PRESCRIBING INFORMATION: For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

LIPICURE-80

(Atorvastatin Calcium Tablets IP 80 mg)

Each film coated tablet contains:
Atorvastatin Calcium IP equivalent to
Atorvastatin 80 mg
Colour : Titanium Dioxide IP
Exciepients : Q.S.

DESCRIPTION
Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3 hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-b, d-dihydroxy-5-(1-methylethyl)-3-phenyl-4 [(phenylamino) carbonyl]-LH-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42.

CLINICAL PHARMACOLOGY
Mechanism of action
Atorvastatin is a selective, competitive inhibitor of HMGCoA reductase enzyme. HMGCoA reductase enzyme is rate-limiting enzyme responsible for the conversion of 3hydroxy-3methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor. Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMGCoA reductase and cholesterol synthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.
Approximately 70% of circulating inhibitory activity for HMGCoA reductase is attributed to active metabolites.

Pharmacokinetics
Absorption and Distribution:
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 (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥ 98% bound to plasma proteins.

Metabolism & Elimination
Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. Ortho- and parahydroxylated metabolites are equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. Atorvastatin metabolized by cytochrome P450 3A4 system.
Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. 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. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

INDICATIONS
Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol and triglycerides in adults and children aged 10 years and older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.

DOSAGE AND ADMINISTRATION
Lipicure 80 should be administered once daily.

CONTRAINDICATIONS
Lipicure is contraindicated in patients with hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal. Lipicure is also contraindicated during pregnancy, breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures.

SIDE EFFECTS
Elevated serum ALT levels have been reported in 1.3% of patients receiving atorvastatin. It is dose related and is reversible. Elevated serum CPK levels >3 times upper normal limit have been reported in 2.5% patients on atorvastatin. Only 0.1% of patients reported muscle pain, tenderness, or weakness.

There may be increased chance of rhabdomylosis when atorvastatin is used along with fenofibrate.

The most frequent adverse events with atorvastatin are myalgia, myopathy, constipation, flatulence, dyspepsia, abdominal pain, insomnia, headache, nausea, flatulence, diarrhoea, and asthenia. Other side effects include back pain, arthralgia, hypoesthesia, allergic reactions (including anaphylaxis), angina, chest pain, dizziness, anorexia, paresthesia, vomiting, alopecia, pruritis, rash, muscle cramps, impotence, thrombocytopenia, weight gain, amnesia, tinnitus, urticaria, malaise, peripheral neuropathy, Pancreatitis, myositis, bullous rashes, peripheral oedema, hypoglycaemia, hyperglycaemia, cholestatic jaundice, hepatitis, myopathy, angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome and rhabdomyolysis

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DRUG INTERACTIONS
The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin and azole antifungals.
Antacid: Administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations approximately 35%; however, LDLC 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 coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.
Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.
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: Erythromycin increased 40 % plasma concentrations of atorvastatin.
Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethidrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

WARNINGS
Liver Dysfunction
It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or elevation in dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 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, 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
Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class.Uncomplicated myalgia has been reported in atorvastatin-treated patients. Atorvastatin therapy should be discontinued if markedly elevated creatine phosphokinase (CPK) levels occur or myopathy is diagnosed or suspected.

PRECAUTIONS

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
Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day.
Nursing mothers
Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin should not breast-feed.
Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose).

OVERDOSE
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.

STORAGE
Store below 25°C, protected from moisture.

PRESENTATION
LIPICURE 80 is available in pack of 10 tablets.

Manufactured by :
INTAS
INTAS PHARMACEUTICALS LTD.
Bhagey Khola, Rangpo, East Sikkim-737132, INDIA
85 687 1 8805575

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