# Lipiget® EZ

[Atorvastatin+Ezetimibe]

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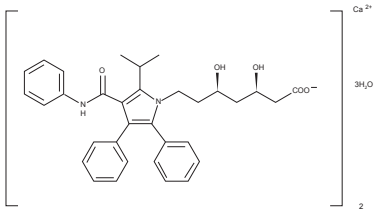
**10mg + 10mg & 20mg + 10mg Tablets**

**DESCRIPTION**

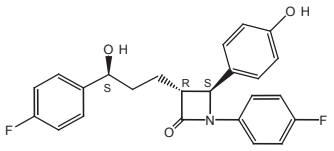
Lipiget EZ is a fixed dose combination of lipid lowering agents atorvastatin and ezetimibe. Atorvastatin inhibits the endogenous synthesis of cholesterol and ezetimibe selectively inhibits the intestinal absorption of cholesterol and related phytosterol.

Chemically, atorvastatin calcium trihydrate is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, ẟ-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 trihydrate**

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

Lipiget EZ Tablets 20mg+10mg
Each tablet contains:
Atorvastatin…20mg
(as atorvastatin calcium trihydrate)
Ezetimibe…10mg

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

*Atorvastatin*

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutarylcoenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor). Atorvastatin reduces total-C, LDL-C and Apo B in both normal volunteers and in patients with homozygous and heterozygous familial hypercholesterolaemia (FH), non-familial forms of hypercholesterolaemia and mixed dyslipidaemia. Atorvastatin also reduces very low density lipoprotein cholesterol (VLDL-C) and triglycerides and produces variable increases in HDL-C and apolipoprotein A-1.

*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.

Distribution:

*Atorvastatin*

Mean volume of distribution of atorvastatin is approximately 400liters. 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 extensively metabolized by the cytochrome P450 isoenzyme CYP3A4 to ortho- and parahydroxylated derivatives. 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 (20mg) 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**

*Prevention of Cardiovascular Disease*

Lipiget EZ (Atorvastatin+Ezetimibe) is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of atorvastatin and in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy.

*Primary Hypercholesterolaemia*

Lipiget EZ (Atorvastatin+Ezetimibe) is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:

- not appropriately controlled with atorvastatin or ezetimibe alone; or
- already treated with atorvastatin and ezetimibe

*Homozygous Familial Hypercholesterolaemia (HoFH)*
Lipiget EZ (Atorvastatin+Ezetimibe) is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

**DOSAGE AND ADMINISTRATION**
*Lipiget EZ (Atorvastatin+Ezetimibe) is not indicated for first-line use.*
Patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Lipiget EZ (Atorvastatin+Ezetimibe) Tablets.

***Dosage in Patients with Primary Hypercholesterolaemia***
Lipiget EZ (Atorvastatin + Ezetimibe) can be administered within the dosage range of 10mg + 10mg to 80mg + 10mg as a single daily dose. The recommended starting dose of Lipiget EZ (Atorvastatin + Ezetimibe) is 10mg + 10mg or 20mg + 10mg once daily. Lipiget EZ (Atorvastatin + Ezetimibe) can be administered at any time of the day, with or without food. Therapy should be individualised according to the target lipid levels, the recommended goal of therapy and the patient's response. After initiation and/or upon titration of Lipiget EZ (Atorvastatin + Ezetimibe), lipid levels should be re-analysed within 2 or more weeks and dosage adjusted according to the patient's response.

***Dosage in Patients with Coronary Heart Disease***
Therapy can be commenced for patients with CHD and a history of ACS who are taking their maximum tolerated dose of atorvastatin and have not achieved recommended target lipid levels. The recommended starting dose of Lipiget EZ (Atorvastatin + Ezetimibe) in patients already treated with atorvastatin should provide ezetimibe dosed as 10mg daily and the dose of atorvastatin already being taken. Lipiget EZ (Atorvastatin + Ezetimibe) is not indicated for first-line use.

***Advice to Patients Currently Taking Ezetimibe and/or Atorvastatin***
To prevent accidental excessive dosing due to inadvertent duplication of administration of ezetimibe and/or atorvastatin, patients currently taking ezetimibe and/or atorvastatin should be advised that Lipiget EZ (Atorvastatin + Ezetimibe) replaces these medications and therefore the current ezetimibe and/or atorvastatin medication(s) should no longer be taken.

***Dosage in Patients with Homozygous Familial Hypercholesterolaemia (HoFH)***
The dosage of Lipiget EZ (Atorvastatin + Ezetimibe) in patients with homozygous familial hypercholesterolemia is 10mg + 10mg or 80mg + 10mg daily. Lipiget EZ (Atorvastatin + Ezetimibe) should be used as an adjunct to other treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

**ADVERSE REACTIONS**
*Common:* Diarrhoea and myalgia.

*Uncommon:* influenza, depression, insomnia, sleep disorder, dysgeusia, paraesthesia, dizziness, headache, dyspnoea, sinus bradycardia, hot flush, abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, frequent bowel movements, stomach discomfort, upset stomach, abdominal distension, constipation, dyspepsia, flatulence, gastritis, nausea, acne, urticaria, arthralgia, back pain, muscle fatigue, muscular weakness, pain in extremity, muscle spasms, musculoskeletal stiffness, asthenia, oedema, fatigue, malaise, ALT and/or AST increased, alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test abnormal, weight increased and blood CK increased.

**"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"**

**CONTRAINDICATIONS**
Atorvastatin + Ezetimibe combination is contraindicated:
- In patients with hypersensitivity to ezetimibe, atorvastatin or any component of this medication.
- In patients with moderate or severe liver dysfunction.
- In patients with active liver disease or unexplained persistent elevations of serum transaminases.
- During pregnancy and lactation.
- In patients with myopathy secondary to other lipid lowering agents.
- In combination with fenofibrate, in patients with gall bladder disease.
- To adminster concomitantly use with fusidic acid.

**PRECAUTIONS**
*Myopathy/Rhabdomyolysis*
Atorvastatin may affect the skeletal muscle and cause myalgia, myositis and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine phosphokinase (CPK) levels (>10 times ULN), myoglobinaemia and myoglobinuria, which may lead to renal failure. Patients must be asked to promptly report muscle pain, cramps or weakness especially if accompanied by malaise or fever. Atorvastatin + Ezetimibe must be discontinued if clinically significant elevation of CPK levels occur or if rhabdomyolysis is diagnosed or suspected.

*Liver Enzyme*
Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Atorvastatin + Ezetimibe should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Liver function tests should be performed before the initiation of treatment and periodically thereafter. If an increase in transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal is recommended.

*Interstitial lung disease*
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. If it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued.

*Diabetes mellitus*
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m$^2$, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

*Lactose*
This formulation contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Effect on Ubiquinone Levels (CoQ10)*
Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed.

*Effects on ability to drive and use machines*
When driving vehicles or operating machines, it should taken into account that dizziness has been reported.

**DRUG INTERACTIONS**
*Erythromycin/Clarithromycin:* Co-administration of atorvastatin and erythromycin or clarithromycin was associated with higher plasma concentrations of atorvastatin. In patients taking clarithromycin the dose of Atorvastatin + Ezetimibe should not exceed 20mg+10mg.

*Protease Inhibitors:* Co-administration of atorvastatin and protease inhibitors was associated with increased plasma concentrations of atorvastatin.

*Itraconazole:* Concomitant administration of atorvastatin (20 to 40mg) and itraconazole (200mg) was associated with an increase in atorvastatin AUC. In patients taking itraconazole the dose of Atorvastatin + Ezetimibe should not exceed 20mg + 10mg.

*Cimetidine:* Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

*Grapefruit Juice:* Concomitant use can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L per day).

*Colestipol:* Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol and atorvastatin were co-administered.

*Cholestyramine:* Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe-glucuronide) approximately 55%.

*Colchicine:* Cases of myopathy have been reported with atorvastatin co-administered with colchicine and caution should be exercised when prescribing Atorvastatin + Ezetimibe with colchicine.

*Inhibitors of Breast Cancer Resistance Protein (BCRP):* Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy; therefore, a dose adjustment of atorvastatin may be necessary.

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

*Boceprevir:* For patients currently taking Atorvastatin + Ezetimibe, the dose of Atorvastatin + Ezetimibe should not exceed a daily dose of 20mg + 10mg during coadministration with boceprevir.

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

*Digoxin:* When multiple doses of digoxin and 10mg atorvastatin were coadministered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

*Oral contraceptives:* Coadministration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethisterone and ethinyl estradiol by approximately 30% and 20%.

**OVERDOSAGE**
In the event of an overdose, symptomatic and supportive measures should be employed. Liver function tests should be performed and serum CPK levels should be monitored.
Due to extensive atorvastatin binding to plasma proteins, haemodialysis 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.
Lipiget EZ (Atorvastatin+Ezetimibe) Tablets 20mg+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:

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