Lipiget™

(ATORVASTATIN)

TABLETS 10mg, 20mg, 40mg

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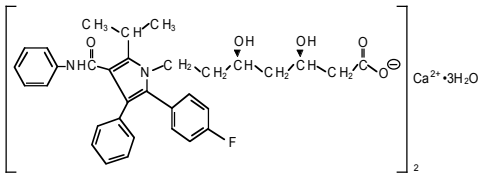
DESCRIPTION

LIPIGET (Atorvastatin) is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Chemically, Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5- (1-methylethyl)-3-phenyl-4[(phenylamino)carbonyl]-1H-pyrrole-1 heptanoic acid, calcium salt (2:1) trihydrate.
The molecular formula is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and the structural formula is:



Atorvastatin calcium trihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

LIPIGET (Atorvastatin) is available for oral administration as:

1. LIPIGET Tablet 10mg
   Each film-coated tablet contains:
   Atorvastatin 10mg
   (as calcium trihydrate salt)

2. LIPIGET Tablet 20mg
   Each film-coated tablet contains:
   Atorvastatin 20mg
   (as calcium trihydrate salt)

3. LIPIGET Tablet 40mg
   Each film-coated tablet contains:
   Atorvastatin 40mg
   (as calcium trihydrate salt)

CLINICAL PHARMACOLOGY

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. The primary site of action of HMG-CoA reductase inhibition is the liver. Inhibition of cholesterol synthesis in the liver leads to upregulation of LDL-receptors and an increase in LDL-catabolism. There is also some reduction of LDL-production as a result of inhibition of hepatic synthesis of very low-density lipoprotein (VLDL), the precursor of LDL-cholesterol. Atorvastatin reduces total cholesterol, LDL-cholesterol and apo B in patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia and mixed dyslipidemias. Ator vastatin also reduces VLDL-cholesterol and triglycerides and produces variable increases in HDL-cholesterol and Apolipoprotein A1.

Pharmacokinetics

Absorption

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. Alth ough 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.

Distribution

Mean volume of distribution of atorvastatin is approximately 381Liters. Atorvastatin is 98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism

Atorvastatin is metabolized by the cytochrome P450 isoenzyme CYP3A4 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 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 to 30 hours due to the contribution of active metabolites.

Special Populations

Geriatric

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects than in young adults. Studies suggest that there is a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger.

Pediatric

Pharmacokinetic data in the pediatric population are not available.

Gender

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction between men and women.

Renal Insufficiency

Renal disease has no influence on the plasma concentr ations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary.

Hepatic Insufficiency

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16- fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease.

THERAPEUTIC INDICATIONS

LIPIGET (Atorvastatin) is indicated:

- As an adjunct to diet to reduce elevated Total-C, LDL-C, Apolipoprotein B, and Triglycerides levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Hyperlipoproteinaemias/Fredrickson Types IIa and IIb).
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (Hypertriglyceridaemia/Fredrickson Type IV).
- For the treatment of patients with primary dysbetalipo proteinemia (Fredrickson Type III) who do not respond adequately to diet.
- To reduce Total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to diet and other non-pharmacological or lipid lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable or inadequate.
- As an adjunct to diet to reduce Total-C, LDL-C, and Apolipoprotein B levels in children with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy LDL-C remains 190mg/dl or LDL-C remains 160mg/dl with positive family history of premature cardiovascular disease and/or two or more other CVD risk factors are present in the pediatric patient.

DOSAGE AND ADMINISTRATION

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

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The recommended starting dose of LIPIGET is 10mg or 20mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40mg once daily. The dosage range of LIPIGET is 10mg to 80mg once daily. LIPIGET can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of LIPIGET should be individualized according to patient characteristics such as goal of therapy and response. After initiation

and/or upon titration of LIPIGET, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Heterozygous Familial Hypercholesterolemia in Children (10-17 years of age)
The recommended starting dose of LIPIGET is 10mg once daily; the maximum recommended dose is 20mg daily. Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolemia
The dosage of LIPIGET in patients with homozygous FH is 10mg to 80mg daily. LIPIGET should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

The following Guidelines may be used to establish treatment goals:

NCEP Guidelines for lipid management

Definite Atherosclerotic Disease*	Two or more other risk factors**	LDL-Cholesterol mg/dL (mmol/L)	
		Initiation Level	Minimum Goal
No	No	≥ 190 (≥ 4.9)	< 160 (< 4.1)
No	Yes	≥ 160 (≥ 4.1)	< 130 (< 3.4)
Yes	Yes or No	≥ 130 (≥ 3.4)	≤ 100 (≤ 2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).
** Other risk factors for coronary heart disease (CHD) include: age (males ≥ 45 years. Females ≥ 55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension, confirmed HDL-C ≤ 35mg/dL (≤ 0.91mmol/l); and diabetes mellitus. Subtract 1 risk factor if HDL-C is > 60mg/dl (≥ 1.6mmol/l).

ADVERSE REACTIONS
Atorvastatin is generally well tolerated. Adverse effects reported commonly include constipation, flatulence, dyspepsia, abdominal pain, headache, dizziness, nausea, myalgia, diarrhoea, asthenia and insomnia, skin rashes, infection.
The following additional adverse effects have been reported very rarely: pancretitis, hepatitis, hypersensitivity syndrome including angioedema, muscle pain or weakness associated with elevated serum CPK levels.

CONTRAINDICATIONS
- Atorvastatin is contraindicated in patients with hypersensitivity to any component of this medication.
- Atorvastatin is also contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases.
- Safety of atorvastatin in pregnancy has not been established, and is contraindicated for use during pregnancy.
- Use of atorvastatin during breast feeding is not recommended, because of the potential for serious adverse effects in nursing infants.

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.

Liver function abnormalities
HMG-CoA reductase inhibitors, like some other lipid lowering therapies, have been associated with biochemical abnormalities of liver function. Liver function tests should be performed before treatment starts, at 6 weeks and 12 weeks after initiation of therapy and any elevation in dose, and periodically thereafter. Liver enzyme changes generally occur in the first three months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should a dose-related and reversible increase in serum ALT or AST of >3 times the upper limit of normal persists; reduction of dose or withdrawal of atorvastatin is recommended. The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have past history of liver disease.

Skeletal Muscle
Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy of 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). Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Pregnancy
Atorvastatin should be administered to women of childbearing age only when such patients are unlikely to conceive and have been informed of the potential hazards. Women of childbearing potential should use adequate contraceptive measures while taking atorvastatin.

Pediatric use
Treatment experience in a pediatric population is limited to doses of atorvastatin upto 80mg daily for 1 year. No clinical and biochemical abnormalities reported in these patients.

Drug Interactions
Cyclosporine, fibric acid derivatives, erythromycin, azole antifungals or niacin:
The risk of myopathy during treatment with drugs belonging to the class of HMG-CoA reductase inhibitors is increased with concurrent administration of these agents.
Antacid: Decreased plasma concentrations of atorvastatin may occur when administered along with an oral antacid suspension containing magnesium and aluminium hydroxides, however LDL-cholesterol reduction is not altered.
Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.
Erythromycin: Plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450.
Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

STORAGE
Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
LIPIGET (Atorvastatin) Tablets 10mg are available in blister pack of 10's.

LIPIGET (Atorvastatin) Tablets 20mg are available in blister pack of 10's.

LIPIGET (Atorvastatin) Tablets 40mg are available in blister pack of 10's.

Keep out of reach of children.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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