SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

EZETROL® 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each EZETROL10 mg tablet contains 10 mg of ezetimibe.

EZETROL contains sugar (55,0 mg of lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off-white capsule-shaped tablets, debossed with “414” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

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

Reduction in Risk of Cardiovascular Events

EZETROL is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin.

Homozygous Familial Hypercholesterolaemia (HoFH)

EZETROL, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH.

4.2 Posology and method of administration

The patient should be on an appropriate lipid-lowering diet and weight loss program where indicated and should continue on this diet during treatment with EZETROL.

Posology

Use in Patients with Primary Hypercholesterolaemia

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.

Use in Patients with Coronary Heart Disease and ACS Event History

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

Special populations

Use in Patients with Renal Impairment/Chronic Kidney Disease

In patients with renal impairment, no dosage adjustment of EZETROL is necessary (see section 5.2*).*

Combination Therapy with Simvastatin

In patients with mild renal impairment (estimated GFR ≥ 60 mL/min/1,73 m^2), no dosage adjustment of EZETROL or simvastatin is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate < 60 mL/min/1,73 m^2, the dose of EZETROL is 10 mg

and the dose of simvastatin is 20 mg once a day in the evening. In such patients, the use of higher doses of simvastatin should be closely monitored (see section 4.4).

Use in the Elderly

No dosage adjustment is required for elderly patients (see section 5).

Paediatric population

Children 6 years of age or older and adolescents: No dosage adjustment is required (see section 5).

Children under 6 years of age: No clinical data on safety and efficacy are available, therefore treatment with EZETROL is contraindicated.

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 contraindicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction due to unknown effects (see section 4.3 and section 5.2).

Co-administration with bile acid sequestrants

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

4.3 Contraindications

- Hypersensitivity to any component of this medication.
- Pregnancy, as no clinical data on exposed pregnancies is available.
- Lactation, as it is not known whether ezetimibe is excreted in human breast milk.

- Children below the age of 6 years.
- Moderate to severe hepatic impairment (Child Pugh score 7 or more).

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

4.4 Special warnings and precautions for use

When EZETROL is to be administered with a statin, 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 (≥ 3 x 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).

Skeletal Muscle

In clinical trials, the incidence of CPK >10 x 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. 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.

Fibrates

The safety and efficacy of EZETROL administered with fibrates have not been established. The co-administration of EZETROL with fibrates other than fenofibrate has not been studied.

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 section 4.8) and the Package Insert for fenofibrate.

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).

Statins

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

Anticoagulants

There have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had EZETROL added to warfarin. If EZETROL is added to warfarin or another coumarin anticoagulant, the INR should be appropriately monitored.

4.5 Interaction with other medicines and other forms of interaction

In preclinical studies, it has been shown that EZETROL does not induce cytochrome P450 medicine metabolising enzymes. No clinically significant pharmacokinetic interactions have

been observed between EZETROL and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4 or N-acetyltransferase.

EZETROL had no significant effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinylestradiol and levonorgestrel), glipizide, tolbutamide or midazolam (see section 4.4). Cimetidine, co-administered with EZETROL, had no effect on the bioavailability of EZETROL.

Antacids

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

Cholestyramine

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

Fibrates

Concomitant fenofibrate or gemfibrozil administration increased total EZETROL concentrations by approximately 1,5- and 1,7-fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of EZETROL administered with fibrates have not been established. The safety and effectiveness of EZETROL co-administered with fenofibrate have been evaluated in a clinical study (see section 4.8); co-administration of EZETROL with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, EZETROL 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.

Statins

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

Additional information on special populations

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 historical healthy control population. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13,2 mL/min/1,73 m^2) who was receiving multiple medications, including ciclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in 12 healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of EZETROL is not recommended in pregnancy, as no clinical data on exposed pregnancies are available (see section 4.3).

Breastfeeding

The use of EZETROL is not recommended during lactation, as it is not known whether ezetimibe is excreted into human breast milk (see section 4.3). Mothers on treatment with EZETROL should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Certain side effects that have been reported with EZETROL may affect some patients' ability to drive or operate machinery. Individual responses to EZETROL may vary (see section 4.8).

4.8 Undesirable effects

The following common (≥ 1 % to < 10 %) or uncommon (≥ 0,1 % to < 1,0 %) medicine related adverse experiences were reported in patients taking EZETROL alone or co-administered with a statin.

EZETROL administered alone:

Investigations

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

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: cough

Gastrointestinal Disorders

Common: abdominal pain, diarrhoea, 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 Conditions

Common: fatigue

Uncommon: chest pain, pain.

EZETROL co-administered with a statin:

Investigations

Common: increased ALT and/or AST

Nervous System Disorders

Common: headache

Uncommon: paraesthesia

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, oedema peripheral.

EZETROL co-administered with fenofibrate:

Gastrointestinal systems disorders

Common: abdominal pain.

Adverse reactions from clinical trials

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 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 x ULN, consecutive) in serum transaminases were 4,5 % (1,9 to 8,8) and 2,7 % (1,2 to 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 to 3,1) and 1,7 % (0,6 to 4,0) for fenofibrate monotherapy and EZETROL co-administered with fenofibrate, respectively (see section 4.4). There were no CPK elevations > 10 x ULN in either treatment group in this study.

Adverse experiences reported in more than or equal to 2 % of patients treated with EZETROL and at an incidence greater than placebo in placebo-controlled studies of EZETROL, regardless of causality assessment, are shown in **Table 1**.

TABLE 1:

Clinical Adverse Reactions Occurring in ≥ 2 % of Patients Treated with EZETROL and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Reaction	**EZETROL 10 mg (%) n=2 396**	**Placebo (%) n=1 159**
Gastrointestinal disorders		
Diarrhoea	4,1	3,7
General disorders and administration site conditions		
Fatigue	2,4	1,5
Infections and infestations		
Influenza	2,0	1,5
Sinusitis	2,8	2,2
Upper respiratory tract infection	4,3	2,5

Musculoskeletal and connective tissue disorders		
Arthralgia	3,0	2,2
Pain in extremity	2,7	2,5

The frequency of less common adverse events was comparable between EZETROL and placebo.

Clinical adverse experiences reported in more than or equal to 2 % of patients and at an incidence greater than statin, regardless of causality assessment, are shown in **Table 2**.

TABLE 2:

Clinical Adverse Reactions Occurring in ≥ 2 % of Patients Treated with EZETROL Co-Administered with a Statin and at an Incidence Greater than Statin, Regardless of Causality

Body System/Organ Class Adverse Reaction	**All Statins*** **(%) n=9 361**	**EZETROL + All Statins*** **(%) n=11 308**
Gastrointestinal disorders		
Diarrhoea	2,2	2,5
General disorders and administration site conditions		
Fatigue	1,6	2,0
Infections and infestations		
Influenza	2,1	2,2
Nasopharyngitis	3,3	3,7

Upper respiratory tract infection	2,8	2,9
Musculoskeletal and connective tissue disorders		
Arthralgia	2,4	2,6
Back pain	2,3	2,4
Myalgia	2,7	3,2
Pain in extremity	1,9	2,1

*All Statins = all doses of all statins

Paediatric (6 to 17 Years of Age) Patients

In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia, the safety and tolerability profile of the group treated with EZETROL was similar to that of adult patients treated with EZETROL (see section 5).

In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia, the safety and tolerability profile of the group co-administered EZETROL and simvastatin was similar to that of adult patients co-administered EZETROL and simvastatin (see section 5).

Laboratory values

In controlled clinical monotherapy trials, the incidence of clinically significant elevations in serum transaminases (ALT and/or AST ≥ 3 x the upper limit of normal (ULN), consecutive) was not statistically different 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).

Clinically significant elevations of creatinine phosphokinase (CPK; ≥ 10 x 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.

For data from sources other than clinical trials/studies data:

Post-marketing Experience

The following adverse effects have been reported in post-marketing experience (frequency not known):

Blood and lymphatic system disorders

Thrombocytopenia

Immune system disorders

Hypersensitivity reactions, including anaphylaxis, rash, urticaria and angioedema

Nervous system disorders

Dizziness, paraesthesia

Psychiatric disorders

Depression

Gastrointestinal disorders

Pancreatitis, constipation

Hepatobiliary disorders

Hepatitis, cholelithiasis, cholecystitis

Musculoskeletal and connective tissue disorders

Myalgia, myopathy/rhabdomyolysis (see section 4.4)

Skin and subcutaneous tissue disorders

Erythema multiforme

Laboratory values

Increased transaminases, increased CPK

General disorders and administration site conditions

Asthenia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In the event of an overdose, symptomatic and supportive measures should be employed. 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, and 40 mg/day to 27 patients with homozygous sitosterolaemia for 26 weeks, was generally well tolerated.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological Classification**:** A 7.5 Serum-cholesterol reducers

5.1 Pharmacodynamic properties

Mechanism of Action

Ezetimibe inhibits the intestinal absorption of cholesterol and related plant sterols.

Ezetimibe in experimental animals inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinylestradiol or the fat soluble vitamins A and D.

5.2 Pharmacokinetic properties

Absorption

After oral administration, ezetimibe is 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.

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 compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine 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 (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity were

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

Special Populations

Paediatric population

The pharmacokinetics of ezetimibe are similar between children ≥ 6 years of age or older and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available.

Geriatric population

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (65 years or older) than in the young (18 to 45 years).

Hepatic Impairment

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. No dosage adjustment is necessary for patients with mild hepatic insufficiency. 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. 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 contraindicated in these patients.

Renal Impairment

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean creatinine clearance (CrCl) ≤ 30 mL/min/1,73m^2), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects (n=9).

An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin had a 12-fold greater exposure to total ezetimibe (see section 4.5).

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 ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EZETROL contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulphate and magnesium stearate.

EZETROL contains lactose

Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take EZETROL.

6.2 Incompatibilities

N/A

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original package.

Keep out of reach of children.

6.5 Nature and contents of container

The product is packed in clear push through or peelable ACLAR®/PVC blisters in pack sizes of 30's.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

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South Africa

8 REGISTRATION NUMBER

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