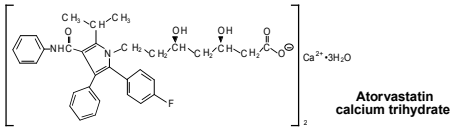
Lipiget™
(ATORVASTATIN)

10mg, 20mg, 40mg Tablets

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 10mg Tablet
   Each film-coated tablet contains:
   Atorvastatin 10mg
   (as atorvastatin calcium trihydrate)
2. LIPIGET 20mg Tablet
   Each film-coated tablet contains:
   Atorvastatin 20mg
   (as atorvastatin calcium trihydrate)
3. LIPIGET 40mg Tablet
   Each film-coated tablet contains:
   Atorvastatin 40mg
   (as atorvastatin calcium trihydrate)

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. Atorvastatin 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. Although 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 in healthy elderly subjects than in young adults. while the lipid effects were comparable to those seen in younger patient populations.

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 concentrations or lipid effects of atorvastatin.

Hepatic Insufficiency
Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

THERAPEUTIC INDICATIONS
Hypercholesterolemia: LIPIGET (Atorvastatin)
indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in adults and children aged 10 years and older with primary hypercholesterolemia, heterozygous familial hypercholesterolemia or combined (mixed) hyperlipidemia when response to diet and other nonpharmacological measures is inadequate.
LIPIGET (Atorvastatin) as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolemia when response to these measures is inadequate.

Prevention of Cardiovascascular Disease: LIPIGET (Atorvastatin) is indicated for the reduction of cardiac ischemic events in patients with asymptomatic or mildly to moderately symptomatic coronary artery disease with a LDL-cholesterol of at least 3.0mmol/L and a triglyceride level of no more than 5.6mmol/L.
LIPIGET (Atorvastatin) is indicated in hypertensive patients with multiple risk factors for coronary heart disease (CHD), which may include diabetes, history of stroke or other cerebrovascular disease, peripheral vascular disease or existing asymptomatic CHD to reduce the risk of non-fatal myocardial infarction and non-fatal stroke.

DOSAGE AND ADMINISTRATION
The patient should be placed on a standard cholesterol-lowering diet before receiving LIPIGET (Atorvastatin) and should continue on this diet during treatment with LIPIGET (Atorvastatin). Doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80mg once a day.
For patients taking interacting drugs that increase plasma exposure to atorvastatin, the starting dose should be 10mg once a day and a maximum dose of less than 80mg may need to be considered. In some cases a dose reduction, or where not practical, a temporary dose suspension may be considered.
Doses above 20mg/day have not been investigated in patients aged <18 years.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia
Adults:
The majority of patients are controlled with 10mg LIPIGET (Atorvastatin) 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.

Children aged 10-17 years:
Doses above 20mg/day have not been investigated.

Heterozygous Familial Hypercholesterolemia
Adults:
Patients should be started with LIPIGET (Atorvastatin) 10mg daily. Doses should be individualized and adjusted every 4 weeks to 40mg daily. Thereafter, either the dose may be increased to a maximum of 80mg daily or a bile acid sequestrant (e.g., colestipol) may be combined with 40mg LIPIGET (Atorvastatin).

Children aged 10-17 years:
Doses above 20mg/day and combination therapies have not been investigated.

Homozygous Familial Hypercholesterolemia
Adults:
In a compassionate-use study of patients with homozygous familial hypercholesterolemia, most patients responded to a dose of 80mg of LIPIGET (Atorvastatin).

Children:
Treatment experience in a pediatric population with doses of LIPIGET (Atorvastatin) up to 80mg/day is limited.

Prevention of Cardiovascular disease
In the primary prevention the dose is 10mg/day. Patients with higher levels will require conventional measurement and dose titration.

Geriatric Use
Adequate treatment experience in adults age 70 or older with doses of LIPIGET (Atorvastatin) up to 80mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population.

The following guidelines may be used to establish treatment goals:

NCEP Treatment Guidelines

LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD* or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129:drug optional)**
2+ Risk factors (10-year risk <20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10% : ≥160
0-1 Risk factor #	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

\# Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

ADVERSE REACTIONS

Atorvastatin is generally well tolerated. Adverse effects reported were:
Common: Constipation, flatulence, dyspepsia, nausea, diarrhea, allergic reactions (including anaphylaxis), insomnia, headache, dizziness, paraesthaesia, hypoesthesia, skin rash, pruritus, myalgia, arthralgia, asthenia, chest pain, back pain, fatigue.

Uncommon: Anorexia, vomiting, pancreatitis, thrombocytopenia, alopecia, hyperglycemia, hypoglycemia, amnesia, peripheral neuropathy, urticaria, alopecia, tinnitus, myopathy, muscle cramps, impotence, malaise, weight gain.

Rare: Hepatitis, cholestatic jaundice, myositis, rhabdomyolysis, peripheral oedema.

Very rare: Dysgeusia, visual disturbance, hepatic failure, angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), hearing loss, tendon rupture, gynecomastia.

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 exceeding 3 times the upper limit of normal.
- 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.
- Atorvastatin is contraindicated in women of child-bearing potential not using appropriate contraceptive measures.

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
Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve. Should an increase in ALT or AST of greater than 3 times the upper limit of normal persist, reduction of dose or 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.

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.

Hemorrhagic Stroke
In a post-hoc analysis of stroke subtypes in patients without CHD who had a recent stroke or TIA there was a higher incidense of hemorrhagic stroke in patients initiated on atorvastatin 80mg compared to placebo. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atrovastatin 80mg is uncertain and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.

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

Drug Interactions

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of *cyclosporin, fibrates, macrolide antibiotics, azole antifungals, HIV-protease inhibitors or naicin* and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria.
Endocrine Function: Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with other drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone and cimetidine.
Clarithromycin: Clarithromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 10mg OD and clarithromycin (500mg BID) resulted in a 4.4 fold increase in atorvastatin AUC. In cases where co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20mg daily. Patients who normally require 40mg or 80mg of atorvastatin should either reduce their dosage during concomitant clarithromycin treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.
Erythromycin: Erythromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 80mg OD and erythromycin (500mg QID) resulted in a 33% increase in exposure to total atorvastatin activity.
Itraconazole: Concomitant administration of atorvastatin 20 to 40mg and itraconazole 200mg daily resulted in a 2.5-3.3 fold increase in atorvastatin AUC. In cases where co-administration of itraconazole with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 40mg daily. Patients who normally require 80mg of atorvastatin should either reduce their dosage during concomitant itraconazole treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.
Protease inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with an approximately two-fold increase in plasma concentrations of atorvastatin.
Diltiazem hydrochloride: Co-administration of atorvastatin 40mg with diltiazem 240mg resulted in a 51% increase in atorvastatin AUC.
Ezetimibe: The use of ezetimibe alone is associated with myopathy. The risk of myopathy may therefore be increased with concomitant use of ezetimibe and atorvastatin.
Grapefruit juice: Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.
Inducers of cytochrome P450 3A4: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin.
Verapamil and Amiodarone: Both verapamil and amiodarone are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.
Oral contraceptives: Administration of atorvastatin with an oral contraceptive containing norethisterone and ethinyl oestradiol produced increases in plasma concentrations of norethisterone and ethinyl oestradiol.
Colestipol: Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were administered together than when either drug was given alone.
Warfarin: Patients receiving warfarin should be closely monitored when Lipiget is added to their therapy.
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.

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) 10mg tablets are available in blister pack of 10's.

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

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

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

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

Manufactured by:

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29-30/27, K.I.A., Karachi, Pakistan

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