SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

EZETROL ™ 10 mg tablet

COMPOSITION

Each EZETROL ™ 10 mg tablet contains 10 mg ezetimibe

PHARMACOLOGICAL CLASSIFICATION

A 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION

EZETROL (ezetimibe) inhibits the intestinal absorption of cholesterol and related plant sterols.

MECHANISM OF ACTION

In human studies, ezetimibe inhibited 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, ethinyl estradiol, or the fat soluble vitamins A and D.

PHARMACOKINETICS

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 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.

Metabolism

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.

Characteristics in Patients

Paediatric Patients

The absorption and metabolism of ezetimibe are similar between children 10 years of age or older and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population less than 10 years of age are not available.

Geriatric Patients

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 Insufficiency

After a single 10 mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1,7 fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. 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 greater than 9) hepatic insufficiency, ezetimibe is contra-indicated in these patients.

Renal Insufficiency

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

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

Gender

Plasma concentrations for total ezetimibe are slightly higher (less than 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.

Race

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences

between Blacks and Caucasians.

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.

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.

CONTRA-INDICATIONS

- 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 into human breast milk.
- Children below the age of 10 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.)

WARNINGS

There have been post-marketing reports of increased International Normalized Ratio in patients who had EZETROL added to warfarin. Most of these patients were also on other medication. If EZETROL is added to warfarin or another coumarin anticoagulant, the International Normalized Ratio (INR) should be appropriately monitored (see **SPECIAL PRECAUTIONS** and **INTERACTIONS)**.

INTERACTIONS

In preclinical studies, it has been shown that EZETROL does not induce cytochrome P450 medicine metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between EZETROL and medicines known to be metabolized 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 (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, midazolam or warfarin during co-administration. However, there have been post-marketing reports of increased International Normalized Ratio in patients who had EZETROL added to warfarin. Most of these patients were also on other medication. If EZETROL is added to warfarin or another coumarin anticoagulant, the International Normalized Ratio (INR) should be appropriately monitored (see **WARNINGS** and **SPECIAL PRECAUTIONS)**. 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 **SIDE EFFECTS**); 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.

Ciclosporine

In a study of eight post renal transplant patients with creatinine clearance of greater than 50 ml/min on a stable dose of ciclosporine, 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/1,73m^2) who was receiving multiple medications, including ciclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporine on Day 7 resulted in a mean 15% increase in ciclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of ciclosporine alone (see **SPECIAL PRECAUTIONS**).

PREGNANCY AND LACTATION

Pregnancy

The use of EZETROL is not recommended in pregnancy, as no clinical data on exposed pregnancies are available (see **CONTRA-INDICATIONS**).

Lactation

The use of EZETROL is not recommended during lactation, as it is not known whether ezetimibe is excreted into human breast milk (see **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

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.

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 the Elderly

No dosage adjustment is required for elderly patients (see **PHARMACOLOGICAL ACTION)**

Use in Paediatric Patients

Children 10 years of age or older: No dosage adjustment is required (see **PHARMACOLOGICAL ACTION).**

Children under 10 years of age: No clinical data on safety and efficacy are available, therefore treatment with EZETROL is contra-indicated.

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 contra-indicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score greater than 9) liver dysfunction due to unknown effects (See **CONTRA-INDICATIONS** and Characteristics in Patients).

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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

The following common (1% to 10%) drug related adverse experiences were reported in patients taking EZETROL alone or co-administered with a statin.

EZETROL administered alone:

Body as a whole – general disorders:

Common: headache

Gastrointestinal systems disorders:

Common: abdominal pain and diarrhoea.

EZETROL co-administered with a statin:

Body as a whole – general disorders:

Common: headache and fatigue

Gastrointestinal systems disorders:

Common: abdominal pain, constipation, diarrhoea, flatulence and nausea,

Musculoskeletal system disorders:

Common: myalgia

Liver and biliary system disorders:

Common: increased alanine transaminase (ALT) and increased aspartate transaminase (AST).

EZETROL co-administered with fenofibrate:

Gastrointestinal systems disorders:

Common: abdominal pain

In a multicenter, 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, 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 **SPECIAL PRECAUTIONS**). 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 Events Occurring in more than or equal to 2% of Patients Treated with EZETROL and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class **Adverse Event**	Placebo (%) n=795	EZETROL 10 mg (%) n=1691
Body as a whole - general disorders		
Fatigue	1,8	2,2
Gastrointestinal system disorders		
Abdominal pain	2,8	3,0
Diarrhoea	3,0	3,7
Infection and infestations		
Infection viral	1,8	2,2

Pharyngitis	2,1	2,3
Sinusitis	2,8	3,6
Musculoskeletal system disorders		
Arthralgia	3,4	3,8
Back pain	3,9	4,1
Respiratory system disorders		
Coughing	2,1	2,3

*Includes patients who received placebo or EZETROL alone reported in Table 2.

Clinical adverse experiences reported in more than or equal to 2% of patients and at an incidence greater than placebo in four placebo-controlled trials where EZETROL was administered alone or initiated concurrently with various statins, regardless of causality assessment, are shown in Table 2.

Table 2*

Clinical Adverse Events Occurring in more than or equal to 2% of Patients and at an Incidence Greater than Placebo, Regardless of Causality, in EZETROL/Statin Combination Studies

Body System/Organ Class **Adverse Event**	Placebo (%) N=259	EZETROL 10 mg (%) n=262	All Statins** (%) n=936	EZETROL + All Statins** (%) n=925
Body as a whole - general disorders				
Chest pain	1,2	3,4	2,0	1,8
Dizziness	1,2	2,7	1,4	1,8
Fatigue	1,9	1,9	1,4	2,8
Headache	5,4	8,0	7,3	6,3
Gastrointestinal system disorders				
Abdominal pain	2,3	2,7	3,1	3,5
Diarrhoea	1,5	3,4	2,9	2,8
Infection and infestations				

Pharyngitis	1,9	3,1	2,5	2,3
Sinusitis	1,9	4,6	3,6	3,5
Upper respiratory tract infection	10,8	13,0	13,6	11,8
Musculoskeletal system disorders				
Arthralgia	2,3	3,8	4,3	3,4
Back pain	3,5	3,4	3,7	4,3
Myalgia	4,6	5,0	4,1	4,5

*Includes four placebo-controlled combination studies in which EZETROL was initiated concurrently with an HMG-CoA reductase inhibitor.

**All statins = all doses of all HMG-CoA reductase inhibitors.

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

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

nausea

pancreatitis

Hepatobiliary disorders

hepatitis

cholelithiasis; cholecystitis

Musculoskeletal and connective tissue disorders

myalgia; arthralgia

myopathy/rhabdomyolysis (see **SPECIAL PRECAUTIONS**).

Skin and subcutaneous tissue disorders:

erythema multiforme

Laboratory values

increased transaminases; increased CPK

LABORATORY VALUES

In controlled clinical monotherapy trials, the incidence of clinically significant elevations in serum transaminases (ALT and/or AST greater than or equal to 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 **SPECIAL PRECAUTIONS**)

Clinically significant elevations of creatinine phosphokinase (CPK; greater than or equal to 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.

SPECIAL PRECAUTIONS

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 (greater than or equal to 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 **SIDE EFFECTS**)

Skeletal Muscle

In clinical trials, the incidence of CPK greater than 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 greater than 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 **SIDE EFFECTS** and the Package Insert for fenofibrate.

Ciclosporine

Caution should be exercised when initiating EZETROL in the setting of ciclosporine. Ciclosporine concentrations should be monitored in patients receiving EZETROL and ciclosporine (see **INTERACTIONS**).

Statins

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

Anticoagulants

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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, was generally well tolerated.

IDENTIFICATION

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

PRESENTATION

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

STORAGE INSTRUCTIONS

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

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

37/7.5/0413

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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