Xerova EZ

Atorvastatin BP & Ezetimibe USP

Composition

Xerova EZ 10/10 mg Tablet: Each film coated tablet contains Atorvastatin Calcium Trihydrate BP equivalent to Atorvastatin 10 mg and Ezetimibe USP 10 mg Tablet

Xerova EZ 20/10 mg Tablet: Each film coated tablet contains Atorvastatin Calcium Trihydrate BP equivalent to Atorvastatin 20 mg and Ezetimibe USP 10 mg Tablet

Pharmacology

Atorvastatin

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; Atorvastatin also reduces LDL production and the number of LDL particles.

Ezetimibe

The molecular target of Ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. 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.

Indication

Xerova EZ is indicated in adults:

• Reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.

• Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments

Dosage & Administration

Route of Administration: Orally.

Swallow **Xerova EZ** tablets whole at any time of day, with or without food.

The dosage range is 10 mg/10 mg to 80 mg/10 mg once daily. Recommended starting dose is 10/10 mg/day or 20/10 mg/day. Recommended starting dose is 40/10 mg/day for patients requiring a greater than 55% reduction in LDL-C.

Contraindication

Atorvastatin and Ezetimibe is contraindicated in patients with:

• Active liver disease or unexplained persistent elevations of hepatic transaminase levels.

• Hypersensitivity to Atorvastatin, Ezetimibe, or any excipients in **Xerova EZ**.

Warning & Precautions

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain CYP3A4 inhibitors, fibric acid derivatives, and cyclosporine. Predisposing factors include advanced age (>65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported.

Liver enzyme abnormalities: Persistent elevations in hepatic transaminase can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.

Side effects

Common adverse reactions (incidence ≥2% and greater than placebo) are: increased ALT, increased AST, and musculoskeletal pain.

Use in Pregnancy and Lactation

Pregnancy: Atorvastatin and Ezetimibe is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid-lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development.

Nursing mothers: It is not known whether Atorvastatin & Ezetimibe is excreted in human milk, but a small amount of another drug in this class does pass into breast milk.

Use in Children & Adolescents

The safety and effectiveness of Atorvastatin and Ezetimibe have not been established in pediatric patients.

Drug Interaction

Other lipid-lowering medications: Use with fenofibrates or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with Atorvastatin and Ezetimibe.

Fenofibrates: Combination increases exposure of Ezetimibe. If cholelithiasis is suspected in a patient receiving Ezetimibe and a fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered.

Cholestyramine: Combination decreases exposure of ezetimibe.

Digoxin: Patients should be monitored appropriately.

Oral contraceptives: Values for norethindrone and ethinyl estradiol may be increased.

Rifampin should be simultaneously coadministered with Atorvastatin and Ezetimibe.

Overdose

No specific treatment of overdosage with Atorvastatin and Ezetimibe can be recommended. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Storage condition

Store below 30°C and dry place, away from light. Keep out of the reach of children.

Commercial pack

Xerova EZ 10/10 mg Tablet:Each commercial box contains 28 tablets in Alu-Alu blister pack.

Xerova EZ 20/10 mg Tablet:Each commercial box contains 28 tablets in Alu-Alu blister pack.

Manufactured By
BEACON®
Pharmaceuticals PLC
Bhaluka, Mymensingh, Bangladesh

LF45601

Xerova

Atorvastatin

COMPOSITION

Xerova 10 Tablet : Each film coated tablet contains Atorvastatin Calcium Trihydrate BP equivalent to Atorvastatin 10 mg.
Xerova 20 Tablet : Each film coated tablet contains Atorvastatin Calcium Trihydrate BP equivalent to Atorvastatin 20 mg.
Xerova 40 Tablet : Each film coated tablet contains Atorvastatin Calcium Trihydrate BP equivalent to Atorvastatin 40 mg.

PHARMACOLOGICAL INFORMATION

Pharmacological Action

Atorvastatin is a liver-selective, competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. It lowers elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and death from coronary heart disease.

Mechanism of Action

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. The HMG-CoA reductase inhibitors can increase plasma HDL levels in some patients, resulting in an additional lowering of risk for CHD. In patients with hypertriglyceridemia, Atorvastatin significantly lowers triglycerides. It is generally accepted that HMG-CoA reductase does not play a direct role in the regulation of triglycerides. Two indirect mechanisms have been suggested to explain the effect of Atorvastatin on triglyceride levels. Substantial reduction of cholesterol synthesis may impair VLDL particle assembly and secretion, resulting in lower triglyceride levels because VLDL transports triglycerides. Marked reductions in hepatic cholesterol levels may lead to increased LDL receptor expression, which in turn causes reductions in triglyceride levels through increased binding of VLDL remnant particles and LDL.

Pharmacokinetic Properties

Absorption: Atorvastatin is rapidly absorbed after oral administration, maximum plasma concentrations occur within 1 to 2h. The extent of absorption increases in proportion to Atorvastatin dose. The absolute bioavailability of Atorvastatin (parent drug) is 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to high pre-systemic 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-Cholesterol reduction is similar whether Atorvastatin is given with or without food.

Distribution: The mean volume of distribution of Atorvastatin is approximately 381 litres. Atorvastatin is 98% bound to plasma proteins. An RBC/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism: In humans, Atorvastatin is extensively metabolized to ortho and para hydroxylated derivatives. In vitro inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of Atorvastatin. Approximately 70% of the HMG-CoA reductase inhibition associated with Atorvastatin has been attributed to its active metabolites. In vitro studies suggest the importance of Atorvastatin metabolism by cytochrome P450 3A4.

Excretion: The mean time of the maximum observed concentration (T_{max}) and elimination half-life ($t_{1/2}$) values are 5.9 h. and 32 h. respectively (with food) and 2.6 h. and 35.7 h. respectively (without food). Biliary excretion is the major route of elimination in humans. Urinary excretion accounts for <5% of the dose.

CLINICAL INFORMATION

Indications

Xerova is indicated as an adjunct to diet to reduce elevated total-C, LDL-C and TG levels in patients with primary hypercholesterolaemia or mixed dyslipidaemia where the primary abnormality is either elevated cholesterol or triglycerides when the response to diet and other non-pharmacological measures are inadequate.
Xerova is also indicated to reduce total-C and LDL-C in patients with heterozygous and homozygous familial hypercholesterolaemia.
Xerova is indicated to increase plasma HDL-C and decrease the LDL-C/HDL-C and total cholesterol/HDL-C ratios.
Xerova is indicated as an adjunct to diet for the treatment of patients with elevated serum triglyceride levels (hypertriglyceridaemia - Fredrickson Type IV) and for the treatment of patients with dysbetalipoproteinaemia who do not respond adequately to diet.
Xerova is indicated for the reduction of cardiac ischaemic events in patients with asymptomatic or mild to moderate symptomatic coronary artery disease with an elevated LDL-cholesterol level.
Xerova has reduced total and LDL-cholesterol concentrations in a few patients with hypercholesterolemia associated with or exacerbated by diabetes mellitus (diabetic dyslipidemia) or renal transplantation. In addition, the drug has reduced total and LDL-cholesterol concentration in hypercholesterolemic patients on peritoneal dialysis or in those with documented atherosclerosis.

Dosage and Administration

Hypercholesterolaemia and Mixed Dyslipidaemia: **Xerova** can be administered within the dosage range of 10-80 mg/day as a single daily dose. Xerova can be taken at any time of the day, with or without food. After initiation or upon titration of Xerova, lipid levels should be re-analysed within 4 weeks and dosage adjusted according to the patient's response.
Primary hypercholesterolaemia and Mixed hyperlipidaemia: The majority of patients are controlled with 10 mg **Xerova** once a day. A therapeutic response is evident within two weeks, and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.
Homozygous Familial Hypercholesterolemia: The usual oral dosage of **Xerova** for the management of homozygous familial hypercholesterolemia is 10-80 mg once daily. The drug may be used as an adjunct to other lipid-lowering therapies or when such therapies are not available.
Hypertriglyceridaemia and Dysbetalipoproteinaemia: The dosage of **Xerova** in this patient group is 10-80 mg daily as a single dose. Doses should be individualized and adjusted according to the patient's response after 4 weeks.

Use in Children

Treatment experience in a pediatric population is limited to doses of Atorvastatin up to 80 mg per day for 1 year in 19 patients (<18 years of age) with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Use in Geriatric Patients

Atorvastatin generally is well tolerated in geriatric patients. The frequency and severity of adverse effects reported in older patients are similar to those in younger adults.

Use in Pregnancy and Lactation

The safety of Atorvastatin in pregnant women has not been established. Currently, most experts recommended that hyperlipoproteinemias in pregnant women be managed with dietary measures since the drug has been shown to be teratogenic in animals and suppression of cholesterol biosynthesis could cause fetal toxicities. It is a drug pregnancy category D. Atorvastatin is distributed into milk. As Atorvastatin has potentially serious adverse reactions in nursing infants, the drug is contraindicated in nursing mother.

Dosage in Patients with Renal Insufficiency

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or on the LDL-C reduction of Atorvastatin, thus no adjustment of the dose is required.

Dosage in Patients with Hepatic Insufficiency

Hepatic Insufficiency: Plasma concentrations of Atorvastatin are markedly increased in patients with chronic alcoholic liver disease. The benefits of therapy should be weighed against the risks when Atorvastatin is to be given to patients with hepatic insufficiency.

Side Effects

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient such as headache, abdominal pain, dyspepsia, nausea, flatulence, constipation, myalgia, insomnia, rhabdomyolysis.

Contraindications

Atorvastatin is contraindicated in active liver disease or unexplained persistent elevations of serum transaminases. It should not be used in patient with hypersensitivity to any component of this medication. It is contraindicated in patient with history of serious adverse reaction to prior administration of HMG-CoA reductase inhibitors. The drug is contraindicated in pregnancy and lactating mother.

Precautions

Liver function tests should be performed before the initiation of treatment and periodically thereafter. **Xerova** should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of Atorvastatin

Interactions

Atorvastatin is metabolised by cytochrome P450 3A4. Based on experience with other HMG-CoA reductase inhibitors caution should be exercised when Atorvastatin is administered with inhibitors of cytochrome P450 3A4 (e.g. cyclosporine, macrolide antibiotics including erythromycin and azole antifungals including itraconazole). The risk of myopathy during treatment with other HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, azole antifungals or niacin. Mibefradil suppress the activity of the liver enzyme cytochrome P450 3A4. So co-administration of Atorvastatin and this drug should be avoided. When multiple doses of Atorvastatin and digoxin were co-administered steady-state plasma digoxin concentrations increased by approximately 20%. Atorvastatin 10 mg has no effect on digoxin levels. Patients taking digoxin should be monitored appropriately. Antacid decreases the plasma concentrations of Atorvastatin approximately 35%. Co-administration with an oral contraceptive containing norethindrone and ethinyl oestradiol increased AUC values for norethindrone and ethinyl oestradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking Atorvastatin. Co-administration of Atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of Atorvastatin.

Overdose and Treatment

There is no specific treatment for Atorvastatin overdosage. If an overdose occurs, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance Atorvastatin clearance.

PHARMACEUTICAL INFORMATION

Storage Condition

Store below 30°C and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Xerova 10 Tablet: Each commercial box contains 28 tablets in Alu-Alu blister pack.
Xerova 20 Tablet: Each commercial box contains 28 tablets in Alu-Alu blister pack.
Xerova 40 Tablet: Each commercial box contains 14 tablets in Alu-Alu blister pack.

Manufactured By
BEACON®
Pharmaceuticals PLC
Bhaluka, Mymensingh, Bangladesh

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