LIPIDEX

Tablets

Composition

Lipidex 10 mg
Each tablet contains 10 mg Atorvastatin (as calcium).

Lipidex 20 mg
Each tablet contains 20 mg Atorvastatin (as calcium).

Lipidex 40 mg
Each tablet contains 40 mg Atorvastatin (as calcium).

Lipidex 80 mg
Each tablet contains 80 mg Atorvastatin (as calcium).

Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.
The liver is its primary site of action and the principal site of cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) clearance.

In animal models, Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of LDL-C receptors on the cell-surface of liver cells, providing for enhanced uptake and catabolism of LDL-C. Atorvastatin reduces LDL-C production and the number of LDL-C particles. Depending on dose, Atorvastatin reduces the number of apolipoprotein-B-containing particles in patients with hypercholesterolaemia. Atorvastatin produces a profound and sustained increase in LDL-C receptor activity coupled with a change in the quality of circulating LDL-C particles.

Atorvastatin reduces total cholesterol (total-C), LDL-C, apolipoprotein-B in normal volunteers, and in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia, mixed dyslipidaemia, and in some patients with homozygous familial hypercholesterolaemia. It also reduces serum triglycerides (TG) and produces variable increases in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A-1 in non-familial hypercholesterolaemia and mixed dyslipidaemias.

Pharmacokinetics and Metabolism
Absorption: Following oral administration, maximum plasma concentrations occur within 1 to 2 hours. The absolute bioavailability of Atorvastatin (parent substance) 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 Cmax and AUC, LDL-C reduction is similar whether Atorvastatin is given with or without food. Plasma Atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared to morning administration. However, LDL-C reduction is the same regardless of the time of drug administration.

Distribution: Mean volume of distribution of Atorvastatin is approximately 381 liters. Atorvastatin is 98% or more bound to plasma proteins.

Metabolism: Atorvastatin is extensively metabolized by cytochrome P450 3A4 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.

Excretion: Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, it does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of Atorvastatin (parent substance) in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of Atorvastatin is recovered in urine following oral administration.

Special Populations
Geriatric: Plasma concentrations of Atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (65 years and older) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of Lipidex.

Paediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of Atorvastatin in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men; however, there is no clinically significant difference in LDL-C reduction with Lipidex between men and women.

Race: Plasma concentrations of Atorvastatin are similar in black and white subjects.

Indications

- Lipidex is indicated as an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, and triglyceride levels in patients with primary hypercholesterolaemia; mixed dyslipidaemia; and heterozygous familial hypercholesterolaemia.
- Lipidex is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.
- Therapy with lipid-lowering agents should be a component of multiple-risk-factor intervention in individuals at increased risk of atherosclerotic vascular disease due to hypercholesterolaemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other non-pharmacological measures has been inadequate.
- Prior to initiating therapy with Lipidex , secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG.

Contraindications

- Hypersensitivity to any component of this medication.
- Active liver disease or unexplained persistent elevations of serum transaminases
- Atorvastatin is contra-indicated in pregnancy, in breast feeding mothers and in women of childbearing potential not using adequate contraceptive measures. An interval of one month should be allowed from stopping Atorvastatin treatment to conception in the event of planning a pregnancy.

Pregnancy and Lactation
Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers.

Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

Warnings

Liver Effects

Persistent elevations (>3 times the upper limit of normal (ULN) occurring on 2 or more occasions) in serum transaminases occurred in 0,7% of patients who received Atorvastatin in clinical trials. The incidence of these abnormalities was 0,2%, 0,2%, 0,6% and 2,3% for 10, 20, 40 and 80 mg respectively.

It is recommended that liver function tests be performed before the initiation of treatment, following each dosage increase, and periodically thereafter. Liver enzyme changes mostly commence in the first 4 months of treatment with Atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, withdrawal of Atorvastatin is recommended.

Atorvastatin 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 contra-indications to the use of Atorvastatin.

Skeletal Muscle

Rhabdomyolysis with or without renal impairment has been reported with the use of HMG-CoA reductase inhibitors.
Myalgia has been reported in patients treated with Atorvastatin.

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatinine phosphokinase (CPK) values greater than 10 times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.
Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

As with other HMG-CoA reductase inhibitors, the risk of myopathy during treatment with Atorvastatin is increased with concurrent administration of immunosuppressive drugs, including cyclosporine, fibric acid derivatives, nicotinic acid, azole antifungals, or erythromycin.

Atorvastatin therapy should be withdrawn in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Adverse Reactions

Atorvastatin is generally well tolerated. Adverse Reactions have usually been mild and transient. The most frequent adverse effects associated with Atorvastatin therapy, in patients participating in controlled clinical studies were diarrhea, constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, arthralgia, asthenia, insomnia, and rash.

The following side effects have also been reported in clinical trials: muscle cramps, myositis, myopathy, paraesthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, impotence, hyperglycemia and hypoglycemia. Allergic reactions have been reported rarely.
Atorvastatin may cause elevation of creatine phosphokinase and dose-related increases in transaminase levels may occur.

Body as a Whole
Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System
Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis. eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomtatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomtatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System
Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis.

Nervous System
Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, in coordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesis, hypertonia.

Musculoskeletal System
Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages
Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System
Urinary tract infection, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses
Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System
Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. Metabolic and Nutrtional Disorders: Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Post Introduction Reports
Adverse events associated with Atorvastatin that have been received since market introduction, that are not listed above, and that may have causal relationship to drug include the following: angioneurotic edema and rhabdomyolysis.

Precautions

General
Before instituting therapy with Atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems.

Pregnancy
Category X

Nursing Mothers

Because of the potential for adverse reactions in nursing infants, women taking Atorvastatin should not breast-feed.

Pediatric Use
Treatment experience in a pediatric population is limited to doses of Atorvastatin up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age.

Geriatric Use
Treatment experience in adults' age $\geq$ 70 years with doses of Atorvastatin up to 80 mg/day has been evaluated .The safety and efficacy of Atorvastatin in this population were similar to those of patients <70 years of age.

Drug Interactions
As with other HMG-CoA reductase inhibitors, the risk of myopathy during treatment with Atorvastatin is increased with concurrent administration of immunosuppressive drugs, fibric acid derivatives, macrolide antibiotics, e.g. erythromycin, azole antifungals, e.g. clotrimazole, or niacin.

Antacid: Co-administration of an oral antacid suspension containing magnesium and aluminum hydroxides with Atorvastatin decreased plasma concentrations of Atorvastatin approximately 35%; however, LDL-C reduction was not altered.

Antipyrine: Because Atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of Atorvastatin decreased approximately 25% when colestipol and Atorvastatin were co-administered. However, LDL-C reduction was greater when Atorvastatin and colestipol were co-administered than when either drug was given alone.

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

Digoxin: Co-administration of multiple doses of Atorvastatin and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of Atorvastatin increased approximately 40% with co-administration of Atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 .

Oral contraceptives: Co-administration of Atorvastatin and an oral contraceptive increased AUC values of norethindrone and ethinyl estradiol approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking Atorvastatin.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving combined Atorvastatin and warfarin therapy for two weeks. Nevertheless, patients receiving Atorvastatin should be closely monitored when Atorvastatin is combined with warfarin therapy.

Other Concomitant Therapy: In clinical studies, Atorvastatin was used concomitantly with antihypertensive agents and oestrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

Dosage and Administration
The patient should be placed on a standard cholesterol-lowering diet before receiving Lipidex and should continue on this diet during treatment with Lipidex.

The usual starting dose is 10 mg once a day. Doses should be individualized according to the baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should only be made after an interval of 4 weeks or more. The maximum recommended dose is 40 mg once a day. Doses may be given at any time of day with or without food.

Primary Non-familial Hypercholesterolaemia and Combined (Mixed) Hyperlipidemia
The majority of patients are controlled with 10 mg Lipidex once a day. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous Familial Hypercholesterolaemia
Patients should be started with Lipidex 10 mg daily. Doses should be individualized and adjusted every 4 weeks to 40 mg daily. Thereafter, a bile acid sequestrant (e.g. colestipol) may be combined with 40 mg Lipidex.

Homozygous Familial Hypercholesterolaemia
Adults: In a compassionate-use, uncontrolled study of 29 patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of Lipidex , with a mean reduction in LDL-C of 20% (range 7% - 53%), although in some patients an increase of LDL-C occurred.
Children: Treatment experience in the homozygous familial hypercholesterolaemia paediatric population with Lipidex is limited.

Dosage in Patients with Renal Insufficiency
Renal disease has no influence on the plasma concentrations nor lipid effects of Lipidex; thus, no adjustment of dose is required.

Dosage in Patients with Hepatic Dysfunction
In patients with moderate to severe hepatic dysfunction, the therapeutic response to Lipidex is unaffected but serum levels of the drug are greatly increased. In patients with chronic alcoholic liver disease, plasma concentrations of Atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Child-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease. Therefore, caution with dosage should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Over Dosage
There is no specific treatment for Atorvastatin over dosage. 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.

Presentation
Lipidex 10, 20, 40 & 80
Box of 28 tablets