1. NAME OF THE MEDICINAL PRODUCT

Ezetrol 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of ezetimibe.

Excipient(s):
Each tablet contains 55 mg of lactose monohydrate

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to off-white, capsule-shaped tablets, approximately 2.60 mm thick, debossed with "414" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Ezetrol 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.

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetrol 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)
Ezetrol is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

A beneficial effect of Ezetrol on cardiovascular morbidity and mortality has not yet been demonstrated.

4.2 Posology and method of administration

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

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

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

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

Use in Paediatric Patients
Initiation of treatment must be performed under review of a specialist.

Children and adolescents ≥ 10 years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche): : No dosage adjustment is required (see section 5.2). The clinical experience in paediatric and adolescent patients (aged 10-17 years old) is, however, limited.

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

Children >6 and < 10 years: There is limited data on safety and efficacy in this age group. (see sections 5.1 and 5.2).

Children <6 years: There is no available data on use of Ezetrol in this age group.

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 sections 4.4 and 5.2.)

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

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

Ezetrol 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 Ezetrol 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 Ezetrol with a statin, consecutive transaminase elevations (≥ 3 X 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 section 4.8.)

In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomized

to receive Ezetrol 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 Ezetrol combined with simvastatin and 0.6% for placebo (see section 4.8).

Skeletal Muscle
In post-marketing experience with Ezetrol, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with Ezetrol. However, rhabdomyolysis has been reported very rarely with Ezetrol monotherapy and very rarely with the addition of Ezetrol 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, Ezetrol, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. 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 (see section 4.8).

In a clinical trial in which over 9000 patients with chronic kidney disease were randomized to receive Ezetrol 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 Ezetrol combined with simvastatin and 0.1% for placebo. (See section 4.8)

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

Paediatric (6 to 17 Years of Age) Patients
Efficacy and safety of Ezetrol in patients 6 to10 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).

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

Efficacy and safety of Ezetrol 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 Ezetrol 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 Ezetrol 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 Ezetrol in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

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

If cholelithiasis is suspected in a patient receiving Ezetrol 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 Ezetrol in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetrol and ciclosporin (see section 4.5).

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

Excipient
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

Interaction studies have only been performed in adults.

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 Ezetrol to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates: In patients receiving fenofibrate and Ezetrol, 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 Ezetrol 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 Ezetrol 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 Ezetrol 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 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, 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 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 Ezetrol in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetrol 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 Ezetrol added to warfarin or fluindione. If Ezetrol is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

4.6 Fertility, pregnancy and lactation

Ezetrol 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:
Ezetrol should be given to pregnant women only if clearly necessary. No clinical data are available on the use of Ezetrol 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:
Ezetrol 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

Clinical Studies and Post-marketing Experience

In clinical studies of up to 112 weeks duration, Ezetrol 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 Ezetrol and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between Ezetrol and placebo.

Ezetrol administered alone or co-administered with a statin:

The following adverse reactions were observed in patients treated with Ezetrol (N=2396) and at a greater incidence than placebo (N=1159) or in patients treated with Ezetrol 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 Ezetrol 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)

Ezetrol 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 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 Ezetrol 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	thrombocytopaenia	Not known
Nervous system disorders:	dizziness; paraesthesia	Not known
Respiratory, thoracic and mediastinal disorders	dyspnoea	Not known
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

Ezetrol 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 Ezetrol and fenofibrate completed 12 weeks of therapy, and 230 patients treated with Ezetrol and fenofibrate (including 109 who received Ezetrol 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 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 sections 4.4 and 4.5).

Paediatric (6 to 17 years of age) Patients
In a study involving paediatric (6 to10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and/or AST (≥ 3X ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥ 10X ULN). No cases of myopathy were 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 (≥ 3X ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10X ULN). No cases of myopathy were reported.

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

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 Ezetrol 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 Ezetrol combined with simvastatin, 9.8% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2% in patients treated with Ezetrol 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 Ezetrol 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 Ezetrol 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 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 section 4.4.)

In clinical trials, CPK >10 X ULN was reported for 4 of 1674 (0.2 %) patients administered Ezetrol alone vs 1 of 786 (0.1 %) patients administered placebo, and for 1 of 917 (0.1 %) patients co-administered Ezetrol and a statin vs 4 of 929 (0.4 %) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with Ezetrol compared with the relevant control arm (placebo or statin alone). (See section 4.4.)

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Ezetrol is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetrol 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, Ezetrol inhibited intestinal cholesterol absorption by 54 %, compared with placebo.

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.
A beneficial effect of Ezetrol on cardiovascular morbidity and mortality has not yet been demonstrated.

CLINICAL TRIALS

In controlled clinical studies, Ezetrol 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 Ezetrol 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 Ezetrol 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 Ezetrol versus placebo, respectively). In addition, Ezetrol, added to on-

going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetrol 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, Ezetrol 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, Ezetrol had no effect on the plasma concentrations of fat-soluble vitamins A, D, and E, no effect on prothrombin time, and, like other lipid lowering agents, did not impair adrenocortical steroid hormone production.

In a multicenter, double-blind, controlled clinical study (ENHANCE), 720 patients with heterozygous familial 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 the ezetimibe/simvastatin combination therapy on carotid artery intima-media thickness (IMT) compared to simvastatin monotherapy. The impact of this surrogate marker on cardiovascular morbidity and mortality is still not demonstrated.

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

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

Clinical Studies in Paediatric Patients (6 to 17 years of age)
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 Ezetrol 10 mg or placebo for 12 weeks.

At week 12, Ezetrol 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 Ezetrol 10 mg co-administered with simvastatin (10, 20 or 40 mg) or simvastatin (10, 20 or 40 mg) alone for 6 weeks, co-administered Ezetrol and 40 mg simvastatin or 40 mg simvastatin alone for the next 27 weeks, and open-label co-administered Ezetrol and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

At Week 6, Ezetrol 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 Ezetrol and 40 mg simvastatin (62 %) attained the NCEP AAP ideal goal (< 2.8 mmol/L [110 mg/dL]) for LDL-C compared to those receiving 40 mg simvastatin (25 %). At Week 53, the end of the open label extension, the effects on lipid parameters were maintained.

The safety and efficacy of Ezetrol 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 Ezetrol co-administered with simvastatin have not been studied in paediatric patients < 10years of age.
The long-term efficacy of therapy with Ezetrol in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

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. Ezetrol 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 Ezetrol 10 mg (n=30) or placebo (n=7). Some patients were receiving other treatments (e.g., statins, resins). Ezetrol 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.

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 Ezetrol 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 Ezetrol 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 Ezetrol 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 Ezetrol combined with simvastatin (n=4650) or placebo (n=4620) as well as the components of this composite.

The primary endpoint analysis showed that Ezetrol combined with simvastatin significantly reduced the risk of major vascular events (749 patients with events in the placebo group vs. 639 in the Ezetrol 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. Ezetrol combined with simvastatin significantly reduced the risk of stroke and any revascularization, with non-significant numerical differences favouring Ezetrol combined with simvastatin for nonfatal MI and cardiac death.

Table 1
Major Vascular Events by Treatment Group in all randomized patients in SHARP[a]

Outcome	Ezetrol 10 mg combined with	Placebo (N=4620)	Risk Ratio (95% CI)	P-value

	simvastatin 20 mg (N=4650)			
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
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 randomized to Ezetrol combined with simvstatin 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 revascularization

The absolute reduction in LDL cholesterol achieved with Ezetrol 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 and therefore the finding of the SEAS trial could not be confirmed by SHARP.

5.2 Pharmacokinetic properties

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

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

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

Biotransformation: Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

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

Special Populations:

Paediatric 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.

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 Ezetrol. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic Insufficiency
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, Ezetrol is not recommended in these patients (see section 4.4).

Renal Insufficiency
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medications, including

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 Ezetrol. 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 Ezetrol 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

Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Povidone (K29-32)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Blisters: Store in the original package in order to protect from moisture.
Bottles: Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Unit Dose peelable blisters of clear polychlorotrifluoroethylene/PVC sealed to vinyl coated aluminium backed with paper and polyester in packs of 7, 10, 14, 20, 28, 30, 50, 98, 100, or 300 tablets.

Push-through blisters of clear polychlorotrifluoroethylene/PVC sealed to vinyl coated aluminium in packs of 7, 10, 14, 20, 28, 30, 50, 84, 90, 98, 100, or 300 tablets.

Unit dose push-through blisters of clear polychlorotrifluoroethylene/PVC coated aluminium in packs of 50, 100 or 300 tablets.

HDPE bottles with polypropylene cap, containing 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon,
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER

MA058/02601

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

20/07/2005 / 17/10/2012

10. DATE OF REVISION OF THE TEXT

08/2013

Package leaflet: Information for the patient

EZETROL 10 mg Tablets

Ezetimibe

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

What is in this leaflet:

1. What EZETROL is and what it is used for

EZETROL is a medicine to lower increased levels of cholesterol

EZETROL lowers levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, EZETROL raises levels of "good" cholesterol (HDL cholesterol).

Ezetimibe, the active ingredient of EZETROL works by reducing the cholesterol absorbed in your digestive tract.

EZETROL adds to the cholesterol-lowering effect of statins, a group of medicines that reduce the cholesterol your body makes by itself.

Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol.

LDL cholesterol is often called “bad” cholesterol because it can build up in the walls of your arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke.

HDL cholesterol is often called “good” cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease.

Triglycerides are another form of fat in your blood that may increase your risk for heart disease.

It is used for patients who cannot control their cholesterol levels by cholesterol lowering diet alone. You should stay on your cholesterol lowering diet while taking this medicine.

EZETROL is used in addition to your cholesterol lowering diet if you have:

- a raised cholesterol level in your blood (primary hypercholesterolaemia [heterozygous familial and non-familial])
    - together with a statin, when your cholesterol level is not well controlled with a statin alone
    - alone, when statin treatment is inappropriate or is not tolerated
- a hereditary illness (homozygous familial hypercholesterolaemia) that increases the cholesterol level in your blood. You will also be prescribed a statin and may also receive other treatments.
- a hereditary illness (homozygous sitosterolaemia, also known as phytosterolaemia) that increases the levels of plant sterols in your blood.

EZETROL does not help you lose weight.

2. What you need to know before you take EZETROL

If you use EZETROL together with a statin, please read the package leaflet of that particular medicine.

Do not take EZETROL if:

- you are allergic (hypersensitive) to ezetimibe or any of the other ingredients of this medicine (see Section 6: Contents of the pack and other information).

Do not take EZETROL together with a statin if:

- you currently have liver problems.
- you are pregnant or breast-feeding.

Warnings and precautions

- Tell your doctor about all your medical conditions including allergies.
- Your doctor should do a blood test before you start taking EZETROL with a statin. This is to check how well your liver is working.
- Your doctor may also want you to have blood tests to check how well your liver is working after you start taking EZETROL with a statin.

If you have moderate or severe liver problems, EZETROL is not recommended.

The safety and efficacy of the combined use of EZETROL and certain cholesterol lowering medicines, the fibrates have not been established.

Children

EZETROL is not recommended for children under age 10.

Other medicines and EZETROL

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without prescription. In particular, tell your doctor if you are taking medicine(s) with any of the following active ingredients:

- ciclosporin (often used in organ transplant patients)
- medicines with an active ingredient to prevent blood clots, such as warfarin, phenprocoumon, acenocoumarol or fluindione (anticoagulants)
- colestyramine (also used to lower cholesterol), because it affects the way EZETROL works
- fibrates (also used to lower cholesterol)

Pregnancy and breast-feeding

Do not take EZETROL with a statin if you are pregnant, are trying to get pregnant or think you may be pregnant. If you get pregnant while taking EZETROL with a statin, stop taking both medicines immediately and tell your doctor.

There is no experience from the use of EZETROL without a statin during pregnancy. Ask your doctor for advice before using EZETROL if you are pregnant.

Do not take EZETROL with a statin if you are breast-feeding, because it is not known if the medicines are passed into breast milk.

EZETROL without a statin should not be used if you are breast-feeding. Ask your doctor for advice.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

EZETROL is not expected to interfere with your ability to drive or to use machinery. However, it should be taken into account that some people may get dizzy after taking EZETROL.

EZETROL contains lactose

EZETROL tablets contain a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take EZETROL

Always take EZETROL exactly as your doctor has told you. Continue taking your other cholesterol-lowering medicines unless your doctor tells you to stop. You should check with your doctor or pharmacist if you are not sure.

- Before starting EZETROL, you should be on a diet to lower your cholesterol.
- You should keep on this cholesterol lowering diet whilst taking EZETROL.

Adults, adolescents and children (10 to 17 years of age): The dose is one EZETROL 10 mg Tablet by mouth once a day.

Take EZETROL at any time of the day. You can take it with or without food.

If your doctor has prescribed EZETROL along with a statin, both medicines can be taken at the same time. In this case, please read the dosage instructions in the package leaflet of that particular medicine.

If your doctor has prescribed EZETROL along with another medicine for lowering cholesterol containing the active ingredient colestyramine or any other medicine containing bile acid sequestrant, you should take EZETROL at least 2 hours before or 4 hours after taking the bile acid sequestrant.

If you take more EZETROL than you should:

Please contact your doctor or pharmacist.

If you forget to take EZETROL:

Do not take an extra dose, just take your normal amount of EZETROL at the usual time the next day.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, EZETROL can cause side effects, although not everybody gets them.

The following terms are used to describe how often side effects have been reported:
- Very common (may affect more than 1 of 10 patients)
- Common (may affect up to 1 of 10 patients)
- Uncommon (may affect up to 1 of 100 patients)
- Rare (may affect up to 1 of 1,000 patients)
- Very rare (may affect up to 1 of 10,000 patients, including isolated reports).

Contact your doctor immediately if you experience unexplained muscle pain, tenderness, or weakness. This is because on rare occasions, muscle problems, including muscle breakdown resulting in kidney damage, can be serious and may become a potentially life-threatening condition.

Allergic reactions, including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which requires treatment right away) have been reported in general use.

When used alone, the following side effects were reported:
Common; abdominal pain; diarrhoea; flatulence; feeling tired.
Uncommon: elevations in some laboratory blood tests of liver (transaminases) or muscle (CK) function; cough; indigestion; heartburn; nausea; joint pain; muscle spasms; neck pain; decreased appetite, pain, chest pain, hot flush; high blood pressure.

Additionally, when used with a statin, the following side effects were reported:
Common: elevations in some laboratory blood tests of liver function (transaminases); headache; muscle pain, tenderness or weakness.
Uncommon: tingling sensation; dry mouth; itching; rash; hives; back pain; muscle weakness; pain in arms and legs; unusual tiredness or weakness; swelling, especially in the hands and feet.

When used with fenofibrate, the following common side effect was reported:
abdominal pain.

Additionally, the following side effects have been reported in general use: dizziness; muscle aches; liver problems; allergic reactions including rash and hives; raised red rash, sometimes with target-shaped lesions (erythema multiforme); muscle pain, tenderness or weakness; muscle breakdown; gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting); inflammation of the pancreas often with severe abdominal pain; constipation, reduction in blood cell counts, which may cause bruising/bleeding (thrombocytopaenia); tingling sensation; depression: unusual tiredness or weakness; shortness of breath..

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store EZETROL

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date stated on the carton or container after "EXP." The expiry date refers to the last day of that month.
- Do not store EZETROL above 30°C.

Blisters: Store in the original package. Bottles: Keep bottles tightly closed. These measures will protect the product from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EZETROL contains

- The active substance is ezetimibe. Each tablet contains 10 mg ezetimibe.
- The other ingredients are: lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium laurilsulfate, magnesium stearate

What EZETROL looks like and contents of the pack

EZETROL tablets are white to off-white, capsule-shaped tablets with code "414" on one side.

Pack sizes:
7, 10, 14, 20, 28, 30, 50, 98, 100 or 300 tablets in push-through blisters or unit dose peelable blisters;
84 or 90 tablets in push-through blisters;
50, 100 or 300 tablets in unit dose push-through blisters;
100 tablets in bottles.

Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Merck Sharp & Dohme Ltd.
Hertford Road
Hoddesdon, Hertfordshire EN11 9BU
United Kingdom

Manufacturer:
SP Labo N. V.
Industriepark 30 – Zone A
B-2220 Heist-op-den-Berg
Belgium

This medicinal product is authorized under the name Ezetrol in Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom.

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