

EZETROL®

(ezetimibe)

LPC-OG0653-T-062023-Malaysia

LOCAL PRODUCT CIRCULAR

Tablets EZETROL® (ezetimibe)

I. THERAPEUTIC CLASS

EZETROL® (ezetimibe) is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols.

II. COMPOSITION

Each tablet of EZETROL for oral administration contains 10 mg ezetimibe.

III. INDICATIONS

Primary Hypercholesterolaemia

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

EZETROL, administered in combination with fenofibrate, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

Prevention of Cardiovascular Events

EZETROL, administered with a statin, is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for revascularization), in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS).

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Homozygous Sitosterolaemia (Phytosterolaemia)

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

IV. DOSAGE AND ADMINISTRATION

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

Use in Patients with Primary Hypercholesterolemia

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

EZETROL may be administered with a statin (in patients with primary hypercholesterolemia) or with fenofibrate (in patients with mixed hyperlipidemia) for incremental effect. For convenience, the daily dose of EZETROL may be taken at the same time as the statin or fenofibrate, according to the dosing recommendations for the respective medications.

If EZETROL 10mg tablets are used in combination with a statin therapy, the dosage instructions

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for that particular statin should be consulted.

When initiating lipid lowering treatment, which includes EZETROL 10mg Tablets and a statin in combination, the indicated usual initial dose of that particular statin should be used or the already established higher statin dose should be continued.

If the statin dose is to be increased for the first time or further, the dosage instructions of that particular statin should be followed (such as dose increase only after at least 4 weeks of regular use of the combination without any change).

The stepwise increase of the statin dose in combination treatment results in a relatively small additional decrease of LDL-C, but increases the risk of dose-related adverse events of the statin. This has to be considered for the risk-benefit-assessment when the statin dose is considered.

Use in Patients with Coronary Heart Disease

Combination Therapy with a Statin

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

Use in the Elderly

No dosage adjustment is required for elderly patients (see *Vb-5. Characteristics in Patients [Special Populations]*). However, greater sensitivity of some older individuals cannot be ruled out.

Use in Pediatric Patients

Children and adolescents ≥ 10 years: No dosage adjustment is required (see *Vb-5.*

Characteristics in Patients [Special Populations]).

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

Use in Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with EZETROL is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction (see VII. PRECAUTIONS and *Vb-5. Characteristics in Patients [Special Populations]*).

Use in Renal Impairment

No dosage adjustment is required for renally impaired patients (see *Vb-5. Characteristics in Patients [Special Populations]*).

Co-administration with bile acid sequestrants

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

V. CLINICAL PHARMACOLOGY

Va. Mechanism of Action

EZETROL is orally active and potent, with a unique mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

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In a 2-week clinical study in 18 hypercholesterolemic patients, EZETROL inhibited intestinal cholesterol absorption by 54 %, compared with placebo. By inhibiting the absorption of intestinal cholesterol, ezetimibe reduces the delivery of cholesterol to the liver. Statins reduce cholesterol synthesis in the liver. Together these distinct mechanisms provide complementary cholesterol reduction. EZETROL, administered with a statin, reduces total-C, LDL-C, Apo B, and TG and increases HDL-C in patients with hypercholesterolemia, beyond either treatment alone. Administration of EZETROL with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, TG, HDL-C, and non-HDL-C in patients with mixed hyperlipidemia.

Clinical studies demonstrate that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride- rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [¹⁴C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat soluble vitamins A and D.

Vb. Pharmacokinetics**Vb-1. Absorption**

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

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as EZETROL 10-mg tablets. EZETROL can be administered with or without food.

Vb-2. Distribution

Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Vb-3. Metabolism

Ezetimibe is metabolized 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.

Vb-4. 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

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11 % of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Vb-5. Characteristics in Patients (Special Populations)***Pediatric Patients***

The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population < 10 years of age are not available. Clinical experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH or sitosterolemia.

Geriatric Patients

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic Insufficiency

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

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease ($n=8$; mean CrCl ≤ 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 cyclosporine) had a 12-fold greater exposure to total ezetimibe.

Gender

Plasma concentrations for total ezetimibe are slightly higher (< 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with EZETROL. Therefore, no dosage adjustment is necessary on the basis of gender.

Race

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

VI. CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

The combination of EZETROL with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All statins are contraindicated in pregnant and nursing women. When EZETROL is administered with a statin in a woman of childbearing potential, refer to the pregnancy category and product labeling for the statin (see VIII. PREGNANCY).

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VII. PRECAUTIONS

When EZETROL is to be administered with a statin or with fenofibrate, please refer to the Package Insert for that particular medication.

Liver Enzymes

In controlled co-administration trials in patients receiving EZETROL with a statin, consecutive transaminase elevations ($\geq 3 \times$ the upper limit of normal [ULN]) have been observed. When EZETROL 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 XI. SIDE EFFECTS).

In the IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with CHD were randomized to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases ($\geq 3 \times$ ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. (See XI. SIDE EFFECTS.)

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with EZETROL 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 $> 10 \times$ ULN was 0.2% for EZETROL vs 0.1% for placebo, and 0.1% for EZETROL co-administered with a statin vs 0.4% for statins alone.

In post-marketing experience with EZETROL, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating EZETROL. However, rhabdomyolysis has been reported very rarely with EZETROL monotherapy and very rarely with the addition of EZETROL to agents known to be associated with increased risk of rhabdomyolysis. All patients starting therapy with EZETROL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. EZETROL and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level > 10 times the ULN indicates myopathy.

In IMPROVE-IT, 18,144 patients with CHD were randomized to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and < 10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, $\geq 5 \times$ 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 XI. SIDE EFFECTS.)

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, EZETROL is not recommended in these patients (see Vb-5. *Characteristics in Patients [Special Populations]*).

Fibrates

The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of EZETROL and fibrates (other than fenofibrate) is not recommended (see X. DRUG INTERACTIONS).

Fenofibrate

If cholelithiasis is suspected in a patient receiving EZETROL and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see XI. SIDE EFFECTS and the Package Insert for fenofibrate).

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Cyclosporine

Caution should be exercised when initiating EZETROL in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving EZETROL and cyclosporine (see X. DRUG INTERACTIONS).

Anticoagulants

If EZETROL is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see X. DRUG INTERACTIONS).

VIII. PREGNANCY

There are no adequate and well-controlled studies of EZETROL in pregnant women. EZETROL should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple dose studies of ezetimibe given in combination with statins in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

When EZETROL is to be administered with a statin, please refer to the Package Insert for that particular statin.

IX. NURSING MOTHERS

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, EZETROL should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

X. DRUG INTERACTIONS

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

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

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Cyclosporine: In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of cyclosporine, a single 10-mg dose of EZETROL resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m²) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see VII. PRECAUTIONS).

Fibrates: The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see XI. SIDE EFFECTS); co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of EZETROL with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

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

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. There have been post-marketing reports of increased International Normalized Ratio in patients who had EZETROL added to warfarin or fluindione. Most of these patients were also on other medications (see VII. PRECAUTIONS).

XI. SIDE EFFECTS

Clinical studies of up to 112 weeks duration in which EZETROL 10 mg daily was administered alone (n=2396), with a statin (n=11,308), or with fenofibrate (n=185) patients demonstrated: EZETROL was generally well tolerated, adverse reactions were usually mild and transient, the overall incidence of side effects reported with EZETROL was similar to that reported with placebo, and the discontinuation rate due to adverse experiences was comparable between EZETROL and placebo.

The following common ($\geq 1/100$, <1/10) or uncommon ($\geq 1/1,000$, <1/100); drug-related adverse experiences were reported in patients taking EZETROL alone (n = 2396) and at a greater incidence than placebo (n=1159), or in patients taking EZETROL co-administered with a statin (n = 11,308) and at a greater incidence than statin administered alone (n=9361).

EZETROL administered alone:

Investigations:

Uncommon: ALT and/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: cough

Gastrointestinal Disorders:

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Common: abdominal pain; diarrhea; flatulence
 Uncommon: dyspepsia; gastroesophageal reflux disease; nausea
 Musculoskeletal and Connective Tissue Disorders
 Uncommon: arthralgia; muscle spasms; neck pain
 Metabolism and Nutrition Disorders:
 Uncommon: decreased appetite
 Vascular Disorders:
 Uncommon: hot flush; hypertension
 General Disorders and Administration Site Condition:
 Common: fatigue
 Uncommon: chest pain; pain

EZETROL co-administered with a statin:

Investigations:

Common: ALT and/or AST increased

Nervous System Disorders:

Common: headache

Uncommon: paresthesia

Gastrointestinal Disorders

Uncommon: dry mouth; gastritis

Skin and Subcutaneous Tissue Disorders

Uncommon: pruritus; rash; urticaria

Musculoskeletal and Connective Tissue Disorders

Common: myalgia

Uncommon: back pain; muscular weakness; pain in extremity

General Disorders and Administration Site Condition

Uncommon: asthenia; edema peripheral

EZETROL co-administered with fenofibrate:

Gastrointestinal Disorders

Common: abdominal pain

In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to 1 year. 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 EZETROL 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 EZETROL co-administered with fenofibrate, respectively (see VII. PRECAUTIONS). There were no CPK elevations $> 10 \times \text{ULN}$ in either treatment group in this study.

Patients with Coronary Heart Disease

In the IMPROVE-IT study, 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, $\geq 5 \times \text{ULN}$ and $<10 \times \text{ULN}$ 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 ($\geq 3 \times \text{ULN}$) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. (See VII. PRECAUTIONS.) Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalizations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

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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 EZETROL (0.5 %) and placebo (0.3 %). In co-administration trials, the incidence was 1.3% for patients treated with EZETROL 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 VII. PRECAUTIONS).

Clinically important elevations of CPK ($\geq 10 \times$ ULN) in patients treated with EZETROL administered alone or co-administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

Post-marketing Experience

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

Blood and lymphatic system disorders: thrombocytopaenia

Nervous system disorders: dizziness; paraesthesia

Gastrointestinal disorders: nausea; pancreatitis; constipation

Skin and subcutaneous tissue disorders: severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilic and systemic symptoms (DRESS) and erythema multiforme

Musculoskeletal and connective tissue disorders: arthralgia; myalgia; myopathy/rhabdomyolysis (See VII. PRECAUTIONS)

General disorders and administration site conditions: asthenia

Immune system disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria

Hepatobiliary disorders: hepatitis; cholelithiasis; cholecystitis; drug-induced liver injury

Psychiatric disorders: depression

XII. OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks was generally well tolerated.

A few cases of overdosage with EZETROL 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.

XIII. STORAGE

Do not store above 30°C (86°F). Store in the original package.

XIV. AVAILABILITY

EZETROL Tablets 10 mg is available in packs of 30s.

XV. APPEARANCE

White to off-white capsule-shaped, debossed tablet.

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XVI. SHELF LIFE

Please refer to the expiry date on the outer carton.

XVII. MANUFACTURER

MSD International GmbH (Singapore Branch)
70 Tuas West Drive, Singapore 628414,
Singapore.

XVIII. PRODUCT REGISTRATION HOLDER

ORGANON MALAYSIA SDN. BHD.
3A-08-02, Level 8, Corporate Tower 3A,
Pavilion Damansara Heights,
No. 3, Jalan Damanlela
50490 Kuala Lumpur, Malaysia.

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