NEW ZEALAND DATA SHEET

EZEMIBE

1. Product Name

Ezemibe, 10 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 10 mg of ezetimibe.

Excipient(s) with known effect: lactose monohydrate.

Allergen Declaration:

Contains lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

White to off-white, capsule shaped bevelled edge tablet debossed with “M” on one side and “EE 1” on other side.

The tablet cannot be halved.

4. Clinical Particulars

4.1 Therapeutic indications

Primary hypercholesterolemia

Ezemibe, 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) hypercholesterolemia.

Homozygous familial hypercholesterolemia (HoFH)

Ezemibe, 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 Ezemibe.

The recommended dose of Ezemibe is 10 mg once daily, used alone or with a statin. Ezemibe can be administered at any time of the day, with or without food. Do not halve the tablet.

Special populations

Use in renal impairment/chronic kidney disease

Monotherapy

In patients with renal impairment, no dosage adjustment of Ezemibe is necessary (see section 5.2).

Combination therapy with simvastatin

In patients with mild renal impairment (estimated GFR ≥ 60 mL/min/1.73 m^2), no dosage adjustment of Ezemibe or simvastatin is necessary. In patients with chronic kidney disease (CKD) and estimated glomerular filtration rate < 60 mL/min/1.73 m^2, the dose of Ezemibe 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 sections 4.4, 5.1 and 5.2).

Use in the elderly

No dosage adjustment is required for elderly patients (see section 5.2).

Use in paediatric patients

Children and adolescents ≥ 10 years: No dosage adjustment is required (see section 5.2).

Children < 10 years: Treatment with Ezemibe 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 5.2).

Co-administration with bile acid sequestrants

Dosing of Ezemibe 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 (see section 6.1).

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

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

The combination of Ezemibe 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 Ezemibe 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 When Ezemibe 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).

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with CHD were randomized to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or

simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin (see section 4.8).

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

Skeletal muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering medicines. In clinical trials, the incidence of CPK > 10 x 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%) 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 Ezemibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Ezemibe and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level > 10 times the ULN indicates myopathy.

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

In a clinical trial in which over 9000 patients with chronic kidney disease were 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).

Hepatic insufficiency

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

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established; therefore, co-administration of Ezemibe 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 4.8 and 5.1), ezetimibe and fenofibrate coadministration must not be used in patients with pre-existing gallbladder disease (see Section 4.3).

Cyclosporine

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

Anticoagulants

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

Use in renal impairment

See Sections 4.2 and 5.2

Use in the elderly

See Sections 4.2 and 5.2

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). 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 hypercholesterolemia 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 studies in paediatric (6 to 17 years of age) patients). Adolescent females should be counselled on appropriate contraceptive methods while on co-administered ezetimibe and simvastatin therapy (see Section 4.3, 4.4 and 4.6).

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.

Paediatric Patients < 10 Years of Age

Ezetimibe 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 in combination with statins has not been studied in children < 10 years of age. Ezetimibe has not been studied in patients younger than 6 years of age (see Section 4.2, 4.8 and 5.1).

Effects on laboratory tests

See Section 4.8.

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.

Cholestyramine

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

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.

Cyclosporine

In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of cyclosporine, a single 10 mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n=17) 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 cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls.

In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of cyclosporine alone (see section 4.3 and 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 (>0.03 mg/kg/day) increased cholesterol in the gallbladder bile ~2- to 3-fold. Although the relevance of this preclinical finding to humans is unknown, co-administration of ezetimibe with fibrates is not recommended until use in patients is studied.

Statins

No clinically significant pharmacokinetic interactions have been 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 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

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. Ezemibe should be used in pregnancy only if the potential benefit exceeds the potential risk.

When Ezemibe is to be administered with a statin, please refer to the data sheet 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).

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.

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). However, caution should be exercised when prescribing to pregnant women.

Breast-feeding

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, therefore, Ezemibe should not be used in breast feeding mothers unless the potential benefit justifies the potential risk to the infant.

Fertility

No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats at doses up to 1000mg/kg/day by oral gavage, corresponding to exposures of approximately 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively (see section 5.3).

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).

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 is 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: Drug-related adverse experiences reported in ≥2% of patients taking ezetimibe co-administered with a statin.

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

The following common (≥ 1/100, < 1/10) or uncommon (≥ 1/1,000, < 1/100) medicine-related adverse experiences have been reported 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: paresthaesia.

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), 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), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n=9067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n=9077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe/simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain

with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 X ULN and <10 X ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. (see section 4.4.) Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalizations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

Patients with chronic kidney disease

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

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 hypercholesterolemia (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 Section 4.4 and 5.1).

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, 4.4 and 5.1).

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 co-administered ezetimibe was similar to that of adult patients co-administered 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 (≥ 10X 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 and 5.1).

Ezetimibe 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 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 hypercholesterolemia (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

Dizziness; paraesthesia.

Gastrointestinal disorders

Pancreatitis; constipation, nausea.

Skin and subcutaneous tissue disorders

Erythema multiforme.

Musculoskeletal and connective tissue disorders

Myalgia; arthralgia, increased CPK, myopathy/rhabdomyolysis (see section 4.4).

General disorders and administration site conditions

Asthenia.

Immune system disorders

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)

Hepatobiliary disorders

Hepatitis; cholelithiasis; cholecystitis, drug induced liver injury, elevations of liver transaminases.

Psychiatric disorders

Depression.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions 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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Ezetimibe is orally active and potent, with a unique mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols).

The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols. Ezetimibe 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.

Pharmacodynamic effects

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.

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.Clinical efficacy and safety

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 10mg 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])
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 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 (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 ezetimibeL 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)**
Week 12							
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 (40mg). Patients were randomised to one of three treatment groups, atorvastatin or simvastatin (80mg), ezetimibe 10mg administered with atorvastatin or simvastatin (40mg), or ezetimibe 10mg administered with atorvastatin or simvastatin (80mg). Results are shown in Table 8. Ezetimibe, administered with atorvastatin (40 or 80mg) or simvastatin (40 or 80mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80mg.

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 hospitalization and all coronary revascularization 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, randomized, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalization 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 randomized 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.

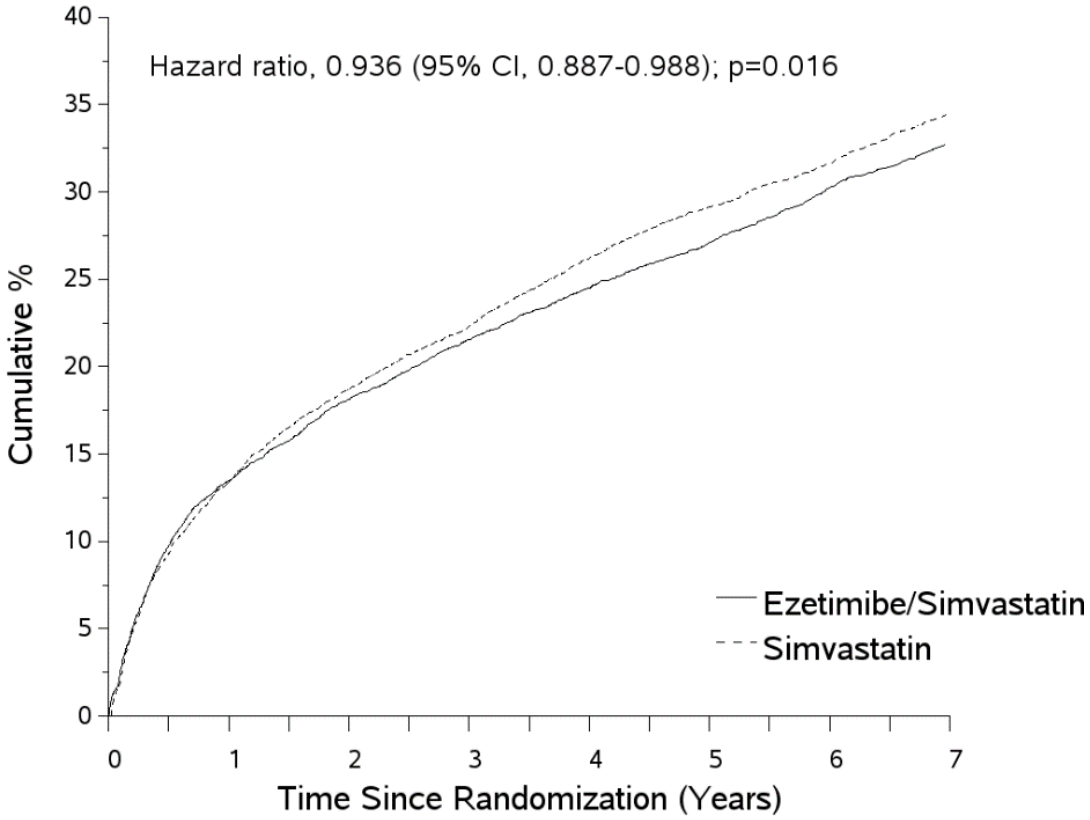
Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 2.1 mmol/L (80 mg/dL) for those on lipid-lowering therapy (n=6390) and 2.6 mmol/L (101 mg/dL) for those not on previous lipid-lowering therapy (n=11594). Prior to the hospitalization 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 hospitalization, or any coronary revascularization procedure occurring at least 30 days after randomized 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 Randomized 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 revascularization after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalization, any revascularization, non-fatal stroke	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalization	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularization after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-hemorrhagic stroke§	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 x 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.

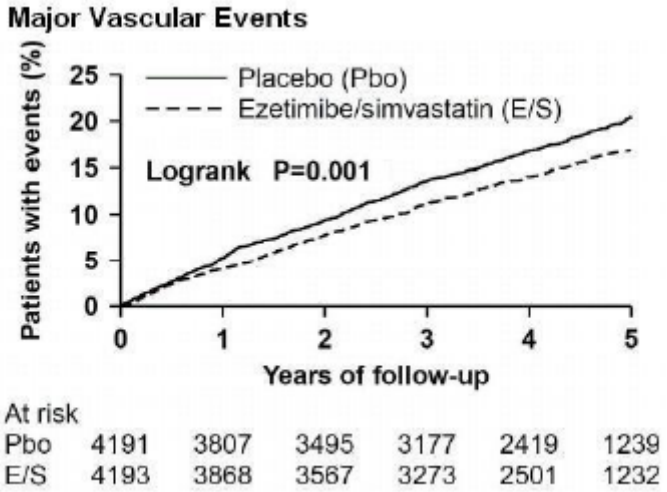
The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularisation procedure) in only those patients initially randomised to the ezetimibe combined with simvastatin (n=4,193) or 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
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 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.

Biotransformation

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major 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.

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). LDLC reduction and safety profile are 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).

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 cyclosporine) 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 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 mg/kg (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 has been 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

Two-year dietary studies with ezetimibe alone conducted 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..

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.

Reproduction

Ezetimibe did not affect the fertility of male or female rats at doses up to 1000mg/kg/day by oral gavage, corresponding to exposures of approximately 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively (see section 4.6).

Development

Ezetimibe showed 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.

Concomitant administration of ezetimibe and statins showed 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.

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.

6. Pharmaceutical Particulars

6.1 List of excipients

Ezemibe tablet also contains:

- lactose monohydrate
- croscarmellose sodium
- hypromellose
- crospovidone
- microcrystalline cellulose
- sodium lauryl sulphate
- magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

PVC/PVdC/Al-VMCH heat seal lacquer blister. Pack-sizes of 30 or 90 tablets.

PVC-ACLAR/Al-VMCH heat seal lacquer blister. Pack-sizes of 30 or 90 tablets.

HDPE Bottle with a PP Cap and absorbent cotton. Pack-sizes of 30 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

25 May 2011

10. Date of Revision of the Text

25 November 2024

Summary table of changes

Section	Summary of new information
4.8, 4.9, 5.2 & 6.3	Minor Editorial Changes
4.4	Addition of Drug induced liver injury with ezetimibe monotherapy
10	Revised Date of Revision of Text