

SUMMARY OF PRODUCT CHARACTERISTICS

Ezetrol®

I. NAME OF MEDICINAL PRODUCT

Ezetrol® 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of ezetimibe.
For excipients see 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White to off-white, capsule-shaped tablets 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.

Studies to demonstrate the efficacy of 'Ezetrol' in the prevention of complications of atherosclerosis have not yet been completed.

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

Children and adolescents ≥ 10 years: No dosage adjustment is required (see section 5.2). However, clinical experience in paediatric and adolescent patients (ages 9 to 17) is limited.

Children < 10 years: No sufficient clinical data are available, therefore 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 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 Contra-indications

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 statin.

Therapy with 'Ezetrol' co-administered with a statin is contra-indicated during pregnancy and lactation.

'Ezetrol' co-administered with a statin is contra-indicated 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 statin.

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.)

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).

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established; therefore, co-administration of 'Ezetrol' and fibrates is not recommended (see section 4.5).

Cyclosporin

Caution should be exercised when initiating ezetimibe in the setting of cyclosporin (see section 4.5).

The quantity of lactose in each tablet (55 mg lactose-monohydrate) is probably not sufficient to induce specific symptoms of lactose intolerance.

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, midazolam, or warfarin during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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

Cholestyramine: Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates: Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5- and 1.7-fold respectively, however these increases are not considered clinically significant.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see section 5.3). Although the relevance of this preclinical finding to humans is unknown, co-administration of ezetimibe with fibrates is not recommended until use in patients is studied.

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

Cyclosporin: In a study of eight post-renal transplant patients with creatinine clearance of >50 ml/min on a stable dose of cyclosporin, 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 from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 ml/min/1.73m²) who was receiving

multiple medications, including cyclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls (see section 4.4).

4.6 Pregnancy and Lactation

'Ezetrol' co-administered with a statin is contra-indicated 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 ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofetal 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.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use of machines have been performed. However, ezetimibe is not expected to affect the ability to drive and use machines.

4.8 Undesirable effects

Clinical studies of 8 to 14 weeks duration in which ezetimibe 10 mg daily was administered alone or with a statin in 3366 patients demonstrated that ezetimibe was generally well tolerated; adverse reactions were usually mild and transient. The overall incidence of side effects reported with ezetimibe was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.

The following common ($\geq 1/100$, $< 1/10$) drug-related adverse experiences were reported in patients taking ezetimibe alone (n=1691) or co-administered with a statin (n=1675):

Ezetimibe administered alone:

Nervous system disorders: headache

Gastro-intestinal disorders: abdominal pain and diarrhoea

Ezetimibe co-administered with a statin:

Nervous system disorders: headache and fatigue

Gastro-intestinal disorders: abdominal pain, constipation, diarrhoea, flatulence and nausea

Musculoskeletal and connective tissue disorders: myalgia.

The following adverse reactions have been reported in post-marketing experience:

[Rare ($\geq 1/10,000$, $< 1/1,000$)]

Immune system disorders:

Rare: hypersensitivity, including angioedema and rash.

Laboratory values

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

Clinically important elevations of CPK (≥ 10 X ULN) in patients treated with ezetimibe administered alone or co-administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

4.9 Overdose

No cases of overdosage with ezetimibe have been reported. Administration of ezetimibe, 50 mg/day, to 15 subjects for up to 14 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.

In the event of an overdose, symptomatic and supportive measures should be employed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cholesterol and triglyceride reducers, 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).

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. The molecular mechanism of action is not fully understood. In a 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe 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 [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. Studies to demonstrate the efficacy of 'Ezetrol' in the prevention of complications of atherosclerosis have not yet been completed.

CLINICAL TRIALS

In controlled clinical studies, ezetimibe, either as monotherapy or co-administered with a statin significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

Primary hypercholesterolaemia

In a double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82%), significantly more patients randomised to ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72% and 19% respectively. The corresponding LDL-C reductions were significantly different (25% and 4% for ezetimibe versus placebo, respectively). In addition, ezetimibe, added to on-going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10% or 0% from baseline, respectively.

In two, double-blind, randomised placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. In addition, ezetimibe had no effect on the plasma concentrations of 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.

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Homozygous sitosterolaemia (phytosterolaemia)

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

5.2 Pharmacokinetic 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 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 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 paediatric population <10 years of age are not available. Clinical experience in paediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH 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 ezetimibe. 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, ezetimibe 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), 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 cyclosporin) had a 12-fold greater exposure to total ezetimibe.

Gender

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

5.3 Preclinical safety data

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

In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2000 times the AUC level for the active metabolites).

In a series of in vivo and in vitro assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The co-administration of ezetimibe with lovastatin resulted in embryo-lethal effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

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, 98, 100, or 300 tablets.

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

Not all pack sizes may be marketed.

6.6 Instructions for use/handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MSD-SP Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

8. MARKETING AUTHORISATION NUMBER

PL 19945/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

3 April 2003

10. DATE OF REVISION OF TEXT

August 2003