Package Insert

ACCORD EZETIMIBE 10 (Ezetimibe Tablets 10 mg)

- **Name and strength of active ingredient**

Ezetimibe 10 mg

- **Product Description**

ACCORD EZETIMIBE 10: White to off white, capsule shaped, flat faced with beveled edge, uncoated tablets, debossed with "10" on one side and plain on other side.

- **Pharmacodynamics & Pharmacokinetics**

Pharmacodynamic properties

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

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

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 Ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated.

Pharmacokinetic properties

Absorption: After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). 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.

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.

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 population
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.

Older people
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 impairment
No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, Ezetimibe is not recommended in these patients.

Renal impairment
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 Ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

- **Indication**

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, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

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

- **Recommended Dosage**

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

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 10mg 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 10mg Tablets 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 instructions of 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 stepwise increase of the statin dose in combination treatment results in a relatively small additional decrease of LDL-C, but increases the risk of dose-related adverse events of the statin. This has to be considered for the risk-benefit-assessment when the statin is considered.

Use in the Elderly
No dosage adjustment is required for elderly patients. However, greater sensitivity of some older individuals cannot be ruled out.

Use in Pediatric 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.

- **Route of Administration**

Oral

- **Contraindications**

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

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

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

Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

- **Warnings & Precautions**

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

Liver Enzymes: 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: 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.

Patients with hepatic impairment: Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, Ezetimibe is not recommended.

Paediatric population: Efficacy and safety of Ezetimibe in patients 6 to 10 years of age with heterozygous familial or non-familial hypercholesterolemia have been evaluated.

Ezetimibe has not been studied in patients younger than 6 years of age.

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 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.

The safety and efficacy of Ezetimibe 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 Ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age.

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 safety and efficacy of Ezetimibe administered with fibrates have not been established.

If cholelithiasis is suspected in a patient receiving Ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued.

Ciclosporin: Caution should be exercised when initiating Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe and ciclosporin.

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

Excipient: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicaments

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.

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 Ezetimibe to cholestyramine may be lessened by this interaction.

Fibrates: 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 (approximately 1.5- and 1.7-fold respectively).

Co-administration of Ezetimibe with other fibrates has not been studied.

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.

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

Ciclosporin: Caution should be exercised when using Ezetimibe and Ciclosporin concomitantly due to increased exposure to both ezetimibe and Ciclosporin. Cyclosporine concentrations should be monitored in patients receiving Ezetimibe and Ciclosporin.

Anticoagulants: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time. However, if Ezetimibe is added to

warfarin, another coumarin anticoagulant, or fluindione, International Normalised Ratio (INR) should be appropriately monitored.

Paediatric population: Interaction studies have only been performed in adults.

- **Statement on usage during pregnancy and lactation**

Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation, please refer to the SPC for that particular statin.

Pregnancy: Ezetimibe 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, embryofoetal development, birth or postnatal development.

Lactation: Ezetimibe 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.

- **Adverse Effects/ Undesirable Effects**

Ezetimibe administered alone or co-administered 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).

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:
Gastrointestinal disorders: abdominal pain (common).

Paediatric (6 to 17 years of age) Patients:
No cases of myopathy were reported.

Patients with Chronic Kidney Disease:
There were no statistically significant increases in the incidence of pre-specified adverse events, including cancer, hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

- **Overdose and Treatment**

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 Conditions**

Store below 30°C. Protect from moisture.

- **Dosage forms and packaging available**

Alu-PVC/Aclar blister pack
Pack size: 10 tablets and 30 tablets

- **Name and address of manufacturer**

INTAS PHARMACEUTICALS LIMITED
Plot No. 457 & 458, Village Matoda, Bavla Road

and Plot No. 191/218P, Village: Chacharwadi,
Tal- Sanand, Ahmedabad, Gujarat, INDIA.

- **Date of revision of PI**

May 2019