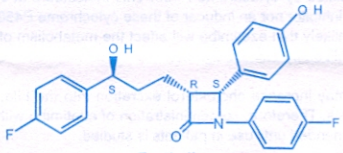
Ezita™
[Ezetimibe]

ازیٹا

TABLETS 10mg

DESCRIPTION
EZITA (Ezetimibe) is the first in a new class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols.
Chemically, ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S) hydroxypropyl]-4(S)-(4hydroxyphenyl)-2-azetidinone. The molecular formula is $C_{24}H_{21}F_2NO_3$ and the structural formula is:



Ezetimibe

QUALITATIVE & QUANTITATIVE COMPOSITION
EZITA is available for oral administration as:
Ezita Tablets 10mg
Each tablet contains:
Ezetimibe...10mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Ezetimibe decreases blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. Unlike other cholesterol-lowering compounds, ezetimibe does not inhibit cholesterol synthesis in the liver nor does it increase bile acid excretion. Ezetimibe acts at the brush border of the small intestine to inhibit the absorption of cholesterol leading to a reduction in the amount of cholesterol delivered to the liver. This in turn causes a reduction of hepatic cholesterol stores and an increase in cholesterol clearance from the blood.

Pharmacokinetics
Absorption
Within 4-12hours (T_{max}) of the oral administration of a 10mg dose to fasting adults, the attained mean ezetimibe peak plasma concentration (C_{max}) was 3.4-5.5ng/ml. Following oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide) in the small intestine and liver. Ezetimibe-glucuronide mean C_{max} values of 45 to 71ng/mL were achieved between 1 and 2 hours (T_{max}). The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 60% for AUC values.

Effect of Food on Oral Absorption
Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe. However, co-administration with a high fat meal increases the C_{max} of ezetimibe by 38%. Ezetimibe can be administered with or without food.

Distribution
Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins. Relative volume of distribution is 107.5L. 20% reabsorbed due to enterohepatic re-circulation.

Metabolism and Excretion
Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Ezetimibe is rapidly metabolized to ezetimibe-glucuronide. 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 a half-life of approximately 22 hours.

Special Populations
Geriatric Patients
In a multiple dose study with ezetimibe given 10mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Pediatric Patients
In a multiple dose study with ezetimibe given 10mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Hepatic Insufficiency
After a single 10mg dose of ezetimibe to patients with mild, moderate, or severe hepatic impairment, the mean AUC values for total ezetimibe are increased approximately 1.7-fold, 3-4 fold, and 5-6 fold respectively, compared to healthy subjects.

Renal Insufficiency
After a single 10mg dose of ezetimibe in patients with severe renal disease (creatinine clearance ≤ 30ml/min), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects.

Drug-Drug Relationship
Gemfibrozil
Concomitant administration of gemfibrozil significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Antacids
Co-administration of ezetimibe with antacids resulted in the decrease of C_{max} value of total ezetimibe by 30%.

HMG-CoA reductase inhibitors
In studies of healthy hypercholesterolemic (LDL-C ≥130mg/dL) adult subjects, concomitant administration of ezetimibe had no significant effect on the bioavailability of statins.

Cholestyramine:
Concomitant administration of cholestyramine with ezetimibe, in healthy hypercholesterolemic adult subjects, decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

INDICATIONS AND USAGE
Ezita is indicated:
- As adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia as monotherapy or as combination therapy with HMG-CoA reductase inhibitors.
- In combination with atorvastatin or simvastatin to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to diet and other non-pharmacological or lipid lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable or inadequate
- As adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

DOSAGE AND ADMINISTRATION
The recommended dose of EZITA (Ezetimibe) is 10mg once daily. EZITA can be administered with or without food.

Combination therapy with an HMG-CoA reductase inhibitor
EZITA (Ezetimibe) may be administered with an HMG-CoA reductase inhibitor for incremental effect. For convenience, the daily dose of EZITA may be taken at the same time as the HMG-CoA reductase inhibitor, according to the dosing recommendations for the HMG-CoA reductase inhibitor.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. EZITA should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate.
See NCEP (National Cholesterol Education Program) Adult Treatment Panel (ATP) III Guidelines, summarized in table below:

Summary of NCEP ATP III Guidelines

LDL Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories			
Risk category	**LDL goal**	**LDL level at which to initiate TLC**	**LDL level at which to consider drug therapy**
CHD or CHD risk equivalent (10-year risk > 20 percent)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (at 100 to 129 mg/dL, drug optional)*
2 or more risk factors (10-year risk <20 percent)	<130 mg/dL	≥130 mg/dL	≥130 mg/dL for 10-year risk of 10 to 20 percent; ≥160 mg/dL for 10-year risk of <10 percent
0 to 1 risk factor**	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (at 160 to 189 mg/dL, LDL-lowering drug optional)

LDL = low-density lipoprotein; CHD = coronary heart disease;
* If an LDL cholesterol level of <100 mg per dL cannot be achieved by therapeutic lifestyle changes, some authorities recommend use of LDL-lowering drugs in this category. Others prefer using drugs that primarily modify triglycerides and HDL (i.e., nicotinic acid or fibrate). Clinical judgment also may call for deferring drug therapy in this subcategory.
** People with zero to one risk factor almost always have a 10-year risk <10 percent; thus, 10-year risk assessment is not necessary in this group.

ADVERSE REACTIONS

Ezetimibe is generally well tolerated. However, some of the most commonly reported adverse effects are:
Body as a whole: Fatigue
Gastrointestinal system disorders: Abdominal pain, diarrhea
Infection and infestations: Infection viral, pharyngitis, sinusitis
Musculo-skeletal system disorders: Arthralgia, back pain
Respiratory system disorders: Coughing.

When ezetimibe is used in combination with an HMG CoA reductase inhibitor, slight increases in serum transaminase levels were noted. This elevation in serum transaminase levels has been shown to be reversible upon discontinuation of ezetimibe and the HMG CoA reductase inhibitor.

CONTRAINDICATIONS

- Ezetimibe is contraindicated in patients with hypersensitivity to any components of this medication.
- Ezetimibe in combination with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

PRECAUTIONS

General
- Prior to initiating therapy with ezetimibe secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), should be excluded or, if appropriate, treated.
- At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.
- Concurrent administration of ezetimibe with a specific HMG CoA reductase inhibitor should be in accordance with the product labeling for that HMG CoA reductase inhibitor.
- All HMG CoA reductase inhibitors are contraindicated in pregnant and nursing women.

Liver Enzymes
When ezetimibe is co-administered with an HMG CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.
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 in these patients.

Pediatric Use
Treatment with ezetimibe in children (<10 years) is not recommended.

Pregnancy
There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Nursing Mothers
Ezetimibe is excreted into human breast milk; therefore, it should not be given to nursing mothers unless the potential benefit justifies the potential risk to the infant.

Drug Interactions

Ezetimibe had no significant effect on a series of probe drugs known to be metabolized by cytochrome P450. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. Therefore, co-administration of ezetimibe with fibrates is not recommended until use in patients is studied.

Cyclosporine: Patients who take both ezetimibe and cyclosporine should be carefully monitored.

STORAGE

Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

EZITA (Ezetimibe) Tablets 10mg are available in blister pack of 10's.

Keep out of reach of children.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan
L02-01201956