# EZEKEM 10 PACK INSERT

# Ezetimibe Tablets 10mg

**1. Name of the medicinal product**

EZEKEM 10 (Ezetimibe Tablets 10mg)

**2. Qualitative and quantitative composition**

Each tablet contains 10 mg of Ezetimibe USP.

Excipient(s) with known effect:

Lactose monohydrate.

For the full list of excipients, see section 6.1.

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This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodiumfree’.

**3. Pharmaceutical form**

Uncoated Tablet.

White to off white capsule shaped, flat faced, bevelled edge tablets, debossed with 'A25' on one side and plain on other side

**4. Clinical particulars**

**4.1 Therapeutic indications**

*Primary Hypercholesterolaemia*

EZEKEM 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.

EZEKEM, 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.

*Prevention of Cardiovascular Events*

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

*Homozygous Familial Hypercholesterolaemia (HoFH)*

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

*Homozygous Sitosterolaemia (Phytosterolaemia)*

EZEKEM is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia

**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 EZEKEM.

*Use in Patients with Primary Hypercholesterolemia*

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

EZEKEM 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 EZEKEM may be taken at the same time as the statin or fenofibrate, according to the dosing recommendations for the respective medications.

If EZEKEM 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 EZEKEM 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 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, EZEKEM 10 mg may be administered with a statin with proven cardiovascular benefit.

*Use in the Elderly*

No dosage adjustment is required for elderly patients (see Section 5.2. Special Populations). 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 (see Section 5.2. Special Populations)

Children < 10 years: Treatment with EZEKEM 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 EZEKEM 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 Special warnings and precautions for use and 5.2. Special Populations).

*Use in Renal Impairment*
No dosage adjustment is required for renally impaired patients (see Section 5.2. Special Populations).

*Co-administration with bile acid sequestrants*
Dosing of EZEKEM should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

**4.3 Contraindications**
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
When EZEKEM is co-administered with a statin, please refer to the package insert for that particular medicinal product.
Therapy with EZEKEM co-administered with a statin is contraindicated during pregnancy and lactation.
EZEKEM co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

**4.4 Special warnings and precautions for use**
When EZEKEM is co-administered with a statin, please refer to the package insert for that particular medicinal product.

Liver Enzymes
In patients receiving EZEKEM with a statin, consecutive transaminase elevations (≥ 3 X the upper limit of normal [ULN]) have been observed. When EZEKEM 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
Cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with EZEKEM. However, rhabdomyolysis has been reported very rarely with EZEKEM monotherapy and very rarely with the addition of EZEKEM 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, EZEKEM, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with EZEKEM should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

Hepatic impairment
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, EZEKEM is not recommended (see section 5.2).

Paediatric population

There is no data on effects of ezetimibe for treatment periods > 12 weeks in 6 to 10 years age group (see sections 4.2, 4.8, 5.1 and 5.2).

There is no data on use of EZEKEM in patients younger than 6 years of age (see sections 4.2 and 4.8).

In adolescent boys (Tanner Stage II or above) and in girls who were at least one year post-menarche aged 10 to 17 years of age with heterozygous familial hypercholesterolaemia, 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, there is no data on effects of ezetimibe for a treatment period > 33 weeks on growth and sexual maturation (see sections 4.2 and 4.8).

There is no data on safety and efficacy of EZEKEM co-administered with doses of simvastatin above 40mg daily in paediatric patients 10 to 17 years of age.

There is no data on safety and efficacy of EZEKEM co-administered with simvastatin in paediatric patients < 10 years of age (see sections 4.2 and 4.8).

There is no data on long-term efficacy of therapy with EZEKEM in patients below 17 years of age to reduce morbidity and mortality in adulthood.

Fibrates

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

If cholelithiasis is suspected in a patient receiving EZEKEM and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

Ciclosporin

Caution should be exercised when initiating EZEKEM in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving EZEKEM and ciclosporin (see section 4.5).

Anticoagulants

If EZEKEM is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Excipient

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

**4.5 Interaction with other medicinal products and other forms of interaction**

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.

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 AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental LDLC reduction due to adding EZEKEM to colestyramine may be lessened by this interaction

Fibrates

In patients receiving fenofibrate and EZEKEM, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8).
If cholelithiasis is suspected in a patient receiving EZEKEM and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).
Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations.
There is no data on co-administration of EZEKEM with other fibrates.
Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. Ezetimibe sometimes increased cholesterol in the gallbladder bile. A lithogenic risk associated with the therapeutic use of EZEKEM cannot be ruled out.

Statins

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

Ciclosporin

There is no data on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients. Caution should be exercised when initiating EZEKEM in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving EZEKEM and ciclosporin (see section 4.4).

Anticoagulants

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had EZEKEM added to warfarin or fluindione. If EZEKEM is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Paediatric population

Interaction data is only available for adults.

**4.6 Fertility, pregnancy and lactation**

EZEKEM co-administered with a statin is contraindicated during pregnancy and lactation (see section 4.3), please refer to the package insert ffor that particular statin.

Pregnancy

EZEKEM should be given to pregnant women only if clearly necessary. No clinical data are available on the use of EZEKEM during pregnancy. Animal data 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

EZEKEM should not be used during lactation. Data on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Fertility

No data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats.

**4.7 Effects on ability to drive and use machines**

No data on the effects on the ability to drive and use machines is available. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

**4.8 Undesirable effects**

List of adverse reactions

Adverse reactions were usually mild and transient.

These reactions are presented by system organ class and by frequency.

Frequencies are defined as: very common; common; uncommon; rare, very rare and not known.

*EZEKEM administered alone:*

Investigations:

Uncommon: ALTand/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: cough

Gastrointestinal Disorders:

Common: abdominal pain; diarrhea; 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 Condition:
Common: fatigue
Uncommon: chest pain; pain

*EZEKEM co-administered with a statin:*
Investigations:
Common: ALT and/or AST increased

Nervous System Disorders:
Common: headache
Uncommon: paresthesia

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; edema peripheral

*EZEKEM co-administered with fenofibrate:*
Gastrointestinal Disorders
Common: abdominal pain

Paediatric (6 to 17 years of age) Patients

In paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia, elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed. There were no elevations of CPK (≥ 10 X ULN). No cases of myopathy were reported.

In adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia, elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed. No cases of myopathy were reported.

Patients with Coronary Heart Disease and ACS Event History

In patients treated with either ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg, the safety profiles were similar during a median follow-up period of 6.0 years.

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.

Laboratory values:

These elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4).

There was no excess of myopathy or rhabdomyolysis associated with EZEKEM (see section 4.4).

**4.9 Overdose**

Administration of ezetimibe, 50 mg/day to healthy patients for up to 14 days, or 40 mg/day to patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. Animal data shows that there is no toxicity observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

A few cases of overdosage with EZEKEM 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.

**5. Pharmacological properties**

**5.1 Pharmacodynamic properties**

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

Mechanism of action

EZEKEM is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. EZEKEM 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 hypercholesterolaemic patients, EZEKEM inhibited intestinal cholesterol absorption.

Pharmacodynamic effects

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 data 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.

Administration of EZEKEM with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

**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 EZEKEM 10 mg tablets. EZEKEM 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 $^{14}$C-ezetimibe (20 mg) to human patients, 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. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

*Elderly*

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 patients treated with EZEKEM. 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, EZEKEM is not recommended in these patients (see section 4.4).

*Renal impairment*

No dosage adjustment is necessary for renally impaired patients.

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

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Hypromellose (Pharmacoat 603)
Microcrystalline cellulose GR 102
Crospovidone XL-10
Sodium laurilsulfate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

**6.4 Special precautions for storage**

Store below 30°C. Protect from light.

**6.5 Nature and contents of container**

EZEKEM 10 is available in packs of 1 x 10's and 3 x 10's.

Each PVC/Aclar Film with Alu Foil Blister containing 10 tablets.

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7. Manufacturer**

Alkem Laboratories Limited,
Village Thana, Baddi,
Tehsil - Nalagarh, District Solan,
Himachal Pradesh, 173205, INDIA
Head Office: ALKEM HOUSE,
Senapati Bapat Marg,
Lower Parel, Mumbai - 400 013

**8. Product Registration Holder**

Ascend Laboratories Sdn Bhd
Level 25, Menara Hong Leong
No. 6, Jalan Damanlela Bukit Damansara
50490 Kuala Lumpur, Malaysia

**9. Marketed by**

SYNERCAM (M) SDN BHD.
A-17-7, Block A, Jaya One, No. 72A,
Jalan Profesor Diraja Ungku Aziz, Seksyen 13,
46200 Petaling Jaya Selangor, Malaysia

**10. Date of revision of the text**

January 2024

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