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
Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin can be started simultaneously with diet.
Prevention of Cardiovascular Disease in Adults
- In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, it is indicated to:
  - Reduce the risk of myocardial infarction
  - Reduce the risk of stroke
  - Reduce the risk for revascularization procedures and angina

- In adult patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, it is indicated to:
  - Reduce the risk of myocardial infarction
  - Reduce the risk of stroke

- In adult patients with clinically evident coronary heart disease, it is indicated to:
  - Reduce the risk of non-fatal myocardial infarction
  - Reduce the risk of fatal and non-fatal stroke
  - Reduce the risk for revascularization procedures
  - Reduce the risk of hospitalization for CHF
  - Reduce the risk of angina

Hyperlipidemia
In hyperlipidemia, it is indicated:
As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in adult patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of adult patients with elevated serum TG levels (Fredrickson Type IV);
- For the treatment of adult patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥ 190 mg/dL or
  b. LDL-C remains ≥ 160 mg/dL and:
     - there is a positive family history of premature cardiovascular disease or
     - two or more other CVD risk factors are present in the pediatric patient

Limitations of Use
It has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

DOSAGEAND ADMINISTRATION
Hyperlipidemia and Mixed Dyslipidemia
The recommended starting dose is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. It can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response. After initiation and / or upon titration of atorvastatin, lipid levels should be analysed within 2 to 4 weeks and dosage adjusted accordingly.
Heterozygous familial hypercholesterolemia in pediatric patients (10 years to17 years of age)
The recommended starting dose is 10 mg/day; the usual dose range is 10 to 20 mg orally once daily. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.
Homozygous Familial Hypercholesterolemia
The dosage in patients with HoFH is 10 to 80mg daily. It should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Lipid-lowering Therapy
It may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution.
Dosage in Patients with Renal Impairment
Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary.
Dosage in patients taking cyclosporine, clarithromycin, itraconazole, or certain protease inhibitors
In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor glecaprevir plus pibrentasvir or letermovir when co-administered with cyclosporine, , therapy with atorvastatin should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, elbasvir plus grazoprevir, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir or letermovir, therapy with atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.In patients taking the HIV protease inhibitor nelfinavir therapy with atorvastatin should be limited to 40 mg.

CONTRAINDICATIONS
It is contraindicated in;
- Active liver disease or unexplained persistent elevations of hepatic transaminase levels.
- Hypersensitivity to any component of this medication.
- Atorvastatin is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit of lipid lowering drugs during pregnancy. 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.
- It is not known whether atorvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because of the potential for serious adverse reactions in a nursing infant, women that breastfeeding is not recommended during treatment with atorvastatin.

WARNINGS AND PRECAUTIONS
Myopathy and Rhabdomyolysis
Atorvastatin may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase (CK) above ten times the upper limit of normal) and rhabdomyolysis (with or without acute renal failure secondary to myoglobinuria). Rare fatalities have occurred as a result of rhabdomyolysis with statin use, 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 use of these products outweighs the increased risk of myopathy and rhabdomyolysis.
Concomitant intake of large quantities, more than 1.2 litres 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. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist 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. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.

Liver Enzymes
Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pre-treatment levels without sequelae. It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated. There have been rare reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin. It 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.

Endocrine Function
Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity
CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class.

Use in Patients with Recent Stroke or TIA
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.

ADVERSE EVENTS
The reported adverse events are rhabdomyolysis, myopathy, alanine aminotransferase increase, myalgia, diarrhoea, 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 LIPITOR
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: 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: 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): 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 inhibitor 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.
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
Atorvastatin is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit of lipid lowering drugs during pregnancy. 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
Heterozygous Familial Hypercholesterolemia (HeFH)
The safety and effectiveness of atorvastatin have been established in paediatric patients, 10 years to 17 years of age, with HeFH as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels when, after an adequate trial of diet therapy, the following are present:
- LDL-C ≥ 190 mg/dL, or
- LDL-C ≥ 160 mg/dL and
  - a positive family history of FH, or premature CVD in a first, or second-degree relative, or
  - two or more other CVD risk factors are present.

Advise post menarchal girls of contraception recommendations, if appropriate for the patient.
The long-term efficacy of atorvastatin therapy initiated in childhood to reduce morbidity and mortality in adulthood has not been established.
The safety and efficacy of atorvastatin have not been established in paediatric patients younger than 10 years of age with HeFH.
Homozygous Familial Hypercholesterolemia (HoFH)
Clinical efficacy of atorvastatin with dosages up to 80mg/day has been evaluated.

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.

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

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خوراک و ہدایات:
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بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
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