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Module 1.3.1	Summary of Product Characteristics	Replaces : 2016-09-06

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ezetimibe Apotex 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg Ezetimibe.

Excipient(s) with known effect:

Each tablet contains 86.5 mg of Lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, flat-face bevelled edge, capsule shaped tablet (3.967 mm x 7.938 mm). Engraved “APO” on one side and “EZ 10” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

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

Ezetimibe Apotex 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 Apotex 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 Apotex 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)

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Ezetimibe Apotex 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 Apotex.

The recommended dose is one Ezetimibe Apotex 10 mg tablet daily.

When Ezetimibe Apotex 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 Apotex 10 mg may be administered with a statin with proven cardiovascular benefit.

Co-administration with bile acid sequestrants

Dosing of 'Ezetimibe Apotex' should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

Older People

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 years: 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 Apotex 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.

Patients with hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (Child Pugh score 5 to 6). Treatment with 'Ezetimibe Apotex' 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.)

Patients with renal impairment

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

Method of administration

Route of administration is oral.

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

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

Ezetimibe Apotex 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 Apotex’ 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 tablets with a statin, consecutive transaminase elevations (≥ 3 X the upper limit of normal [ULN]) have been observed. When ‘Ezetimibe Apotex’ 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 randomized 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 tablets, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe tablets. 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 Apotex’, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with ‘Ezetimibe Apotex’ 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

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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 $\geq 10,000$ 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 randomized 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)

Patients with Hepatic Impairment

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

Paediatric population

Efficacy and safety of ezetimibe in patients 6 to 10 years of age with heterozygous familial or non-familial hypercholesterolemia 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 hypercholesterolemia 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 of simvastatin above 40mg 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 Apotex' 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 Apotex' in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving 'Ezetimibe Apotex' and ciclosporin (see section 4.5).

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Anticoagulants

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

Ezetimibe Apotex contains lactose

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 coadministration. 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 Apotex' to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates: In patients receiving fenofibrate and 'Ezetimibe Apotex', physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see section 4.4 and 4.8).

If cholelithiasis is suspected in a patient receiving 'Ezetimibe Apotex' 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 insufficiency who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to

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total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in 12 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 Apotex in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe Apotex 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 postmarketing 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 Apotex’ 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 Apotex 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).

Breast-feeding:

Ezetimibe Apotex 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, or 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:

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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 co-administered 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
Investigations	ALT and/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	cough	Uncommon
Gastrointestinal Common Disorders	abdominal pain; diarrhoea; flatulence	Common
	dyspepsia; gastrooesophageal reflux disease; nausea	Uncommon
Musculoskeletal and Connective Tissue Disorders	arthralgia; muscle spasms; neck pain	Uncommon
Metabolism and Nutrition Disorders	decreased appetite	Uncommon
Vascular Disorders	hot flush; hypertension	Uncommon
General Disorders and Administration Site Condition	fatigue	Common
	chest pain, pain	Uncommon
Additional adverse reactions with 'Ezetimibe' co-administered with a statin		
System organ class	Adverse reactions	Frequency
Investigations	ALT and/or AST increased	Common
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
Post-marketing Experience (with or without a statin)		
System organ class	Adverse reactions	Frequency
Blood and lymphatic system disorders	thrombocytopenia	Not known
Nervous system disorders:	dizziness; paraesthesia	Not known
Respiratory, thoracic and mediastinal disorders	dyspnoea	Not known

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Gastrointestinal disorders	pancreatitis; constipation	Not known
Skin and subcutaneous tissue disorders	erythema multiforme	Not known
Musculoskeletal and connective tissue disorder	myalgia; myopathy/rhabdomyolysis (see section 4.4)	Not known
General disorders and administration site conditions	asthenia	Not known
Immune system disorders	hypersensitivity, including rash, urticaria, anaphylaxis and angio-oedema	Not known
Hepatobiliary disorders	hepatitis; cholelithiasis; cholecystitis	Not known
Psychiatric disorders	depression	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 ($>3 \times \text{ULN}$, 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 population (6 to 17 years of age)

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 ($\geq 3 \times \text{ULN}$, 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 ($\geq 10 \times \text{ULN}$). 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 ($\geq 3 \times \text{ULN}$, 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 ($\geq 10 \times \text{ULN}$). 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 ($n=9067$; 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

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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 $\geq 10,000$ IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases ($\geq 3 \times$ 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 ($> 3 \times$ ULN) occurred in 0.7% of patients treated with ezetimibe combined with simvastatin compared with 0.6% of patients treated with placebo. In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for ezetimibe combined with simvastatin, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

Laboratory values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST $\geq 3 \times$ ULN, consecutive) was similar between ezetimibe (0.5%) and placebo (0.3%). In coadministration 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 $> 10 \times$ 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 the national reporting system listed in Appendix V.*

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

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

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 [¹⁴C]-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 ongoing 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

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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 the 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 hypercholesterolemia were randomized 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 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.

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

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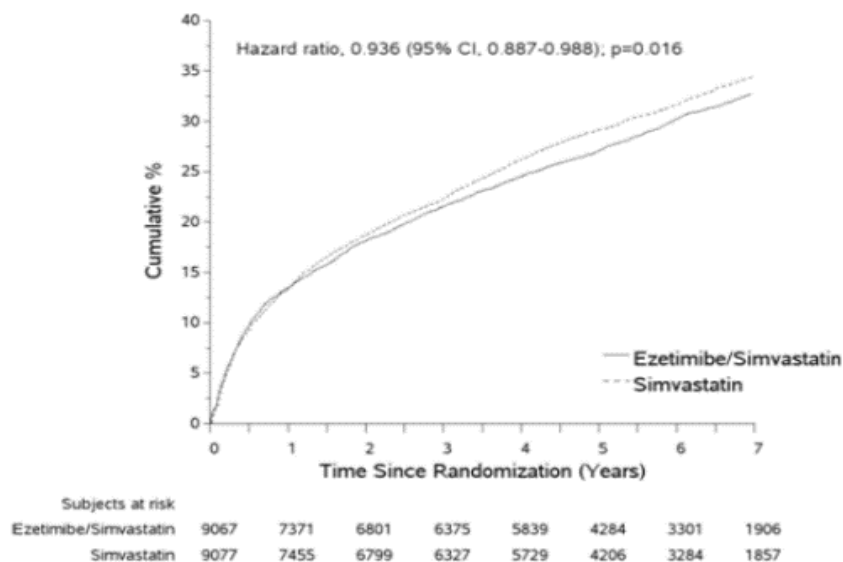


Table 1
Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE-IT

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 nonfatal 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 requiring hospitalisation,	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035

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any revascularisation, non-fatal stroke						
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.

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 coadministered 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.

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

The Study of Heart and Renal Protection (SHARP) was a multi-national, randomized, 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 m². 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 revascularization procedure) in only those patients initially randomized to the ezetimibe combined with simvastatin (n=4193) or placebo (n=4191) groups. Secondary analyses included the same composite analyzed for the full cohort randomized (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 randomized patients are presented in Table 1. Ezetimibe combined with simvastatin significantly reduced the risk of stroke and any revascularization, 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 randomized patients in SHARP^a

<u>Outcome</u>	Ezetimibe 10 mg combined with simvastatin 20 mg (N=4650)	<u>Placebo</u> (N=4620)	<u>Risk Ratio</u> (95% CI)	<u>P-value</u>
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 Revascularization	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004

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Major Atherosclerotic Events (MAE) ^b	526(11.3%)	619(13.4%)	0.83 (0.74-0.94)	0.002
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^aIntention-to-treat analysis on all SHARP patients randomized to ezetimibe combined with simvastatin or placebo either at baseline or year 1

^bMAE; defined as the composite of nonfatal myocardial infarction, coronary death, non-hemorrhagic stroke, or any revascularization

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.

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 1873 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 randomized 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, nonfatal myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), hospitalization 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 the 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

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ezetimibe when administered as ezetimibe 10-mg tablets. 'Ezetimibe Apotex' 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 ¹⁴C-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 patients

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 and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

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 insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic insufficiency, 'Ezetimibe Apotex' 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 $\text{CrCl} \leq 30$ ml/min/1.73m²), 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.

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LDL-C reduction and safety profile are comparable between men and women treated with 'Ezetimibe Apotex'. 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 coadministered 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

Povidone K30
Croscarmellose sodium
Lactose monohydrate
Sodium lauryl sulfate
Microcrystalline cellulose (PH 102)
Magnesium stearate
Colloidal silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC/Aluminumblister: Blister pack containing 28, 30, 50, 90, 98 and 100 tablets.

OPA/Aluminum/PVC/Aluminum blister: Blister pack containing 28, 30, 50, 90, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally