AtOva®

Atorvastatin
10 mg, 20 mg and 40 mg Tablet

Description

Atova® is a preparation of atorvastatin. Atorvastatin is a member of the drug class of statins, used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, and to prevent cardiovascular disease.

The primary use of atorvastatin is for the treatment of dyslipidemia and the prevention of cardiovascular disease. It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels.

Mode of Action

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 (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. 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 is effective in reducing LDL-C in patients with homozygous familial hypercholesterolemia, a population that has not usually responded to lipid-lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of total-C, LDL-C, apolipoprotein B, and triglycerides while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

Indications

Hypercholesterolemia

Atova® 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 nonpharmacological measures is inadequate.

Atova® 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.

Prevention of cardiovascular disease

Prevention of cardiovascular events in patients estimated to have a high risk for a first or subsequent cardiovascular event, as an adjunct to correction of other risk factors.

Dosage and Administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualized according to baseline LDL-C levels, the goal of therapy and patient response, using current consensus guidelines. Atova® may be given at any time of day, with or without food.

Usual Adult Dose

Primary hypercholesterolemia and Combined (mixed) hyperlipidemia:

Usual dose 10 mg daily; increased if necessary up to 80 mg daily, dose to be increased at intervals of at least 4 weeks.

Heterozygous familial hypercholesterolemia and Homozygous familial hypercholestrolemia:

Initially 10 mg daily for at least 4 weeks, then increased if necessary to 40 mg daily for at least a further 4 weeks, then increased if necessary up to 80 mg daily.

Primary prevention of cardiovascular events in patients at high risk of a first cardiovascular event:

20 mg daily, dose can be increased if necessary.

Secondary prevention of cardiovascular events:

80 mg once daily.

Pediatric Use

Heterozygous familial hypercholesterolemia

Child 10–18 years: Initially 10mg once daily, increased if necessary at intervals of at least 4 weeks to usual max. 20mg once daily.

Homozygous familial hypercholesterolemia

Child 10–18 years: Initially 10mg once daily, increased if necessary at intervals of at least 4 weeks to usual max. 80mg once daily.

Child less than 10 years: Not indicated.

Use in the elderly

Patients >70 years: No dose adjustment necessary.

Renal impairment

In chronic kidney disease, for primary and secondary prevention of cardiovascular events, initially 20 mg once daily, increased if necessary (on specialist advice if eGFR < 30 mL/minute/1.73 m^2); max. 80 mg once daily.

Hepatic impairment

Atova® should be used with caution in patients with hepatic impairment. Atova® is contraindicated in patients with active liver disease.

Contraindications

Atova® is contraindicated:

- in patients with hypersensitivity to atorvastatin or to any of the excipients.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (3 x ULN).
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

Special Warnings and Precautions

Statins should be used with caution in following conditions:

elderly, high alcohol intake, history of liver disease, hypothyroidism, patients at increased risk of muscle toxicity, including myopathy or rhabdomyolysis (e.g. those with a personal or family history of muscular disorders, previous history of muscular toxicity and a high alcohol intake).

Muscle effects:

Muscle toxicity can occur with all statins, however the likelihood increases with higher doses and in certain

patients. Statins should be used with caution in patients at increased risk of muscle toxicity, including those with a personal or family history of muscular disorders, previous history of muscular toxicity, a high alcohol intake, renal impairment or hypothyroidism.

In patients at increased risk of muscle effects, a statin should not usually be started if the baseline creatine kinase concentration is more than 5 times the upper limit of normal (some patients may present with an extremely elevated baseline creatine kinase concentration, for example because of a physical occupation or rigorous exercise—specialist advice should be sought regarding consideration of statin therapy in these patients).

Hypothyroidism:

Hypothyroidism should be managed adequately before starting treatment with a statin.

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

Atova® is metabolized by cytochrome P450 3A4. Concomitant administration of Atova® 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 Atova® 80 mg with clarithromycin (500 mg twice daily) compared to that of Atova® alone. Therefore, in patients taking clarithromycin, caution should be used when the Atova® dose exceeds 20 mg.

Combination of Protease Inhibitors

Atorvastatin AUC was significantly increased with concomitant administration of Atova® with everal combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of Atova® alone.Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of Atova® should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing Atova® and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of Atova® should not exceed 20 mg and should be used with caution. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of Atova® should not exceed 40 mg and close clinical monitoring is recommended.

Itraconazole

Atorvastatin AUC was significantly increased with concomitant administration of Atova® 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, caution should be used when the Atova® 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 Atova® 10 mg and cyclosporine 5.2 mg/kg/day compared to that of Atova® alone.

Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered

with gemfibrozil, concomitant administration of Atova® with gemfibrozil should be avoided.

Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, Atova® should be administered with caution when used concomitantly with other fibrates.

Niacin

The risk of skeletal muscle effects may be enhanced when Atova® is used in combination with niacin; a reduction in Atova® dosage should be considered in this setting.

Rifampin Or Other Inducers Of Cytochrome P450 3A4

Concomitant administration of Atova® 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 Atova® with rifampin is recommended, as delayed administration of Atova® after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Digoxin

When multiple doses of Atova® and digoxin were co-administered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives

Co-administration of Atova® 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 Atova®.

Warfarin

Atova® had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Use during Pregnancy and Lactation

Pregnancy

Pregnancy Category X: Teratogenic effects.

Atorvastatin is contraindicated during pregnancy. Statins should be avoided in pregnancy as congenital anomalies have been reported and the decreased synthesis of cholesterol possibly affects fetal development.

Breastfeeding

Atorvastatin is contraindicated during breastfeeding. It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. Because of the potential for serious adverse reactions, women taking Atorvastatin should not breast-feed their infants.

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment. Statins should be discontinued 3 months before attempting to conceive as congenital anomalies have been reported and the decreased synthesis of cholesterol possibly affects fetal development.

Fertility

In animal studies atorvastatin had no effect on male or female fertility.

Side Effects

Common or very common: Back pain, epistaxis, hyperglycemia, nasopharyngitis, pharyngeolaryngeal pain.

Uncommon

Anorexia, blurred vision, chest pain, hypoglycemia, malaise, neck pain, peripheral edema, pyrexia, tinnitus, weight gain.

Rare

Cholestasis, Hepatitis, jaundice, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Very rare

Gynecomastia, hearing loss, hepatic failure, interstitial lung disease, lupus erythematosus-like reactions, pancreatitis.

Frequency not known

Alopecia, altered liver function tests, amnesia, arthralgia, asthenia, depression, dizziness, fatigue, gastro-intestinal disturbances, headache, hypersensitivity reactions, hyperglycemia - may be associated with the development of diabetes mellitus (particularly in those already at risk of the condition) myalgia, myopathy, myositis, paresthesia, peripheral neuropathy, pruritus, rash, rhabdomyolysis, sexual dysfunction, sleep disturbance, thrombocytopenia, urticarial, visual disturbance.

Muscle effects

The risk of myopathy, myositis, and rhabdomyolysis associated with statin use is rare. Although myalgia has been reported commonly in patients receiving statins, muscle toxicity truly attributable to statin use is rare. Muscle toxicity can occur with all statins, however the likelihood increases with higher doses.

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If muscular symptoms or raised creatine kinase occur during treatment, other possible causes (e.g. rigorous physical activity, hypothyroidism, infection, recent trauma, and drug or alcohol addiction) should be excluded before statin therapy is implicated, particularly if statin treatment has previously been tolerated for more than 3 months. When a statin is suspected to be the cause of myopathy, and creatine kinase concentration is markedly elevated (more than 5 times upper limit of normal), or if muscular symptoms are severe, treatment should be discontinued. If symptoms resolve and creatine kinase concentrations return to normal, the statin should be reintroduced at a lower dose and the patient monitored closely; an alternative statin should be prescribed if unacceptable side-effects are experienced with a particular statin. Statins should not be discontinued in the event of small, asymptomatic elevations of creatine kinase. Routine monitoring of creatine kinase is unnecessary in asymptomatic patients.

Hyperglycemia

Statins should not be discontinued if there is an increase in the blood-glucose concentration or HbA1C as the benefits continue to outweigh the risks. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Interstitial lung disease

If patients develop symptoms such as dyspnoea, cough, and weight loss, they should seek medical attention.

Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance and is unlikely to be of benefit.

Pharmaceutical Precautions

Keep out of the reach of children. Store below 30°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

Commercial Pack

Atova® 10 Tablet: Box containing 30 tablets in 3 x 10's blister strip, each tablet contains Atorvastatin Calcium INN equivalent to Atorvastatin 10 mg.

Atova® 20 Tablet: Box containing 20 tablets in 2 x 10's blister strip, each tablet contains Atorvastatin Calcium INN equivalent to Atorvastatin 20 mg.

Atova® 40 Tablet: Box containing 20 tablets in 2 x 10's blister strip, each tablet contains Atorvastatin Calcium INN equivalent to Atorvastatin 40 mg.

BEXIMCO PHARMA

Manufactured by
BEXIMCO PHARMACEUTICALS LTD.
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