Lipiget™ EZ

[Atorvastatin+Ezetimibe]

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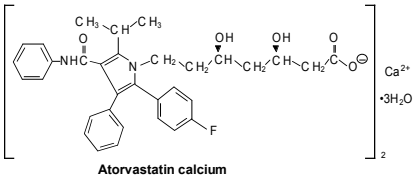
10mg+10mg Tablets

DESCRIPTION

LIPIGET EZ is a fixed dose combination of lipid lowering agents atorvastatin and ezetimibe . Atorvastatin inhibits the endogenous synthesis of cholesterol and ezetimibe selectively inhibits the intestinal absorption of cholesterol and related phytosterol.

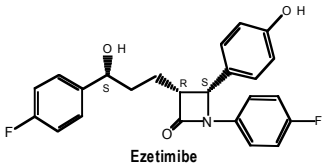
Chemically, atorvastatin calcium trihydrate is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, 8-dihydroxy-5- (1-methylethyl)-3-phenyl 4[(phenylamino)carbonyl]-1H-pyrrole-1 heptanoic acid, calcium salt (2:1) trihydrate.

The molecular formula is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and the structural formula is:



Atorvastatin calcium

Chemically, ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S) hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The molecular formula is $C_{24}H_{21}F_2NO_3$ and the structural formula is:



Ezetimibe

QUALITATIVE AND QUANTITATIVE COMPOSITION

LIPIGET EZ (Atorvastatin+Ezetimibe) is available for oral administration as:

LIPIGET EZ Tablets 10mg+10mg
Each tablet contains:
Atorvastatin … 10mg
(as atorvastatin calcium trihydrate)
Ezetimibe … 10mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Atorvastatin

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. The primary site of action of HMG-CoA reductase inhibition is the liver. Inhibition of cholesterol synthesis in the liver leads to upregulation of LDL-receptors and an increase in LDL-catabolism. There is also some reduction of LDL-production as a result of inhibition of hepatic synthesis of very low-density lipoprotein (VLDL), the precursor of LDL-cholesterol. Atorvastatin reduces total cholesterol, LDL-cholesterol and apo B in patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia and mixed dyslipidemias. Atorvastatin also reduces VLDL-cholesterol and triglycerides and produces variable increases in HDL-cholesterol and Apolipoprotein A1.

Ezetimibe

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.

Pharmacokinetics

Absorption:

Atorvastatin

Atorvastatin is rapidly absorbed after oral administration, maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Ezetimibe

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. Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10mg tablets. It can be administered with or without food.

Distribution:

Atorvastatin

Mean volume of distribution of atorvastatin is approximately 381liters. Atorvastatin is 98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88% to 92% to human plasma proteins, respectively.

Metabolism:

Atorvastatin

Atorvastatin is metabolized by the cytochrome P450 isoenzyme CYP3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Ezetimibe

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%-20% and 80%-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:

Atorvastatin

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20-30 hours due to the contribution of active metabolites.

Ezetimibe

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 feces and urine, respectively, over a 10 day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Special Populations

Atorvastatin

Geriatrics: Plasma concentrations of atorvastatin are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC).

Hepatic Impairment: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

Ezetimibe

Hepatic Impairment

After a single 10mg 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). No dosage adjustment is necessary for patients with mild hepatic insufficiency. In patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on day 1 and day 14 compared to healthy subjects. 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.

THERAPEUTIC INDICATIONS

Primary Hypercholesterolemia

LIPIGET EZ (Atorvastatin+Ezetimibe) is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HoFH)

LIPIGET EZ (Atorvastatin+Ezetimibe) is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

DOSAGE AND ADMINISTRATION

The recommended dose of LIPIGET EZ (Atorvastatin+Ezetimibe) is one tablet daily.

The patient should be on an appropriate standard cholesterol-lowering diet and should continue on this diet during treatment with LIPIGET EZ (Atorvastatin+Ezetimibe). Therapy should be individualized according to the baseline LDL-C level, the recommended goal of therapy and the patient's response. (See below NCEP Adult Treatment Panel Guidelines). LIPIGET EZ (Atorvastatin+Ezetimibe) can be taken at any time of the day with or without food.

The following guidelines may be used to establish treatment goals:

NCEP Treatment Guidelines LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD* or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129:drug optional)**
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor #	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

#Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

ADVERSE REACTIONS

Atorvastatin+Ezetimibe combination is generally well tolerated. Adverse reactions reported were increased transaminases, upper respiratory tract infection, headache, myalgia, back pain, arthralgia, sinusitis, pharyngitis, abdominal pain, diarrhea and fatigue.

CONTRAINDICATIONS

Atorvastatin+Ezetimibe combination is contraindicated:

- In patients with hypersensitivity to ezetimibe, atorvastatin or any component of this medication.
- In patients with active liver disease or unexplained persistent elevations of serum transaminases.
- During pregnancy and lactation.
- In children below 10 years of age.
- Use of ezetimibe is not recommended with fibrates.

PRECAUTIONS

Myopathy/Rhabdomyolysis

Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin+Ezetimibe combination should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Liver Enzymes

Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose and periodically (e.g., semi annually) thereafter. Liver enzyme changes generally occur in the first three months of treatment with atorvastatin. Should an increase in ALT or AST of >3 times the upper limit of normal persist, withdrawal of atorvastatin+ezetimibe combination is recommended.

Drug Interactions

Erythromycin, fibric acid derivatives, azole antifungals or niacin:
The risk of myopathy during treatment with drugs belonging to the class of HMG-CoA reductase inhibitors is increased with concurrent administration of these agents.

Gemfibrozil
Concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

Cyclosporine:
Cyclosporine concentrations should be monitored in patients receiving atorvastatin+ezetimibe combination and cyclosporine due to increased exposure to both ezetimibe and cyclosporine.

Antacids:
Decreased plasma concentrations of atorvastatin may occur when atorvastatin+ezetimibe combination is administered along with an oral antacid suspension containing magnesium and aluminum hydroxides, however, LDL-cholesterol reduction is not altered.

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

Ketoconazole, spironolactone and cimetidine:
HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Caution should be exercised if atorvastatin+ezetimibe combination is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone and cimetidine.

Digoxin:
Administration of multiple doses of atorvastatin with digoxin increases the steady state plasma digoxin concentration by approximately 20%. Patients taking digoxin should be monitored appropriately when atorvastatin+ezetimibe combination is initiated.

Oral Contraceptives:
Co-administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyl oestradiol produces increased plasma concentrations of norethindrone and ethinyl oestradiol. These increases should be considered when selecting an oral contraceptive for a patient taking atorvastatin+ezetimibe combination.

Alcohol:
The product should be used with caution in patients who consume substantial quantities of alcohol.

OVERDOSAGE

In the event of an overdose, general supportive measures should be adopted as required. Liver function tests and serum CPK levels should be monitored.

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

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

LIPIGET EZ (Atorvastatin+Ezetimibe) Tablets 10mg+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 (PVT) LIMITED
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