Lipodar®

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Atorvastatin Calcium

DESCRIPTION:
Lipodar® (as atorvastatin calcium (2:1) 3H2O) is a synthetic lipid lowering agent.
Inactive Ingredients: Magnesium stearate, croscarmellose sodium, hydroxypropylcellulose, lactose, calcium carbonate, polysorbate 80, cellulose, microcrystalline, hypromellose, titanium dioxide, macrogol.

PHARMACOLOGY:
- Atorvastatin is a selective competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.
- Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentration occurs within 1 to 2 hours.
- Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥ 98% bound to plasma proteins.
- Atorvastatin is metabolized by cytochrome P450 3A4 to ortho-and parahydroxylated derivatives and various beta-oxidation products.
- Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20-30 hours due to the contribution of active metabolites.
- Geriatric: Plasma concentrations of atorvastatin and its active metabolites 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: Concentrations of atorvastatin and its active metabolites in women differ from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
- Renal insufficiency: Renal disease has no influence on the plasma concentration or lipid effects of atorvastatin and its active metabolites.
- Hepatic Insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased in patients with chronic alcoholic liver disease.

INDICATIONS:
Lipodar® is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolemia including familial hypercholesterolemia (heterozygous variant) or combined (mixed) hyperlipidemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate.
Lipodar® is also indicated 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.

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

SIDE EFFECTS:
The drug is generally well-tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to the drug.
The most frequent (1% or more) adverse effects associated with therapy in patients participating in controlled clinical studies are constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, asthenia, diarrhea, and insomnia. As with other HMG-CoA reductase inhibitors, elevated serum transaminases have been reported in patients receiving the drug. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (>3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on therapy. These elevations were dose related and were reversible in all patients.
Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on therapy with the drug, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% drug-treated patients. Of these patients, 0.1% had concurrent muscle pain, tenderness, or weakness. The following rare adverse effects have been reported. Not all effects listed have necessarily been associated with drug therapy: myositis, myopathy, rhabdomyolysis, paresthesia, peripheral neuropathy, pancreatits, hepatitis, cholestatic jaundice, anaroxia, vomiting, alopecia, pruritus, rash, Arthralgia, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), impotence, hyperglycemia, hypoglycemia, chest pain, dizziness, thrombocytopenia and allergic reactions including angioneurotic edema.

WARNINGS AND PRECAUTIONS:
- Liver effects: 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 transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of drug is recommended.
  The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
- Skeletal muscle effects: Uncomplicated myalgia, including muscle cramps, has been reported in drug treated patients. The drug therapy should be discontinued if markedly elevated creatine phosphokinase (CPK) levels occur or myopathy is diagnosed or suspected. Patients who develop any signs or symptoms suggestive of myopathy should have CPK levels measured. Should significant increases in CPK (greater than ten times the upper limit of normal) persist, reduction of dose or withdrawal of drug is recommended.
- Pregnancy and lactation: **Lipodar®** is contraindicated in pregnancy and while breast feeding. Women of childbearing potential should use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not yet been proven. There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or fetuses. The development of rat offspring was delayed and post-natal survival reduced during exposures of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure). In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. It is not known whether this drug or its metabolites are excreted in human milk.
- Effects on ability to drive and use machines: There is no pattern of reported adverse events suggesting that patients taking the drug will have any impairment of ability to drive and use hazardous machinery.
- Atorvastatin was not carcinogenic in rats. Atorvastain did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests without metabolic activation and in 1 in vivo assay. In animal studies atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

DRUG INTERACTIONS:
- The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporin, fibric acid derivatives, macrolide antibiotics, including erythromycin, azole antifungals, or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria.
- Atorvastatin is metabolized by cytochrome P450 3A4.
  Based on experience with other HMG-CoA reductase inhibitors, caution should be exercised when the drug is administered with inhibitors of cytochrome P450 3A4 (e.g. cyclosporins, macrolides antibiotic including erythromycin and clarithromycin, and azole antifungals including itraconazole). The effect of inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) on atorvastatin is unknown. The possible interaction with other substrates of this isozyme is unknown but should be considered for other drugs with a narrow therapeutics index, for example, antiarrhythmic agents class III including amiodarone.
- In clinical studies in which the drug was administered with antihypertensives or hypoglycemic agents, no clinically significant interactions were seen.
- Amlodipine: Atorvastatin pharmacokinetics were not altered by the co-administration of atorvastatin 80 mg and amlodipine 10 mg at steady state.
- Erythromycin, Clarithromycin: Co-administration of atorvastatin 10 mg OD and erythromycin (500 mg QID), or atorvastatin 10 mg OD and clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4 were associated with higher plasma concentrations of atorvastatin. Clarithromycin increased the Cmax and AUC of atorvastatin by 56% and 80% respectively.
- Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.
- Oral contraceptives: Co-administeration of the drug with an oral contraceptive produced increases in concentrations of norethindrone and ethinyl estradiol. These increased concentrations should be considered when selecting oral contraceptive doses.
- Colestipol: Plasma concentrations of atorvastatin and its active metabolites were lower (approximately 25%) when colestipol was coadministered with atorvastatin.
  However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.
- Antacid: Co-administration of the drug with an oral antacid suspension containing magnesium and aluminum hydroxides decreased plasma concentration of atorvastatin and its active metabolites approximately 35%. However, LDL-C reduction was not altered.
- Warfarin: Co-administration of the drug and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of treatment. Nevertheless, patients receiving warfarin should be closely monitored when the drug is added to their therapy.
- Phenazone: Co-administration of multiple doses of the drug and phenazone showed little or no detectable effect in the clearance of phenazone.
- Cimetidine: An interaction study with cimetidine and atorvastatin was conducted, and no interaction was seen.

DOSAGE AND ADMINISTRATION:
- The patient should be placed on a standard cholesterol-lowering diet before receiving **Lipodar®** and should continue on this diet during treatment with **Lipodar®**. The usual starting dose is 10 mg once a day. Doses should be individualized 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 80 mg once a day. Doses may be given at any time of a day with or without food.
- Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia: The majority of patients are controlled with 10 mg **Lipodar®** 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.
  For patients with established coronary heart disease or other patients at increased risk of ischemic events, the treatments goal is LDL-C < 3 mmol /L (or < 115 mg/dL) and the total cholesterol < 5mmol (or < 190 mg/dL).
- Heterozygous Familial Hypercholesterolemia: Patients should be started with **Lipodar®** 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum 80 mg daily or a bile acid sequestrant combined with 40 mg **Lipodar®**.
- Homozygous Familial Hypercholestrolemia: In a compassionate-use study of 64 patients, there were 46 patients for whom confirmed LDL receptor information was available. From these 46 patients, the mean percent reduction in LDL-C was approximately 21% . The drug was administered at doses up to 80 mg/day. The dosage of **Lipodar®** in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily. **Lipodar®** should be used as an adjunct to other lipid lowering treatments (eg. LDL apheresis) in these patients or if such treatments are unavailable.
- Dosage in Patients with Renal Insufficiency: Renal disease has no influence on the plasma concentrations nor lipid effects of **Lipodar®**; thus, no adjustment of dose is required.
- Geriatric Use: Efficacy and safety in patients older than 70 using recommended doses is similar to that seen in general population.
- Pediatric Use: Pediatric use should only be carried out by specialist. Experience in pediatrics is limited to a small number of patients (age 4-17 years) with severe dyslipidemias, such as homozygous familial hypercholesterolemia. The recommended starting dose in this population is 10 mg. The dose may be increased to 80 mg daily, according to the response and tolerability. Developmental safety data in this population have not been evaluated.

OVERDOSAGE:
Specific treatment is not available for **Lipodar®** overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests and serum CPK levels should be monitored. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

PRESENTATIONS:
Lipodar® 10 film coated tablets: Packs of 10, 30 tablets. Each tablet contains 10 mg Atorvastatin (as atorvastatin calcium (2:1) 3H2O).
Lipodar® 20 film coated tablets: Packs of 10, 30 tablets. Each tablet contains 20 mg Atorvastatin (as atorvastatin calcium (2:1) 3H2O).
Lipodar® 40 film coated tablets: Packs of 30 tablets. Each tablet contains 40 mg Atorvastatin (as atorvastatin calcium (2:1) 3H2O).
Lipodar® 80 film coated tablets: Packs of 30 tablets. Each tablet contains 80 mg Atorvastatin (as atorvastatin calcium (2:1) 3H2O).

STORAGE CONDITIONS:
Store in a dry place below 25°C.

This is a medicament.
- *Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.*
- *Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold you the medicament.*
- *The doctor and the pharmacist are experts in medicine, its benefits and its risks.*
- *Do not, by yourself, interrupt the period of treatment prescribed.*
- *Do not repeat the same prescription without consulting your doctor.*

Keep medicament out of reach of children

Manufactured by Dar Al Dawa, Na'ur - Jordan

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