120x260mm

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Lipirex®
(Atorvastatin)

Highnoon

COMPOSITION
Lipirex 10mg Film-coated Tablet:
Each film-coated tablet contains:
Atorvastatin (as calcium trihydrate salt) 10mg
Lipirex 20mg Film-coated Tablet:
Each film-coated tablet contains:
Atorvastatin (as calcium trihydrate salt) 20mg
Lipirex 40mg Film-coated Tablet:
Each film-coated tablet contains:
Atorvastatin (as calcium trihydrate salt) 40mg

DESCRIPTION
Lipirex (atorvastatin calcium trihydrate) is a synthetic lipid lowering agent.

MECHANISM OF ACTION
Atorvastatin is a coenzyme A (HMG-CoA) reductase inhibitor (or statin) is a lipid regulating drug with action on plasma lipid similar to those of simvastatin. 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. Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction.

PHARMACOKINETICS
Atorvastatin is rapidly absorbed from the gastrointestinal tract. It has low absolute bioavailability about 12% due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, its primary site of action. Atorvastatin is metabolized by the cytochrome P450 isoenzyme CYP3A4 to several active metabolites. It is 98% bound to plasma proteins. The mean plasma elimination half-life of atorvastatin is about 14 hours although the half-life of inhibitory activity for HMG-CoA reductase is about 20 to 30 hours due to contribution of the active metabolites. Atorvastatin is excreted as metabolites primarily in the bile.

INDICATIONS AND USAGE
Lipirex is indicated:
- To reduce the risk of:
  - Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD
  - MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD
  - Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD
- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in:
  - Adults with primary hyperlipidemia
  - Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH)
- As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the treatment of adults with:
  - Primary dysbetalipoproteinemia
  - Hypertriglyceridemia

DOSAGE AND ADMINISTRATION
- Take Lipirex orally once daily at any time of the day, with or without food.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating Lipirex, and adjust the dosage if necessary.

Recommended Dosage in Adult Patients
The recommended starting dose is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily. Patients who require reduction in LDL-C greater than 45% may be started at 40 mg once daily.

Recommended Dosage in Pediatric Patients 10 Years of age and older with HeFH.
The recommended starting dose is 10 mg once daily. The dosage range is 10 mg to 20 mg once daily.

Recommended Dosage in Pediatric Patients 10 Years of age and older with HoFH
The recommended starting dose is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily.

Dosage Modifications Due to Drug Interactions
Concomitant use of atorvastatin with the following drugs requires dosage modification;

Anti-Viral Medications
- In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed atorvastatin 20 mg once daily.
- In patients taking nelfinavir, do not exceed atorvastatin 40 mg once daily.

Select Azole Antifungals or Macrolide Antibiotics
- In patients taking clarithromycin or itraconazole, do not exceed atorvastatin 20 mg once daily.

CONTRAINDICATIONS
It is contraindicated in;
- Acute liver failure or decompensated cirrhosis.
- Hypersensitivity to atorvastatin or any excipients of this product. Hypersensitivity reactions, including anaphylaxis, angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported.

WARNINGS AND PRECAUTIONS
Myopathy and Rhabdomyolysis
Atorvastatin may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase (CK) and rhabdomyolysis (with or without acute renal failure secondary to myoglobinuria). Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis in patients treated with statins, including atorvastatin.

Risk factors for Myopathy: Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher atorvastatin dosage.

Steps to prevent or reduce the risk of myopathy and rhabdomyolysis: Atorvastatin exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with atorvastatin is not recommended. Atorvastatin dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin coadministered with lipid-modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of the use of these products outweighs the increased risk of myopathy and rhabdomyolysis.
Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking atorvastatin.
Discontinue atorvastatin if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Muscle symptoms and CK increases may resolve if atorvastatin is discontinued. Temporarily discontinue atorvastatin in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).
Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the atorvastatin dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Immune-Mediated Necrotizing Myopathy
There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persists despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue atorvastatin if IMNM is suspected.

Hepatic Dysfunction
Increases in serum transaminases have been reported with use of atorvastatin. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. There have been rare reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury. Consider liver enzyme testing before atorvastatin initiation and when clinically indicated thereafter. It is contraindicated in patients with acute liver failure or decompensated cirrhosis. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue atorvastatin.

Increases in HbA1c and Fasting Serum Glucose Levels
Increases in HbA1c and fasting serum glucose levels have been reported with statins, including atorvastatin. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

Increased risk of hemorrhagic stroke in patients on atorvastatin 80 mg with recent hemorrhagic stroke
In a post-hoc analysis of the Stroke Prevention by aggressive reduction in cholesterol levels a higher incidence of hemorrhagic stroke was seen as well as the incidence of nonfatal hemorrhagic stroke was also observed in atorvastatin. Consider the risk/benefit of use of atorvastatin 80 mg in patients with recent hemorrhagic stroke.

ADVERSE EVENTS
The reported adverse events are rhabdomyolysis, myopathy, alanine aminotransferase increase, myalgia, diarrhea, arthralgia, abdominal pain, nausea, nasopharyngitis, dyspepsia, increased hepatic enzymes (increased ALT, increased AST), musculoskeletal pain, muscle weakness, muscle spasm, pain in extremity, urinary tract infection insomnia and pharyngeolaryngeal pain.
The additional reported adverse reactions are malaise, pyrexia, abdominal discomfort, flatulence, hepatitis, cholestasis, musculoskeletal pain, muscle fatigue, muscle spasms, neck pain, joint swelling, liver function test abnormal, hyperglycemia, nightmare, epistaxis, urticaria, vision blurred, tinnitus, white blood cells urine positive, anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), myositis, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, pancreatitis, interstitial lung disease, immune mediated necrotizing myopathy, an autoimmune myopathy, proximal muscle weakness, back pain, anorexia, chest pain, hypoglycemia, malaise, peripheral edema, weight gain, gynecomastia, hearing loss and cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion).

DRUG INTERACTIONS
Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with atorvasttain
Atorvastatin is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp, or BCRP). The plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters.

Cyclosporine: Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin and cyclosporine, an inhibitor of CYP3A4 and OATP1B1. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with atorvastatin. The coadministration of atorvastatin with cyclosporine should be avoided.

Gemfibrozil: Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with atorvastatin.

Anti-Viral Medications *(Tipranavir plus ritonavir, glecaprevir plus pibrentasvir, lopinavir plus ritonavir, simeprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir, nelfinavir, and ledipasvir plus sofosbuvir):* Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin with many anti-viral medications, which are inhibitors of CYP3A4 and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2). Cases of myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir plus sofosbuvir with atorvastatin. Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with atorvastatin is not recommended. In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin.In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed atorvastatin 20 mg. In patients taking nelfinavir, do not exceed atorvastatin 40 mg. Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with atorvastatin. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Antifungal or Macrolide Antibiotics *(Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole):* Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin with antifungals or macrolide antibiotics, due to inhibition of CYP3A4 and/or transporters In patients taking clarithromycin or itraconazole, do not exceed atorvastatin 20 mg. Consider the risk/benefit of concomitant use of other azole antifungals or macrolide antibiotics with atorvastatin. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Niacin: Cases of myopathy and rhabdomyolysis have been observed with concomitant use of lipid-modifying dosages of niacin (>1 gram/day niacin) with atorvastatin. Consider if the benefit of using lipid-modifying dosages of niacin concomitantly with atorvastatin outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Fibrates (Other Than Gemfibrozil): Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with atorvastatin. Consider if the benefit of using fibrates concomitantly with atorvastatin outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Grapefruit Juice: Grapefruit juice consumption, especially excessive consumption, more than 1.2 liters/daily, can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis. Avoid intake of large quantities of grapefruit juice, when taking atorvastatin.

Colchicine: Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with atorvastatin. Consider the risk/benefit of concomitant use of colchicine with atorvastatin. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Drug interactions that may decrease exposure to atorvastatin

Rifampin or Other Inducers of Cytochrome P450 3A4:
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 and inhibitors of OATP1B1 can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous coadministration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. Administer atorvastatin and rifampin simultaneously.

Atorvastatin Effects on Other Drugs
Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady state plasma digoxin concentrations increased. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased plasma concentration of norethindrone and ethinyl estradiol. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Coumarin Anticoagulants: If atorvastatin is added to warfarin, a coumarin anticoagulant, the International Normalized Ratio (INR) should be appropriately monitored.

USE IN SPECIFIC POPULATIONS
Pregnancy
Discontinue atorvastatin when pregnancy is recognized. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol. Atorvastatin may cause fetal harm when administered to a pregnant woman. Atorvastatin should be discontinued as soon as pregnancy is recognized. Limited published data on the use of atorvastatin are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage.

Nursing Mother
Atorvastatin is contraindicated during breastfeeding. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. It is not known whether atorvastatin is present in human milk, but it has been shown that another drug in this class passes into human milk. Because of the potential for serious adverse reactions in a breastfed infant, advise women that breastfeeding is not recommended during treatment with atorvastatin.

Females and Males of Reproductive Potential
Contraception
Atorvastatin may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with atorvastatin.

Paediatric Use
The safety and effectiveness of atorvastatin as an adjunct to diet to reduce LDL-C have been established in pediatric patients 10 years of age and older with HeFH. The safety and effectiveness of atorvastatin as an adjunct to other LDL-C-lowering therapies to reduce LDL-C have been established in pediatric patients 10 years of age and older with HoFH. The safety and effectiveness of atorvastatin have not been established in pediatric patients younger than 10 years of age with HeFH or HoFH, or in pediatric patients with other types of hyperlipidemia (other than HeFH or HoFH).

Geriatric Use
No overall differences in safety or effectiveness were observed between these old age and younger population. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin should be prescribed with caution in the elderly.

Hepatic Impairment
Atorvastatin is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels.

Renal Impairment
Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor all patients with renal impairment for development of myopathy. Renal impairment does not affect the plasma concentrations of atorvastatin, therefore there is no dosage adjustment in patients with renal impairment.

OVERDOSAGE
There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Lipirex 10mg Film-coated Tablets:
Alu. PVC. Blister Pack of 1x10's.
Alu. PVC. Blister Pack of 2x7's.
Alu. PVC. Blister Pack of 2x10's.
Lipirex 20mg Film-coated Tablets:
Alu. PVC. Blister Pack of 1x10's.
Alu. PVC. Blister Pack of 2x7's.
Alu. PVC. Blister Pack of 2x10's.
Lipirex 40mg Film-coated Tablets:
Alu. PVC. Blister Pack of 1x10's.
Alu. PVC. Blister Pack of 2x7's.
Alu. PVC. Blister Pack of 2x10's.

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(اے ٹورواسٹیٹن)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14003290