TORALAC®

Atorvastatin Calcium

Description:
TORALAC® (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.
Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).
Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis 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.
Atorvastatin has been shown to reduce concentrations of total-cholesterol (30-46%), LDL-cholesterol (41-61%), apolipoprotein B (34-50%), and triglycerides (14-33%) while producing variable increases in HDL-cholesterol and apolipoprotein A_1.
Properties:
Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1-2 hours. Extent of absorption increases in proportion to Atorvastatin dose. After oral administration, Atorvastatin tablets are 95-99% bioavailable. 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 of Atorvastatin is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.
Distribution: Mean volume of distribution of Atorvastatin is approximately 381 liter, and ≥ 98% of it is bound to plasma proteins.
Metabolism: Atorvastatin is metabolized by cytochrome P450 3A4 to ortho-and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation.
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. However, Atorvastatin does not appear to undergo significant enterohepatic recirculation.
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 to 30 hours due to the contribution of active metabolites.
Indications:
• **TORALAC®** is indicated as an adjunct to diet for the reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate.
• **TORALAC®** is also indicated to reduce total-cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.
Dosage and administration:
Patient notes:
1. The patient should be placed on a standard cholesterol-lowering diet before receiving **TORALAC®** and should continue on this diet during treatment.
2. Dosage should be individualized according to baseline LDL-cholesterol levels, the goal of therapy and patient response.
3. The usual starting dose of **TORALAC®** is 10 mg once a day. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose of **TORALAC®** is 80 mg once a day.
4. Each daily dose of **TORALAC®** is given all at once and may be given at any time of the day with or without food.
5. For patients with established coronary heart disease or other patients at increased risk of ischemic events, the treatment goal is LDL-cholesterol < 3 mmol/l (or < 115 mg/dl) and total cholesterol < 5 mmol/l (or < 190 mg/dl).
6. dosage consideration in:
a. 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. Efficacy and safety in patients older than 70 using recommended doses are similar to that seen in the general population.
b. Pediatric: Pharmacokinetic data in the pediatric population for Atorvastatin are not available, and pediatric use should only be carried out by specialists.
Experience in pediatrics is limited to a small number of patients (age 4-17 years) with severe dyslipidemias, such as homozygous familial hypercholesterolaemia. The recommended starting dose in this population is 10 mg of Atorvastatin per day. 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.
c. 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.
d. Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of Atorvastatin and its active metabolites; thus, no adjustment of the dose is required.
e. Hepatic insufficiency: Plasma concentrations of Atorvastatin and its active metabolites are markedly increased in patients with chronic Alcoholic liver disease.
• ***Primary hypercholesterolaemia and combined hyperlipidaemia:*** The majority of patients are controlled with **TORALAC®** 10 my once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.
• ***Heterozygous familial hypercholesterolaemia:*** Patients should be started with **TORALAC®** 10 my daily. Doses should be individualized and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 my daily or a bile acid sequestrant may be combined with 40 mg **TORALAC®** once daily.
• ***Homozygous familial hypercholesterolaemia:*** The dosage of **TORALAC®** in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily. **TORALAC®** should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.
Contraindications:
• Atorvastatin 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 (ULN).
• Myopathy.
• During pregnancy, while breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures.
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 ULN persist, reduction of the 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 effects:** Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterized by markedly elevated creatine phosphokinase (CPK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.
• **Before the treatment:** Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. The CPK level should be measured before starting statin treatment in the following situations:
- Renal impairment.
- Hypothyroidism.
- Personal or familial history of hereditary muscular disorders.
- Previous history of muscular toxicity with a statin or fibrate.
- Previous history of liver disease and/or where substantial quantities of Alcohol are consumed.
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.
In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.
CPK should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK levels are significantly elevated at baseline (> 5 times ULN), treatment should not be started and its levels should be re-measured within 5 to 7 days later to confirm the results.
• **Whilst on treatment:**
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with Atorvastatin, their CPK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CPK levels are elevated to ≤ 5x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK levels return to normal, then re-introduction of Atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Atorvastatin must be discontinued if clinically significant elevation of CPK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.
- Risk of rhabdomyolysis is increased when Atorvastatin is administered concomitantly with certain medicaments such as: Ciclosporin, Erythromycin, Clarithromycin, Itraconazole, Ketoconazole, Nefazodone, Niacin, Gemfibrozil, other Fibric acid derivates or HIV-protease inhibitors.
Patients Notes:
Patients should be aware of the following information:
• Patients should notify their doctor if they have the following symptoms: unusual flitigue or weakness; loss of appetite; upper belly pain; dark-colored urine; or yellowing of the skin or the whites of the eyes.
• Memory loss and confusion have been reported with statin use. These events were generally not serious and went away once the drug was no longer being taken.
• Increases in blood sugar levels with statin use.
Monitoring Liver Enzymes: Liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter.
• **Effects on ability to drive and use machines:** There is no pattern of reported adverse events suggesting that patients taking Atorvastatin will have any impairment of ability to drive and use hazardous machinery.

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Use during pregnancy and lactation:
Pregnancy category **X**
Atorvastatin is contraindicated in pregnancy and while breast feeding. Women of child-bearing 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. The development of rat offspring was delayed and post-natal survival reduced during exposure 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.
Drug interactions:
The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of Ciclosporin, 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. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed.
• Inhibitors of cytochrome P450 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Interaction may occur when Atorvastatin is administered with inhibitors of cytochrome P450 3A4 (e.g. Ciclosporin, macrolide antibiotics including Erythromycin and Clarithromycin, Nefazodone, azole antifungals including Itraconazole and HIV protease inhibitors). Concomitant administration can lead to increased plasma concentrations of Atorvastatin. Therefore, special caution should be exercised when Atorvastatin is used in combination with such drugs.
• Inhibitors of P-glycoprotein: Atorvastatin and Atorvastatin-metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. Ciclosporin) can increase the bioavailability of Atorvastatin.
• Erythromycin, Clarithromycin: Coadministration of Atorvastatin 10 mg once daily and Erythromycin (500 mg, 4 times daily), or Atorvastatin 10 mg once daily and Clarithromycin (500 mg twice daily), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of Atorvastatin. Clarithromycin increased the Cmax and AUG of Atorvastatin by 56% and 80% respectively.
• Itraconazole: Concomitant administration of Atorvastatin 40 mg and Itraconazole 200 mg daily resulted in a 3-fold increase in Atorvastatin AUC.
• Protease inhibitors: Coadministration of Atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of Atorvastatin.
• Grapefruit juice: Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in Atorvastatin AUC of 37% and a decreased AUC of 20.4% for the active orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2 liter daily for 5 days) increased AUC of Atorvastatin 2.5 fold and AUC of active (Atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. Concomitant intake of large quantities of grapefruit juice and Atorvastatin is therefore not recommended.
• Inducers of cytochrome P450 3A4: 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 therapeutic index, for example, antiarrhythmic agents class III including Amiodarone.
• Gemfibrozil / Fibric acid derivatives: The risk of Atorvastatin-induced myopathy may be increased with the concomitant use of Fibric acid derivatives. According to results of in vitro studies the metabolic pathway of Atorvastatin via glucuronidation is inhibited by Gemfibrozil. This may possibly lead to increased plasma levels of Atorvastatin.
• Digoxin: When multiple doses of Digoxin and 10 mg Atorvastatin were coadministered, steady-state plasma Digoxin concentrations were unaffected. However, Digoxin concentrations increased approximately 20% following administration of Digoxin with 80 mg Atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. Patients taking Digoxin should be monitored appropriately.
• Oral contraceptives: Coadministration of Atorvastatin with an oral contraceptive produced increases in plasma concentrations of Norethindrone and Ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.
• Colestipol: Plasma concentrations of Atorvastatin and its active metabolites were lower (by 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: Coadministration of Atorvastatin with an oral antacid suspension containing Magnesium and Aluminum hydroxides decreased plasma concentrations of Atorvastatin and its active metabolites approximately 35%; however, LDL-cholesterol reduction was not altered.
• Warfarin: Coadministration of Atorvastatin and Warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of Atorvastatin treatment. Nevertheless, patients receiving Warfarin should be closely monitored when Atorvastatin is added to their therapy.
• Phenazone: Coadministration of multiple doses of Atorvastatin 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.
• Amlodipine: Atorvastatin pharmacokinetics was not altered by the coadministration of Atorvastatin 80 mg and Amlodipine 10 mg at steady state.
• Other: In clinical studies in which Atorvastatin was administered with antihypertensive or hypoglycaemic agents, no clinically significant interactions were seen.
Side effects:
The most commonly expected side effects are mainly gastrointestinal, including constipation, flatulence, dyspepsia, abdominal pain and usually ameliorate on continued treatment.
Less than 2% of the patients were discontinued from clinical trials due to side effects attributed to Atorvastatin.
Based on data from clinical studies and extensive post-marketing experience, the side effects profile for Atorvastatin is as follows.
Gastrointestinal disorders:
Common: Constipation, flatulence, dyspepsia, nausea, diarrhea.
Uncommon: Anorexia, vomiting.
Blood and lymphatic system disorders:
Uncommon: Thrombocytopenia.
Increased blood sugar and glycosylated hemoglobin (HbAlc) levels has been have been reported with statin use.
Immune system disorders:
Common: Allergic reactions.
Very rare: Anaphylaxis.
Endocrine disorders:
Uncommon: Alopecia, hyperglycaemia, hypoglycaemia, pancreatitis.
Psychiatric:
Common: Insomnia
Uncommon: Amnesia.
Nervous system disorders:
Common: Headache, dizziness, paraesthaesia, hypoesthesia.
Uncommon: Peripheral neuropathy.
Hepato-biliary disorders:
Rare: Hepatitis, cholestatic jaundice.
Skin/Appendages:
Common: Skin rash, pruritus.
Uncommon: Urticaria.
Very rare: Angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).
Ear and Labyrinth disorders:
Uncommon: Tinnitus
Musculoskeletal disorders:
Common: Myalgia, arthralgia.
Uncommon: Mopathy.
Rare: Myositis, rhabdomyolysis.
Reproductive system disorders:
Uncommon: Impotence.
General disorders:
Common: Asthenia, chest pain, back pain, peripheral edema.
Uncommon: Malaise, weight gain.
Information about the potential for generally non serious and reversible cognitive side effects (memory loss, confusion, etc.).
Overdosage:
Specific treatment is not available for Atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CPK levels should be monitored. Due to extensive Atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance Atorvastatin clearance.
Storage conditions:
Store at room temperature (15-30°C).
Presentation:
TORALAC® 10: Each film coated tablet contains Atorvastatin Calcium equivalent to Atorvastatin 10 mg in packs of 30 tablets.
TORALAC® 20: Each film coated tablet contains Atorvastatin Calcium equivalent to Atorvastatin 20 mg in packs of 30 tablets.
TORALAC® 40: Each film coated tablet contains Atorvastatin Calcium equivalent to Atorvastatin 40 mg in packs of 30 tablets.
TORALAC® 80: Each film coated tablet contains Atorvastatin Calcium equivalent to Atorvastatin 80 mg in packs of 30 tablets.
Hospital packs are also available.
Excipients:-
Microcrystalline Cellulose, Lactose, Croscarmellose sodium, Calcium Carbonate, Magnesium Stearate, Opadry & Simethicone Emulsion.

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 the medicament.
· The doctor and the pharmacist are experts in medicine, its benefits and risks.
· Do not by yourself interrupt the period of treatment prescribed for you.
· Do not repeat the same prescription without consulting your doctor.
· Keep medicament out of the reach of children.

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