

Ezita™

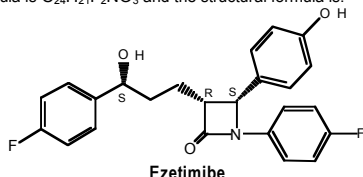
[Ezetimibe]

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10mg TABLETS

DESCRIPTION

EZITA (Ezetimibe) is the lipid-lowering compound 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 $C_{24}H_{27}F_2NO_3$ and the structural formula is:



QUALITATIVE & QUANTITATIVE COMPOSITION

EZITA (Ezetimibe) 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 4-12 hours (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 Impairment

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 Impairment

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

THERAPEUTIC INDICATIONS

Ezita (Ezetimibe) 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 (Ezetimibe) 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 (Ezetimibe) 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 (Ezetimibe) 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 the 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 fibrates). 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: Cough

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 ezetimibe or any component of the product.
- 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 Impairment

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 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.

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%.

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.

Fibrates:

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.

OVERDOSAGE

A few cases of overdosage with ezetimibe have been reported. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

STORAGE

Store at 25°C (Excursions permitted between 15°C-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.

To be sold on prescription of a registered medical practitioner only.

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

Manufactured by:



Getz
pharma

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