct)**
Week12							
Ezetimibe	**85**	**-1.54 (-21)**	**-1.56 (-28)**	**-0.31 (-22)**	**+0.03 (+2)**	**-0.03 (-4)**	**-1.57 (-26)**
Placebo	**42**	**0.13 (0)**	**-0.07 (-1)**	**-0.01 (-1)**	**+0.02 (+1)**	**+0.04 (+4)**	**0.11 (0)**

a Baseline – on no lipid-lowering drug
b For triglycerides, median absolute and geometric median % change from baseline
c Absolute change from baseline expressed as mmol/L for all parameters except Apo B, which is in g/L
d Mean percent change from baseline

Ezetimibe has not been studied in patients younger than 6 years of age.

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 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 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%)
Sub-group 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 Cardiovascular Disease

Ezetimibe in combination with simvastatin has been shown in the IMPROVE-IT trial (details below) to reduce the major cardiovascular events of non-fatal myocardial infarction and stroke in patients with coronary heart disease and a history of Acute Coronary Syndrome. Total mortality, cardiovascular mortality and rates of unstable angina requiring hospitalisation and all coronary revascularisation were unchanged. There was a small increase in the rate of haemorrhagic stroke that was not statistically significant. The incremental benefit is expected to be similar with co-administration of other statins shown to be effective in reducing the risk of cardiovascular events but this has not been demonstrated in studies similar to IMPROVE- IT.

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 ≤3.2 mmol/L (≤125 mg/dL) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤2.6 mmol/L (≤100 mg/dL) 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.

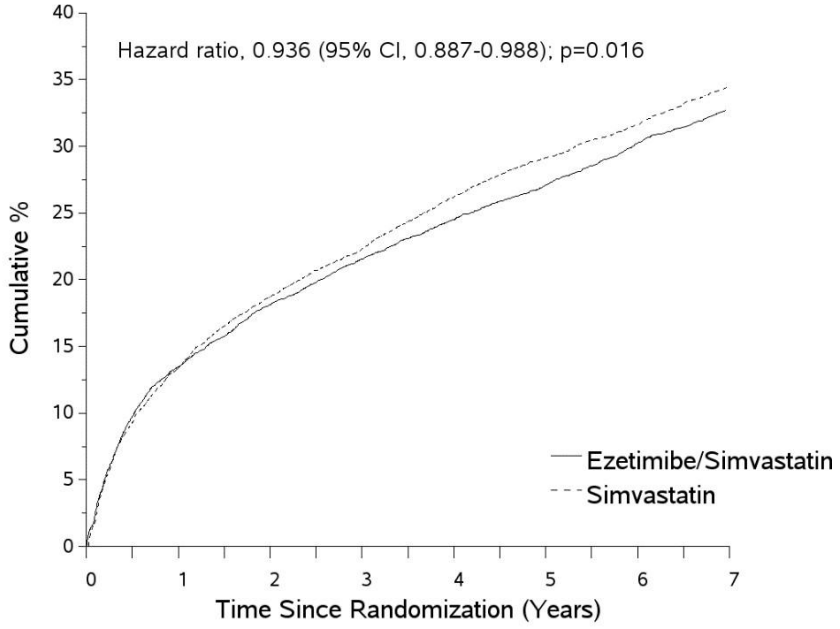
Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 2.1 mmol/L (80 mg/dL) for those on lipid-lowering therapy (n=6390) and 2.6 mmol/L (101 mg/dL) for those not on previous lipid-lowering therapy (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 1.4 mmol/L (53.2 mg/dL) for the ezetimibe/simvastatin group and 1.8 mmol/L (69.9 mg/dL) 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 provided incremental benefit in reducing the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with simvastatin alone (relative risk reduction of 6.4%, 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.) This incremental benefit is expected to be similar with coadministration of other statins shown to be effective in reducing the risk of cardiovascular events. Total mortality was unchanged in this high risk group (see Table 9).

There was an overall benefit for all strokes; however there was a small non-significant increase in haemorrhagic stroke in the ezetimibe-simvastatin group compared with simvastatin alone (see Table 9). The risk of haemorrhagic stroke for ezetimibe co-administered with higher potency statins in long-term outcome studies has not been evaluated.

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.

Figure 1 Effect of ezetimibe and simvastatin 40 mg or 80 mg on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke



Subjects at risk								
Ezetimibe/Simvastatin	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

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

Outcome	Ezetimibe/ Simvastatin 10/40 mg* (N=9067)		Simvastatin 40 mg† (N=9077)		Hazard Ratio (95% CI)	p-value
	N	K-M %‡	n	K-M %‡		
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 revascularisation 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 hospitalisation, any revascularisation, 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 hospitalisation	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618

Outcome	Ezetimibe/ Simvastatin 10/40 mg* (N=9067)		Simvastatin 40 mg† (N=9077)		Hazard Ratio (95% CI)	p-value
	N	K-M %‡	n	K-M %‡		
Coronary revascularisation 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§	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, 1.070)	0.782

* 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.

† 27% were uptitrated to simvastatin 80 mg.

‡ Kaplan-Meier estimate at 7 years.

§ 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 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) >3×ULN 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.

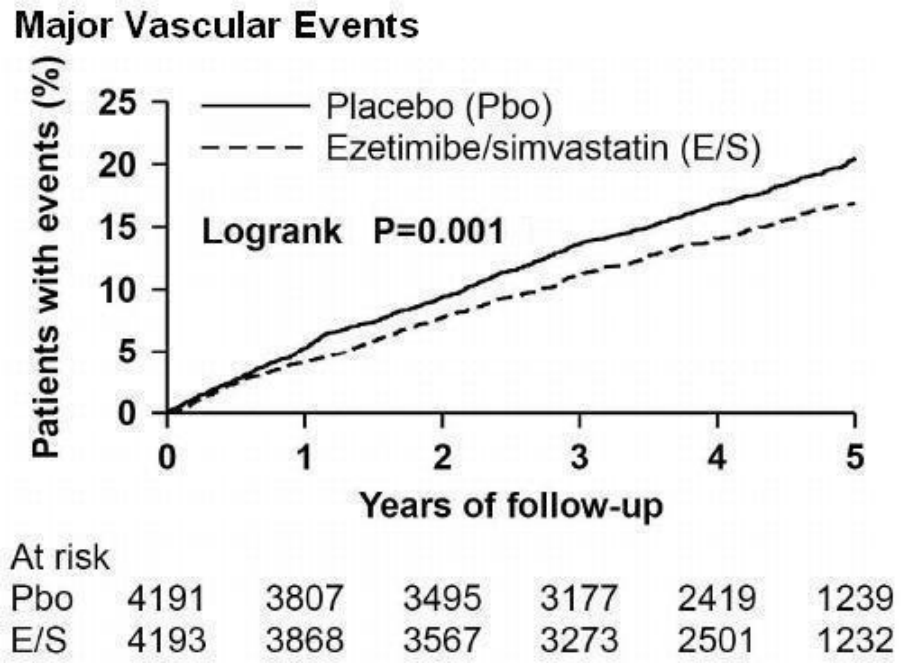
The primary endpoint analysis showed that ezetimibe combined with simvastatin significantly reduced the risk of MVE (749 patients with events in the placebo group vs. 639 in the ezetimibe combined with simvastatin

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 2). 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 2 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 10. 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 10 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

Outcome	Ezetimibe 10 mg combined with simvastatin 20 mg (N=4,650)	Placebo (N=4,620)	Risk Ratio (95% CI)	P-value
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 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.

Homozygous Sitosterolaemia (Phytosterolaemia)

A study was conducted to assess the efficacy of ezetimibe in the treatment of homozygous sitosterolaemia. In this multicentre, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolaemia were randomised 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.

Effect of Food on Oral Absorption

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 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 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.

Excretion

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.

Characteristics in Patients (Special Populations)

Paediatric Patients

The absorption and metabolism of ezetimibe are similar between children and adolescents (≥ 10 years) and adults. Limited PK data are available in children aged ≥6 to 10 years of age. Pharmacokinetic data in the paediatric population <6years 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). LDL-C reduction and safety profile is comparable between elderly and young subjects treated with ezetimibe. 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal Insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 mL/min/1.73 m^2), the mean AUC 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 is 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

Genotoxicity

Ezetimibe alone or in combination with a statin (simvastatin, lovastatin, pravastatin or atorvastatin) or fenofibrate did not cause gene mutation in bacteria or chromosomal damage in human peripheral lymphocytes or bone marrow cells in mice.

Carcinogenicity

Two year dietary studies with ezetimibe alone in mice and rats showed no evidence of carcinogenic potential. The highest ezetimibe dose (500 mg/kg/day) in mice corresponds to exposure levels of approximately 4 and ≥ 150 times the adult human exposure for ezetimibe and total ezetimibe, respectively, based on AUC. Exposures in rats at the highest dose (1500 mg/kg/day in males and 500mg/kg/day in females) correspond to approximately 2 and 14 times the adult human exposure for ezetimibe and total ezetimibe respectively.

There are no carcinogenicity studies with ezetimibe/statin or ezetimibe/fenofibrate combinations.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 10 mg tablet contains croscarmellose sodium, mannitol, butylated hydroxyanisole, magnesium stearate, povidone, sodium stearylfumarate and sodium lauryl sulfate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in either PVC/PCTFE (Aclar)/AL or PVC/PVdC/AL blister packs of 10 and 30 tablets.

HDPE bottles of 500 and 1000 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 396896 - EZETIMIBE VIATRIS ezetimibe 10 mg tablet blister pack

AUST R 468268 - EZETIMIBE VIATRIS ezetimibe 10 mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

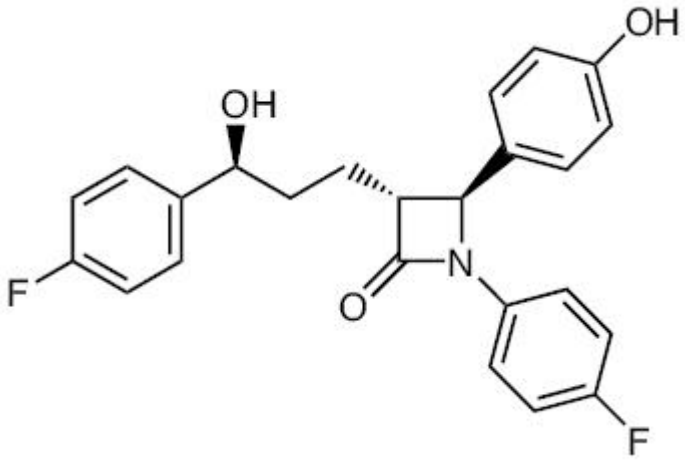
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

EZETIMIBE VIATRIS, 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

Chemical Structure



CAS Number

The CAS registry number is 163222-33-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

11/10/2023

10 DATE OF REVISION

02/11/2026

Summary Table of Changes

Section Changed	Summary of New Information
3	Update visual ID with debossing detail

EZETIMIBE VIATRIS_pi\Nov26/00