"For the use only of a Registered Medical Practitioner"

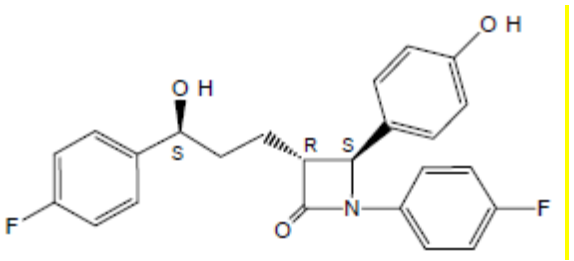
PRESCRIBING INFORMATION

ZETEZE TABLETS
(Ezetimibe Tablets 10 mg)

COMPOSITION
Each tablet contains
Ezetimibe…….. 10 mg
Excipients(s): Lactose monohydrate, povidone, croscarmellose sodium, sodium lauryl sulphate, pregelatinised starch, magnesium stearate.

PRODUCT DESCRIPTION
ZETEZE tablets are white to off white capsule shaped uncoated tablets with 'E 10' debossed on one side and plain on other side.

DESCRIPTION
Ezetimibe belongs to a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)- 3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



EZETIMIBE
STRUCTURAL FORMULA

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

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

Ezetimibe inhibited intestinal cholesterol absorption by 54% in hypercholesterolaemic patients.

Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low- density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

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.

Pharmacokinetics

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 ezetimibe 10-mg tablets. Ezetimibe 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 reported. 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: Ezetimibe is excreted primarily in the faeces via bile; after an oral dose, about 78% is excreted in the faeces, mainly as ezetimibe, and about 11% is excreted in the urine, mainly as the glucuronide.

Pharmacokinetics in 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. Pharmacokinetics 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 patient with HoFH.

Geriatric patients

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

Hepatic insufficiency
After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects.

In multiple-dose pharmacokinetics of ezetimibe (10 mg for 14 days), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9) verses healthy individuals.

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.

Renal insufficiency
Approximately 1.5-fold increase in mean AUC for total ezetimibe has been reported in patients with severe renal disease receiving single 10-mg dose of ezetimibe compared to healthy individuals. This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients. Also 12-fold greater exposure to total ezetimibe was reported in one of the individual (post-renal transplant and receiving multiple medications, including cyclosporin).

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.

Race
Based on meta-analysis, there were no pharmacokinetic differences between Black and Caucasians.

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

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

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

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetimibe co-administered with a statin, is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozygous Sitosterolaemia (Phytosterolaemia)
Ezetimibe is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia.

DOSE AND METHOD OF ADMINISTRATION

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

Use in Patients with Primary Hypercholestrolemia

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

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

If ezetimibe 10 mg tablets are used in combination with a statin therapy, the dosage instructions for that particular statin should be consulted.

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

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

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

Use in Patients with Coronary Heart Disease

Combination therapy with a statin

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

Use in the Elderly

No dosage adjustment is required for elderly patients. However greater sensitivity of some older individual cannot be ruled out.

Use in Paediatric Patients

Children and adolescents ≥ 10 years: No dosage adjustment is required.
Children <10 years: Treatment with ezetimibe 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 ezetimibe is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction.

Use In Renal Impairment

No dosage adjustment is required for renally impaired patients.

Co-Administration with Bile Acid Sequestrants
Dosing of ezetimibe should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity reactions including anaphylaxis, angioedema, rash and urticaria have been reported with ezetimibe.
- Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.
- Therapy with ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation.

WARNINGS AND PRECAUTIONS
When ezetimibe is to be administered with a statin or with fibrate, please refer to the product information for that particular medication.

Liver enzymes
Consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been reported in patients receiving ezetimibe with a statin.
When ezetimibe is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin.

Skeletal muscle
Cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe 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, ezetimibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with ezetimibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Hepatic insufficiency
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe is not recommended.

Paediatric (10 to 17 Years of Age) Patients
Efficacy and safety of ezetimibe co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in adolescent boys (Tanner stage II or above) and in girls who were at least one year post-menarche.

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.
The safety and efficacy of ezetimibe co-administered with doses simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age.

Ezetimibe has not been studied in patients younger than 10 years of age or in pre-menarchal girls. The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates
The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore co-administration of ezetimibe and fibrate (other than fenofibrate) is not recommended. If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder studies are indicated and alternative lipid lowering therapy should be considered.

Cyclosporin
Caution should be exercised when initiating ezetimibe in the setting of cyclosporin. Cyclosporin concentrations should be monitored in patients receiving ezetimibe and cyclosporin.

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

DRUG INTERACTIONS
It has been reported that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been reported between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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

Colestyramine: Concomitant colestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide). The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to colestyramine may be lessened by this interaction.

Fibrates: Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.
In patients receiving fenofibrate and ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease.

If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued. Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations.

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

Cyclosporin: Increased plasma concentrations of ezetimibe have been reported with concomitant administration of cyclosporine in renal transplant patients, patient with severe renal insufficiency and healthy subjects. Caution should be exercised when initiating ezetimibe in the setting of cyclosporin. Cyclosporin concentrations should be monitored in patients receiving ezetimibe and cyclosporin.

Anticoagulants: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time. However, cases of increased International Normalised

Ratio (INR) have been reported in patients who had ezetimibe added to warfarin or fluindione. If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored.

SIDE EFFECTS/ ADVERSE REACTIONS

Ezetimibe 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 ezetimibe 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

Ezetimibe co-administered with fenofibrate:
Abdominal pain (common), clinically important elevations (>3 X ULN, consecutive) in serum transaminases, cholecystectomy

Paediatric (10 to 17 years of age) Patients
In patients with heterozygous familial hypercholesterolaemia

- Elevations of ALT and/or AST (≥3X ULN, consecutive) were reported in patients receiving ezetimibe/simvastatin;

- Elevation of CPK (≥ 10X ULN) was reported in patients receiving ezetimibe/simvastatin. No cases of myopathy were reported.

Laboratory values
Clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) levels have been reported in patient receiving ezetimibe with or without a statin. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

The CPK >10 X ULN was reported in patient receiving ezetimibe with or without a statin. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe verses patients receiving no treatment or statins.

Upper respiratory tract infections sinusitis, nasopharyngitis, and influenza have also been reported.

The following additional adverse reactions have been reported
Blood and lymphatic system disorders: thrombocytopenia
Nervous system disorders: dizziness; paraesthesia
Respiratory, thoracic and mediastinal disorders: dyspnoea
Gastro-intestinal disorders: pancreatitis; constipation
Skin and subcutaneous tissue disorders: erythema multiforme
Musculoskeletal and connective tissue disorders: myalgia; myopathy/rhabdomyolysis
General disorders and administration site conditions: asthenia
Immune system disorders: hypersensitivity, including rash, urticaria, anaphylaxis and angioedema
Hepatobiliary disorders: hepatitis, cholelithiasis, cholecystitis
Psychiatric disorders: depression.

USE IN SPECIAL POPULATION
Pregnancy and Lactation
Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation; please refer to the product information of that particular statin.

- **Pregnancy**

Ezetimibe should be given to pregnant women only if clearly necessary. No clinical information is available on the use of ezetimibe during pregnancy. In animals, the use of ezetimibe in monotherapy has shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development.

- **Lactation**

Ezetimibe should not be used during lactation. Ezetimibe has reported to be secreted into breast milk of rats. It is not known if ezetimibe is secreted into human breast milk.

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 report.

OVERDOSE
A few cases of overdosage with ezetimibe 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.

STORAGE
Store below 30^{o}C and protect from moisture. Store in the original package.

PACK SIZE:
Aluminium foil coated with VMCH (Blister) with Cold form blister pack of 14's, Box of 2 x 14's.

DATE OF REVISION
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PRODUCT REGISTRATION HOLDER/MANUFACTURED BY:

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