SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ezetimibe MSN 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of ezetimibe.

Excipient(s) with known effect:
Each tablet contains 60 mg of lactose (as monohydrate).

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to off-white capsule shaped tablets (approximately 8 mm length and 4 mm width) debossed with “E10” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia
Ezetimibe MSN co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone.

Ezetimibe MSN monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

Prevention of Cardiovascular Events
Ezetimibe MSN is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin.

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetimibe MSN co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Homozygous Sitosterolaemia (Phytosterolaemia)
Ezetimibe MSN is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

4.2 Posology and method of administration

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

Route of administration is oral. The recommended dose is one Ezetimibe MSN 10 mg tablet daily. Ezetimibe MSN can be administered at any time of the day, with or without food.

When Ezetimibe MSN is added to a statin, either the indicated usual initial dose of that particular statin or the already established higher statin dose should be continued. In this setting, the dosage instructions for that particular statin should be consulted.

Use in Patients with Coronary Heart Disease and ACS Event History
For incremental cardiovascular event reduction in patients with coronary heart disease and ACS event history, Ezetimibe MSN 10 mg may be administered with a statin with proven cardiovascular benefit.

Co-administration with bile acid sequestrants
Dosing of Ezetimibe MSN should occur either $\underline{\geq}$ 2 hours before or $\underline{\geq}$ 4 hours after administration of a bile acid sequestrant.

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

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

Children and adolescents ≥ 6: The safety and efficacy of ezetimibe in children aged 6 to 17 years has not been established. Current available data are described in sections 4.4, 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

When ezetimibe is administered with a statin, the dosage instructions for the statin in children should be consulted.

Children <6 years: The safety and efficacy of Ezetimibe in children aged < 6 years has not been established. No data are available.

Hepatic impairment
No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Treatment with Ezetimibe MSN is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction. (see sections 4.4 and 5.2.).

Renal impairment
No dosage adjustment is required for renally impaired patients (see section 5.2).

Method of administration
This medicinal product is for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

When ezetimibe is co-administered with a statin, please refer to the SPC for that particular medicinal product.

Therapy with ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation.

Ezetimibe co-administered 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 is co-administered with a statin, please refer to the SPC for that particular medicinal product.

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

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n = 9,067) or simvastatin 40 mg daily (n = 9,077). 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 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 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 post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of Ezetimibe MSN to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level >10 times the ULN, ezetimibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. 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 (see section 4.8).

In IMPROVE-IT, 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n=9,067) or simvastatin 40 mg daily (n=9,077). During a median follow-up of 6.0 years, the incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and < 10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 times ULN and < 10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10,000 IU/L without evidence of renal injury (see section 4.8).

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).

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

Paediatric population
Efficacy and safety of ezetimibe in patients 6 to10 years of age with heterozygous familial or non-familial hypercholesterolaemia have been evaluated in a 12-week placebo-controlled clinical trial.

Effects of ezetimibe for treatment periods > 12 weeks have not been studied in this age group (see sections 4.2, 4.8, 5.1 and 5.2).

Ezetimibe has not been studied in patients younger than 6 years of age (see sections 4.2 and 4.8).

Efficacy and safety 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 (Tanner Stage II or above) and in girls who were at least one year post-menarche.

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 and sexual maturation have not been studied (see sections 4.2 and 4.8)

The safety and efficacy of ezetimibe co-administered with doses simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age.

The safety and efficacy of ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age (see sections 4.2 and 4.8).

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.

Fibrates
The safety and efficacy of ezetimibe administered with fibrates have not been established.

If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

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

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

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug 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.

In clinical interaction studies, 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 area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates
In patients receiving fenofibrate and ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8).

If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).

Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively).

Co-administration of ezetimibe with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile but not in all species (see section 5.3). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

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

Ciclosporin
In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medications demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ezetimibe and ciclosporin (see section 4.4).

Anticoagulants
Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation (see section 4.3), please refer to the SPC for that particular statin.

Pregnancy:
ezetimibe should be given to pregnant women only if clearly necessary. No clinical data are available on the use of ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development (see section 5.3).

Lactation
Ezetimibe should not be used during lactation. Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated list of adverse reactions (clinical studies and post-marketing experience)
In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2,396 patients, with a statin in 11,308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.

Ezetimibe administered alone or co-administered with a statin:

The following adverse reactions were observed in patients treated with ezetimibe (n = 2,396) and at a greater incidence than placebo (n = 1,159) or in patients treated with ezetimibe co-administered with a statin (n = 11,308) and at a greater incidence than statin administered alone (n = 9,361). Post-marketing Adverse reactions were derived from reports containing ezetimibe either administered alone or with a statin. Adverse reactions observed in clinical studies of ezetimibe (as a monotherapy or co-administered with a statin) or ezetimibe reported from post-marketing use either administered alone or with a statin are listed in Table 1. These reactions are presented by system organ class and by frequency.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 1
Adverse Reactions

System organ class Frequency	Adverse reaction
Blood and lymphatic system disorders	
Not known	thrombocytopaenia
Immune system disorders	
Not known	hypersensitivity; including rash; urticaria; anaphylaxis and angio-oedema

Metabolism and nutrition disorders	
Uncommon	decreased appetite
Psychiatric disorders	
Not known	depression
Nervous system disorders	
Common	headache
Uncommon	paraesthesia
Not known	dizziness
Vascular disorders	
Uncommon	hot flush; hypertension
Respiratory, thoracic and mediastinal disorders	
Uncommon	cough
Not known	dyspnoea
Gastrointestinal disorders	
Common	abdominal pain; diarrhoea; flatulence
Uncommon	dyspepsia; gastrooesophageal reflux disease; nausea; dry mouth; gastritis
Not known	pancreatitis; constipation
Hepatobiliary disorders	
Not known	hepatitis; cholelithiasis; cholecystitis
Skin and subcutaneous tissue disorders	
Uncommon	pruritus; rash; urticaria
Not known	erythema multiforme
Musculoskeletal and connective tissue disorders	
Common	myalgia
Uncommon	arthralgia; muscle spasms; neck pain; back pain; muscular weakness; pain in extremity
Not known	myopathy/rhabdomyolysis (see section 4.4)
General disorders and administration site conditions	
Common	fatigue
Uncommon	chest pain; pain; asthenia; oedema peripheral
Investigations	
Common	ALT and/or AST increased
Uncommon	blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal

Ezetimibe co-administered with fenofibrate:
Gastrointestinal disorders: abdominal pain (common)

In a multicentre, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidaemia, 625 patients were treated for up to 12 weeks and 576 patients for up to 1 year. In this study, 172 patients treated with ezetimibe and fenofibrate completed 12 weeks of therapy, and 230 patients treated with ezetimibe and fenofibrate (including 109 who received Ezetimibe MSN alone for the first 12 weeks) completed 1 year of therapy. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95 % CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4.5 % (1.9, 8.8) and 2.7 % (1.2, 5.4) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6 % (0.0, 3.1) and 1.7 % (0.6, 4.0) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively (see sections 4.4 and 4.5).

Paediatric (6 to 17 years of age) Patients

In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and/or AST (≥ 3 X 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 X ULN). No cases of myopathy were reported.

In a separate study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥ 3 X 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 X ULN). No cases of myopathy were reported.

These trials were not suited for comparison of rare adverse drug reactions.

Patients with Coronary Heart Disease and ACS Event History
In the IMPROVE-IT study (see section 5.1), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n = 9,067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n = 9,077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe/simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and < 10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 times ULN and < 10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥ 3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin (see section 4.4). Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalisations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

Patients with Chronic Kidney Disease
In the Study of Heart and Renal Protection (SHARP) (see section 5.1), involving over 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 (> 3X ULN) occurred in 0.7% of patients treated with ezetimibe combined with simvastatin compared with 0.6% of patients treated with placebo (see section 4.4). In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for ezetimibe combined with simvastatin, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

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

In clinical trials, CPK >10 X ULN was reported for 4 of 1,674 (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. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone). (see section 4.4.).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. In animals, no toxicity was observed after single oral doses of 5,000 mg/kg of ezetimibe in rats and mice and 3,000 mg/kg in dogs.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 has a 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; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54 %, compared with placebo.

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 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.
Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

Clinical efficacy and safety
In controlled clinical studies, ezetimibe either as monotherapy or co-administered with a statin significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C),

apolipoprotein B (Apo B), and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

Primary Hypercholesterolaemia
In a 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 (2.6 to 4.1 mmol/l [100 to 160 mg/dL], 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 %), significantly more patients randomised to ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72 % and 19 %, respectively. The corresponding LDL-C reductions were significantly different (25 % and 4 % for ezetimibe versus placebo, respectively). In addition, ezetimibe, added to on-going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10 % or 0 % from baseline, respectively.

In two, double-blind, randomised placebo-controlled, 12-week studies in 1,719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C (13 %), LDL-C (19 %), Apo B (14 %), and TG (8 %) and increased HDL-C (3 %) compared to placebo. In addition, ezetimibe had no effect on the plasma concentrations of fat-soluble vitamins A, D, and E, no effect on prothrombin time, and, like other lipid lowering agents, did not impair adrenocortical steroid hormone production.

In a multicenter, double-blind, controlled clinical study (ENHANCE), 720 patients with heterozygous familial hypercholesterolaemia were randomised to receive ezetimibe 10 mg in combination with simvastatin 80 mg (n = 357) or simvastatin 80 mg (n = 363) for 2 years. The primary objective of the study was to investigate the effect of the ezetimibe/simvastatin combination therapy on carotid artery intima-media thickness (IMT) compared to simvastatin monotherapy. The impact of this surrogate marker on cardiovascular morbidity and mortality is still not demonstrated.

The primary endpoint, the change in the mean IMT of all six carotid segments, did not differ significantly (p= 0.29) between the two treatment groups as measured by B-mode ultrasound. With ezetimibe 10 mg in combination with simvastatin 80 mg or simvastatin 80 mg alone, intima-medial thickening increased by 0.0111 mm and 0.0058 mm, respectively, over the study's 2 year duration (baseline mean carotid IMT 0.68 mm and 0.69 mm respectively.

Ezetimibe 10 mg in combination with simvastatin 80 mg lowered LDL-C, total-C, Apo B, and TG significantly more than simvastatin 80 mg. The percent increase in HDL-C was similar for the two treatment groups. The adverse reactions reported for ezetimibe 10 mg in combination with simvastatin 80 mg were consistent with its known safety profile.

Paediatric population
In a multicentre, double-blind, controlled study, 138 patients (59 boys and 79 girls), 6 to 10 years of age (mean age 8.3 years) with heterozygous familial or non-familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 3.74 and 9.92 mmol/L were randomised to either ezetimibe 10 mg or placebo for 12 weeks.

At week 12, ezetimibe significantly reduced total-C (-21% vs. 0%), LDL-C (-28% vs. -1%), Apo-B (-22% vs. -1%), and non-HDL-C (-26% vs. 0%) compared to placebo. Results for the two treatment groups were similar for TG and HDL-C (-6% vs. +8%, and +2% vs. +1%, respectively).

In a multicentre, double-blind, controlled study, 142 boys (Tanner Stage II and above) and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years) with heterozygous familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 4.1 and 10.4 mmol/L were randomised to either ezetimibe 10 mg co-administered with simvastatin (10, 20 or 40 mg) or simvastatin (10, 20 or 40 mg) alone for 6 weeks, co-administered ezetimibe and 40 mg simvastatin 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.

At Week 6, ezetimibe co-administered with simvastatin (all doses) significantly reduced total-C (38% vs 26%), LDL-C (49% vs 34%), Apo B (39% vs 27%), and non-HDL-C (47% vs 33%) compared to simvastatin (all doses) alone. Results for the two treatment groups were similar for TG and HDL-C (-17% vs -12% and +7% vs +6%, respectively). At Week 33, results were consistent with those at Week 6 and significantly more patients receiving ezetimibe and 40 mg simvastatin (62%) attained the NCEP AAP ideal goal (< 2.8 mmol/L [110 mg/dL]) for LDL-C compared to those receiving 40 mg simvastatin (25%). At Week 53, the end of the open-label extension, the effects on lipid parameters were maintained.

The safety and efficacy of ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. The safety and efficacy of ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age. 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.

Prevention of Cardiovascular Events
The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicenter, randomised, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalisation for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤ 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 = 9,067) or simvastatin 40 mg (n = 9,077) 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 = 6,390) and 101 mg/dL 2.6 mmol/L (101 mg/dL) for those not on previous lipid lowering therapy (n = 11,594). 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 2,572 of 9,067 patients (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2,742 of 9,077 patients (7-year KM rate 34.67%) in the simvastatin alone group. (See Figure 1 and Table 2.) This incremental benefit is expected to be similar with co-administration 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 2).

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 2). 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/Simvastatin on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

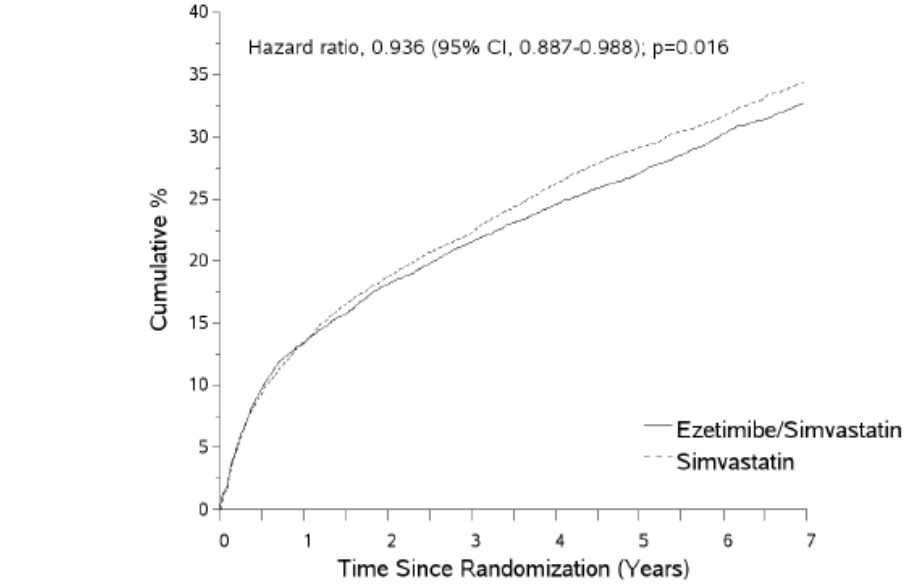


Table 2
Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE-IT

Outcome	**Ezetimibe/Simvastatin 10/40 mg[a] (n=9,067)**		**Simvastatin 40 mg[b] (n=9,077)**		**Hazard Ratio (95% CI)**	**p-value**
	n	**K-M %[c]**	**n**	**K-M %[c]**		
Primary Composite Efficacy Endpoint						
(CV death, Major coronary Events and non-fatal stroke)	2,572	32.72%	2,742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, non-fatal MI, urgent coronary revascularisation after 30 days	1,322	17.52%	1,448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3,089	38.65%	3,246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalisation, any revascularisation, non-fatal stroke	2,716	34.49%	2,869	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
Coronary revascularisation after 30 days	1,690	21.84%	1,793	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%	1,118	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-haemorrhagic stroke [d]	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Haemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1,215	15.36%	1,231	15.28%	0.989 (0.914, 1.070)	0.782

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

Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)
The Study of Heart and Renal Protection (SHARP) was a multi-national, randomised, placebo controlled, double-blind study conducted in 9,438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. A total of 4,650 patients were allocated to a fixed dose combination of ezetimibe 10 mg 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 and 63% were male, 72% Caucasian, 23% diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 108 mg/dL. After one year, including patients no longer taking study medication, LDL-C was reduced 26 % relative to placebo by simvastatin 20 mg alone and 38% by ezetimibe 10 mg combined with simvastatin 20 mg.

The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as non-fatal 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 analyzed 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 major vascular events (749 patients with events in the placebo group vs. 639 in the ezetimibe combined with simvastatin group) with a relative risk reduction of 16% (p = 0.001).

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

The individual components of MVE in all randomised patients are presented in Table 3. Ezetimibe combined with simvastatin significantly reduced the risk of stroke and any revascularisation, with non significant numerical differences favouring ezetimibe combined with simvastatin for non-fatal MI and cardiac death.

Table 3
Major Vascular Events by Treatment Group in all randomised patients in SHARP[a]

Outcome	**Ezetimibe MSN 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
Non-fatal 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 MSN combined with simvastatin or placebo either at baseline or year 1
[b] MAE; defined as the composite of non-fatal myocardial infarction, coronary death, non-haemorrhagic stroke, or any revascularisation

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

Homozygous Familial Hypercholesterolaemia (HoFH)
A double-blind, randomised, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, who were receiving atorvastatin or simvastatin (40 mg) with or without concomitant LDL apheresis. Ezetimibe co-administered with atorvastatin (40 or 80 mg) or simvastatin (40 or 80 mg), significantly reduced LDL-C by 15 % compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg.

Homozygous Sitosterolaemia (Phytosterolaemia)
In a double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolaemia were randomised to receive Ezetimibe MSN 10 mg (n=30) or placebo (n=7). Some patients were receiving other treatments (e.g., statins, resins). Ezetimibe MSN significantly lowered the two major plant sterols, sitosterol and campesterol, by 21 % and 24 % from baseline, respectively. The effects of decreasing sitosterol on morbidity and mortality in this population are not known.

Aortic Stenosis
The Simvastatin and Ezetimibe for the Treatment of Aortic Stenosis (SEAS) study was a multi-center, double-blind, placebo-controlled study with a median duration of 4.4 years conducted in 1,873 patients with asymptomatic aortic stenosis (AS), documented by Doppler-measured aortic peak flow velocity within the range of 2.5 to 4.0 m/s. Only patients who were considered not to require statin treatment for purposes of reducing atherosclerotic cardiovascular disease risk were enrolled. Patients were randomised 1:1 to receive placebo or co-administered ezetimibe 10 mg and simvastatin 40 mg daily.

The primary endpoint was the composite of major cardiovascular events (MCE) consisting of cardiovascular death, aortic valve replacement (AVR) surgery, congestive heart failure (CHF) as a result of progression of AS, non fatal myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), hospitalisation for unstable angina, and nonhemorrhagic stroke. The key secondary endpoints were composites of subsets of the primary endpoint event categories.

Compared to placebo, ezetimibe/simvastatin 10/40 mg did not significantly reduce the risk of MCE. The primary outcome occurred in 333 patients (35.3%) in the ezetimibe / simvastatin group and in 355 patients (38.2%) in the placebo group (hazard ratio in the ezetimibe / simvastatin group, 0.96; 95%

confidence interval, 0.83 to 1.12; p = 0.59). Aortic valve replacement was performed in 267 patients (28.3%) in the ezetimibe / simvastatin group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; p = 0.97). Fewer patients had ischemic cardiovascular events in the ezetimibe / simvastatin group (n=148) than in the placebo group (n=187) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; p = 0.02), mainly because of the smaller number of patients who underwent coronary artery bypass grafting.

Cancer occurred more frequently in the ezetimibe/simvastatin group (105 versus 70, p = 0.01). The clinical relevance of this observation is uncertain as in the bigger SHARP trial the total number of patients with any incident cancer (438 in the ezetimibe/ simvastatin versus 439 placebo group) did not differ. In addition, in the IMPROVE-IT trial the total number of patients with any new malignancy (853 in the ezetimibe/simvastatin group versus 863 in the simvastatin group) did not differ significantly and therefore the finding of SEAS trial could not be confirmed by SHARP or IMPROVE-IT.

5.2 Pharmacokinetic properties

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

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10-mg tablets. 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 drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

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

Special Populations:
Paediatric population
The pharmacokinetics of ezetimibe are similar between children ≥ 6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric 17 and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

Elderly
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 are comparable between elderly and young subjects treated with Ezetimibe MSN. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic impairment
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment ezetimibe is not recommended in these patients (see section 4.4).

Renal impairment
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 ml/min/1.73 m2), 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 (approximately 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.

5.3 Preclinical safety data

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥ 0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamics interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2000 times the AUC level for the active metabolites).
In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1,000 mg/kg/day. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)

Croscarmellose sodium (E468)
Sodium lauril sulfate
Cellulose, microcrystalline PH 102
Crospovidone type B (E1202)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years

After first opening of the bottle: 100 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque High Density Polyethylene (HDPE) bottles with a child resistant polypropylene (PP) screw cap and induction liner (made up of pulp, wax and aluminium) containing 100 tablets (1 bottle) or 300 tablets (3 bottles containing 100 tablets each), placed in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MSN Labs Europe Limited,
KW20A, Corradino Park
Paola PLA 3000, Malta

8. MARKETING AUTHORISATION NUMBER

MA1478/00501

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

17th December 2024

10. DATE OF REVISION OF THE TEXT

December 2024