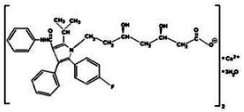
HYPOLIP®

हाइपोलिप

(AtorvastatinCalcium)

DESCRIPTION:

HYPOLIP 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. The empirical formula of atorvastatin calcium is (C33H34 FN2O5)2Ca•3H2O and its molecular weight is 1209.42. Its structural formula is:



CLINICAL PHARMACOLOGY:

Mechanism of Action:

HYPOLIP 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. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk. 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 hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; HYPOLIP also reduces LDL production and the number of LDL particles. HYPOLIP reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s). A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C. HYPOLIP reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. HYPOLIP also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. HYPOLIP reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. HYPOLIP reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacodynamics:

HYPOLIP, 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. Individualization of drug dosage should be based on therapeutic response.

Pharmacokinetics:

Absorption: HYPOLIP is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to HYPOLIP dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% 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 HYPOLIP is given with or without food. Plasma HYPOLIP concentrations are lower (approximately 30% for Cmax 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 HYPOLIP is approximately 381 liters. HYPOLIP is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, Atorvastatin is likely to be secreted in human milk.

Metabolism: HYPOLIP is extensively metabolized 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 HYPOLIP. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of HYPOLIP metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of HYPOLIP in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: HYPOLIP 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 HYPOLIP 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 HYPOLIP is recovered in urine following oral administration.

Specific Populations:

Geriatric: Plasma concentrations of HYPOLIP are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.

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

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

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

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of HYPOLIP since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of HYPOLIP are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11¬ fold increased, respectively, in patients with Childs-Pugh B disease.

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 non-pharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, HYPOLIP can be started simultaneously with diet.

Prevention of Cardiovascular Disease: 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, HYPOLIP is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke • Reduce the risk for revascularization procedures and angina.

In 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, HYPOLIP is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke.
In patients with clinically evident coronary heart disease, HYPOLIP 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: HYPOLIP 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 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 patients with elevated serum TG levels (Fredrickson Type IV); For the treatment of 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 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 boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia 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: HYPOLIP has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

DOSAGE & ADMINISTRATION:
Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb): The recommended starting dose of HYPOLIP 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. The dosage range of HYPOLIP is 10 to 80 mg once daily. HYPOLIP can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of HYPOLIP should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or upon titration of HYPOLIP, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.
Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age): The recommended starting dose of HYPOLIP is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). 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 of HYPOLIP in patients with homozygous FH is 10 to 80 mg daily. HYPOLIP 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: HYPOLIP 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 HYPOLIP; thus, dosage adjustment in patients with renal dysfunction is not necessary.
Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir: In patients taking cyclosporine, therapy should be limited to HYPOLIP 10 mg once daily. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, for doses of HYPOLIP exceeding 20 mg, appropriate clinical assessment is recommended to ensure that the lowest dose necessary of HYPOLIP is employed.

ADVERSE DRUG REACTIONS:
Causes headache, altered liver function test and gastrointestinal effects including nausea, vomiting, diarrhea.Rash and hypersensitivity reaction have been reported rarely. Also angioedema, anorexia, neuropathy, impotence, chest pain, hypoglycemia, hyperglycemia reported.

CONTRAINDICATIONS:
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.
- Hypersensitivity to any component of this medication.
- Pregnancy: Women who are pregnant or may become pregnant. HYPOLIP may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. 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. There are no adequate and well-controlled studies of Atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. HYPOLIP 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, HYPOLIP should be discontinued immediately and the patient apprised of the potential hazard to the fetus.
- Nursing mothers: 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 statins have the potential for serious adverse reactions in nursing infants, women who require HYPOLIP treatment should not breastfeed their infants.

DRUG INTERACTIONS:
The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole).
Strong Inhibitors of CYP 3A4: HYPOLIP is metabolized by cytochrome P450 3A4. Concomitant administration of HYPOLIP with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.
Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of HYPOLIP 80 mg with clarithromycin (500 mg twice daily) compared to that of HYPOLIP alone. Therefore, in patients taking clarithromycin, caution should be used when the HYPOLIP dose exceeds 20 mg.
Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of HYPOLIP 40 mg with ritonavir plus saquinavir (400 mg twice daily) or HYPOLIP 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) compared to that of HYPOLIP alone. Therefore, in patients taking HIV protease inhibitors, caution should be used when the HYPOLIP dose exceeds 20 mg.
Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of HYPOLIP 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, caution should be used when the HYPOLIP dose exceeds 20 mg.
Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).
Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of HYPOLIP 10 mg and cyclosporine 5.2 mg/kg/day compared to that of HYPOLIP alone. In cases where co-administration of HYPOLIP with cyclosporine is necessary, the dose of HYPOLIP should not exceed 10 mg.
Rifampin or other Inducers of Cytochrome P450 3A4: Concomitant administration of HYPOLIP with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of HYPOLIP with rifampin is recommended, as delayed administration of HYPOLIP after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.
Digoxin: When multiple doses of HYPOLIP and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.
Oral Contraceptives: Co-administration of HYPOLIP and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol. These increases should be considered when selecting an oral contraceptive for a woman taking HYPOLIP.
Warfarin: HYPOLIP had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

OVERDOSE:
There is no specific treatment for HYPOLIP 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 HYPOLIP clearance.

PRESENTATION:
HYPOLIP 5:
- Eachfilm tablet contains: Atorvastatin Calcium equivalent to Atorvastatin 5 mg.
  Packaging: 30 Tablets X 5 Blisters

HYPOLIP 10:
- Each film tablet contains: Atorvastatin Calcium equivalent to Atorvastatin 10 mg.
  Packaging: 30 Tablets X 5 Blisters

HYPOLIP 20:
- Each film tablet contains: Atorvastatin Calcium equivalent to Atorvastatin 20 mg.
  Packaging: 30 Tablets X 5 Blisters

HYPOLIP 40:
- Each film tablet contains: Atorvastatin Calcium equivalent to Atorvastatin 40 mg.
  Packaging: 30 Tablets X 5 Blisters

ID: 01 pi HLT 20

Manufactured by:
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