xxxxxxxx-8883

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

MODLIP

(Atorvastatin Calcium Tablets, 10 mg and 20 mg)

COMPOSITION

MODLIP-10: Each film coated tablet contains Atorvastatin calcium equivalent to Atorvastatin 10mg.

MODLIP-20: Each film coated tablet contains Atorvastatin calcium equivalent to Atorvastatin 20mg.

PHARMACOLOGICAL CLASSIFICATION

Serum-cholesterol reducers, HMG-CoA reductase inhibitor.

PHARMACOLOGICAL 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.

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

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 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 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 381litres. Atorvastatin is 98% or more bound to plasma proteins.

Metabolism: Atorvastatin is extensively metabolised 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. 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 C_{max} 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 Atorvastatin.

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

Gender: Plasma concentrations of atorvastatin in women differ however, there is no clinically significant difference in LDL-C reduction with Atorvastatin between men and women.

INDICATIONS

Modlip is indicated as an adjunct to diet to reduce elevated total-cholesterol and triglyceride levels in patients with primary hypercholesterolaemia; and mixed dysbetalipoproteinemia type IIa and type IIb.

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. Safety and efficacy of atorvastatin in children have not yet been established.

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 is higher with 40 and 80mg.

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 creatine phosphokinase (CPK) values greater than 10 times the upper limit of normal, should be considered in any patient with diffuse myalgias, 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, (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

DOSAGE AND ADMINISTRATION

Patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin.

Doses should be individualised 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) Hyperlipidaemia (Type IIA and IIB):

The majority of patients are controlled with 10 mg 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.

Heterozygous Familial Hypercholesterolaemia:

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

Homozygous Familial Hypercholesterolaemia:

The dosage of Atorvastatin in adult patients with homozygous familial hypercholesterolaemia is 10 mg to 80 mg daily.

Dosage in Patients with Renal Insufficiency:

Renal disease has no influence on the plasma concentrations nor lipid effects of Atorvastatin; 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 Atorvastatin 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.

ADVERSE REACTIONS

The most frequent adverse effects associated with Atorvastatin therapy, are diarrhoea, 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, hyperglycaemia and hypoglycaemia. Allergic reactions have been reported rarely.

Atorvastatin may cause elevation of creatine phosphokinase and dose-related increases in transaminase levels may occur.

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 (nicotinic acid).

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

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.

Cholestyramine: No data is available.

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.

OVERDOSAGE

There is no specific treatment for atorvastatin over dosage. In the event of an over dose, the patient should be treated symptomatically, and supportive measures instituted as required.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 30°C, protected from moisture

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

PRESENTATION

MODLIP-10: It is available as white to off white, round, biconvex, beveled edge, film-coated tablets with “10” debossed on one side, in strip of 10 tablets.

MODLIP-20: It is available as white to off white, round, biconvex, beveled edge, film-coated tablets with “20” debossed on one side, in strip of 10 tablets.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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