SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ezetimibe MEVON 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of ezetimibe.

Excipient(s) with known effect:
Each tablet contains 39.01 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
The tablets are white and oblong tablets with 8.0 mm ± 0.2 mm length and 4.4 mm ± 0.2 mm width.

4. CLINICAL PARTICLULARS

4.1. Therapeutic indications

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

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetimibe MEVON co-administered with atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolaemia (Phytosterolaemia)
Ezetimibe MEVON is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels 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 MEVON.

The recommended dose is one Ezetimibe MEVON 10 mg tablet daily.
When Ezetimibe MEVON 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.

Co-administration with bile acid sequestrants

Dosing of Ezetimibe MEVON should occur either ≥ 2 hours before or ≥ 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 ≥ 10 years: No dosage adjustment is required.

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

Hepatic impairment
No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Treatment with Ezetimibe MEVON 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
Monotherapy
In patients with renal impairment, no dosage adjustment of ezetimibe is necessary (see section 5.2).

Combination therapy with simvastatin
In patients with mild renal impairment (estimated GFR ≥60 mL/min/1.73 m2), no dosage adjustment of ezetimibe or simvastatin is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73m^2, the dose of ezetimibe 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.

Method of administration
Route of administration is oral. Ezetimibe MEVON can be administered at any time of the day, with or without food.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
When Ezetimibe MEVON is co-administered with a statin, please refer to the SmPC for that particular medicinal product.

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

Ezetimibe MEVON 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 SmPC 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 MEVON is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin (see section 4.8.).

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

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

Skeletal Muscle

In 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 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 MEVON 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=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 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 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).

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

Patients with hepatic impairment

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

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 MEVON in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ezetimibe and ciclosporin. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with ciclosporin, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe (see section 4.5).

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

Excipient
Ezetimibe MEVON contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 MEVON, 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 MEVON 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 MEVON in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe MEVON 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 MEVON co-administered with a statin is contraindicated during pregnancy and lactation (see section 4.3), please refer to the SmPC for that particular statin.

Pregnancy
Ezetimibe MEVON 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 MEVON 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 2396 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 MEVON administered alone or co-administered with a statin:
The following adverse reactions were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159) or in patients treated with ezetimibe coadministered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361). Post marketing Adverse reactions were derived from reports containing ezetimibe either administered alone or with a statin.

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)

Ezetimibe monotherapy		
System organ class	**Adverse reactions**	**Frequency**
Metabolism and Nutrition Disorders	decreased appetite	Uncommon
Vascular Disorders	hot flush; hypertension	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	cough	Uncommon
Gastrointestinal Disorders	abdominal pain; diarrhoea; flatulence	Common
	dyspepsia; gastrooesophageal reflux disease; nausea	Uncommon
Musculoskeletal And Connective Tissue Disorders	arthralgia; muscle spasms; neck pain	Uncommon
General Disorders And Administration Site Condition	fatigue	Common
	chest pain, pain	Uncommon
Investigations	ALT and/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal	Uncommon
Additional adverse reactions with ezetimibe co-administered with a statin		
System organ class	**Adverse reactions**	**Frequency**
Nervous System Disorders	headache	Common
	paraesthesia	Uncommon
Gastrointestinal Disorders	dry mouth; gastritis	Uncommon
Skin And Subcutaneous Tissue Disorders	pruritus; rash; urticaria	Uncommon

Musculoskeletal And Connective Tissue Disorders	myalgia	Common
	back pain; muscular weakness; pain in extremity	Uncommon
General Disorders And Administration Site Condition	asthenia; oedema peripheral	Uncommon
Investigations	ALT and/or AST increased	Common
Post-marketing Experience (with or without a statin)		
System organ class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	thrombocytopaenia	Not known
Immune system disorders	hypersensitivity, including rash, urticaria, anaphylaxis and angiooedema	Not known
Psychiatric disorders	depression	Not known
Nervous system disorders	dizziness; paraesthesia	Not known
Respiratory, Thoracic and Mediastinal Disorders	dyspnoea	Not known
Gastrointestinal Disorders	pancreatitis; constipation	Not known
Hepatobiliary disorders	hepatitis; cholelithiasis; cholecystitis	Not known
Skin And Subcutaneous Tissue Disorders	erythema multiforme	Not known
Musculoskeletal And Connective Tissue Disorders	myalgia; myopathy/rhabdomyolysis (see section 4.4)	Not known
General Disorders And Administration Site Condition	asthenia	Not known

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 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).

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

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

Patients with Chronic Kidney Disease

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

Laboratory values:

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

In clinical trials, CPK >10 X ULN was reported for 4 of 1674 (0.2 %) patients administered ezetimibe alone vs 1 of 786 (0.1 %) patients administered placebo, and for 1 of 917 (0.1 %) patients co-administered ezetimibe and a statin vs 4 of 929 (0.4 %) patients administered a statin alone. 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 the Vigilance and Compliance Branch of the Health Products Regulation Group (HPRG) of the Health Sciences Authority (HSA).

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 5000 mg/kg of ezetimibe in rats and mice and 3000 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 PROPRIETIES

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 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 1719 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.

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

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

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

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 1). The risk of haemorrhagic stroke for ezetimibe coadministered 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.

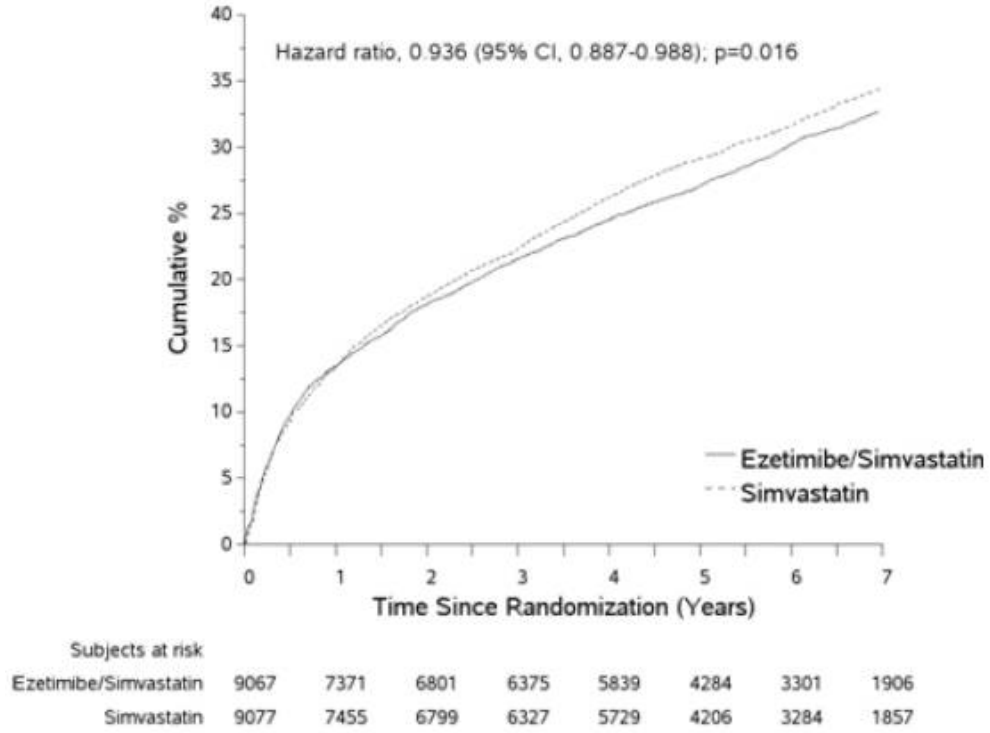

Figure 1: Effect of Ezetimibe/Simvastatin on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

Table 1: Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE-IT

Outcome	**Ezetimibe/Simvastatin 10/40 mg[a] (N=9067)**		**Simvastatin 40 mg[b] (N=9077)**		**Hazard Ratio (95% CI)**	**P-value**
	n	K-M % [c]	n	K-M % [c]		
Primary Composite Efficacy Endpoint						
(CV death, Major Coronary Events and non-fatal stroke)	2572	32.72 %	2742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, nonfatal MI, urgent coronary, revascularisation after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, nonfatal MI, unstable angina	2716	34.49%	2869	36.20%	0.945 (0.897,	0.035

requiring hospitalisation, any revascularisation, non-fatal stroke					0.996)	
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	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-hemorrhagic stroke d	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Hemorrhagic stroke	59	0.77 %	43	0.59 %	1.377 (0.930, 2.040)	0.110
Death from any cause	1215	15.36 %	1231	15.28 %	0.989 (0.914, 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 9438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. A total of 4650 patients were allocated to a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg and 4620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 and 63 % were male, 72 %

Caucasian, 23 % diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 ml/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 108 mg/dL. 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 nonfatal MI or cardiac death, stroke, or any revascularisation procedure) in only those patients initially randomised to the ezetimibe combined with simvastatin (n=4193) or placebo (n=4191) 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=4650) or placebo (n=4620) as well as the components of this composite.

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

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 2. 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 2: Major Vascular Events by Treatment Group in all randomised patients in SHARP[a]

Outcome	Ezetimibe 10 mg combined with simvastatin 20 mg (N=4650)	Placebo (N=4620)	Risk Ratio (95% IC)	P-value
Major Vascular Events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any 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 hemorrhagic 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 10 mg (n=30) or placebo (n=7). Some patients were receiving other treatments (e.g., statins, resins). Ezetimibe 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.

5.2. Pharmacokinetic proprieties

General pharmacokinetics

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

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10 mg tablets. Ezetimibe 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 entero hepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination

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

Special Populations

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

Older people
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. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic impairment
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, 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 pharmacodynamic 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 1000 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
Croscarmellose sodium
Sodium laurilsulfate
Cellulose, microcrystalline
Sodium stearyl fumarate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

Tablets are packed in PVC/PE/PVdC blister with Aluminium.

Ezetimibe MEVON 10 mg tablets is supplied in blister packs of 28 tablets.

6.6. Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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Solstice Business Center
Singapore 536209

8. DATE OF REVISION OF THE TEXT

Mar 2022