

PACKAGE INSERT TEMPLATE FOR ATORVASTATIN TABLET

Brand or Product Name

[Product name] Tablet 10mg

[Product name] Tablet 20mg

[Product name] Tablet 40mg

[Product name] Tablet 80mg

Name and Strength of Active Substance(s)

Atorvastatin calciummg equivalent to atorvastatin 10mg

Atorvastatin calciummg equivalent to atorvastatin 20mg

Atorvastatin calciummg equivalent to atorvastatin 40mg

Atorvastatin calciummg equivalent to atorvastatin 80mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)

eg White, circular flat beveled edge tablets marked '10' on one side]

Pharmacodynamics

Atorvastatin calcium is a synthetic lipid-lowering agent, which 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.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia, atorvastatin reduces total-C (total cholesterol), LDL-C (low-density lipoprotein cholesterol), and apo B (apolipoprotein B). Atorvastatin also reduces VLDL-C (very-low-density lipoprotein cholesterol) and TG (triglycerides) and produces variable increases in HDL-C (high-density lipoprotein cholesterol).

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 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 in patients with homozygous familial hypercholesterolemia, a population that has not normally responded to lipid-lowering medication.

Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration. Individualization of drug dosage should be based on therapeutic response.

Pharmacokinetics

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within one to two hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared with solutions. The absolute bioavailability of atorvastatin 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 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 with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is $\geq 98\%$ bound to plasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism

Atorvastatin 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 atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In vitro studies also indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Atorvastatin coadministration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by cytochrome P450 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other cytochrome P450 3A4 substrates. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin 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

Elderly - Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy, elderly subjects (aged ≥ 65 years) than in young adults.

Children - Pharmacokinetic studies have not been conducted in the pediatric population.

Gender - Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. However, there were no clinically significant differences in lipid effects between men and women.

Renal Insufficiency - Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. 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 atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency - Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

Indication

Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with

primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia), combined (mixed) hyperlipidemia (*Fredrickson* Types IIa and IIb), elevated serum triglyceride levels (*Fredrickson* Type IV), and for patients with dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet.

Atorvastatin is also indicated for the reduction of total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia when response to diet and other non-pharmacological measures are inadequate.

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, atorvastatin 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, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin 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.

Pediatric Patients (10-17 years of age)

Atorvastatin is indicated 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

Recommended Dosage

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat underlying medical problems. The patient should continue on a standard cholesterol-lowering diet during treatment with atorvastatin. The dosage range is 10 to 80 mg once daily. Doses may be given any time of the day, with or without food. Starting and maintenance dosage should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks, and dosage adjusted accordingly.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia

The majority of patients are controlled with 10 mg atorvastatin once a day. A therapeutic response is evident within two weeks, and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.

Homozygous Familial Hypercholesterolemia

Most patients responded to 80 mg of atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of atorvastatin 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.

Use in Patients with Hepatic Insufficiency

See section Contraindications and Warnings and Precautions.

Use in Patients with Renal Insufficiency

Renal disease has no influence on the plasma concentrations or on the LDL-C reduction with atorvastatin. Thus, no adjustment of the dose is required.

Use in the Elderly

No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Use in Children

Treatment experience in a pediatric population is limited to doses of atorvastatin up to 80mg/day for one year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients.

Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin should be avoided.

In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary employed.

In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

Mode of Administration

Oral

Contraindications

Atorvastatin is contraindicated in patients who have:

- Hypersensitivity to any component of this medication,
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal,

or who are:

Pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. Atorvastatin 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 to the fetus.

Warnings and Precautions

Hepatic Effects

As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin given at doses of 10, 20, 40 and 80 mg.

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve(s). Should an increase in ALT or AST of greater than three times the upper limit of normal persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases.

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 contraindications to the use of atorvastatin.

Skeletal Muscle Effects

Myalgia has been reported in atorvastatin-treated patients. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report 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. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, ~~az~~azole antifungals, colchicines, telaprevir, boceprevir, or the combination of tipranavir/ritonavir. Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. CYP 3A4 is the primary hepatic isozymes known to be involved in the biotransformation of atorvastatin.

Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy (see section Interaction with other medicaments). Atorvastatin may cause an elevation of creatine phosphokinase.

As with other drugs in this class, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. Atorvastatin therapy should be temporarily withheld or discontinued 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, (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Hemorrhagic Stroke

There is higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo. Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke.

Effects on ability to drive and use machines

None known.

Interactions with Other Medicaments

[Specific package insert requirement for statins]

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin or cytochrome P450 3A4 inhibitors (eg erythromycin and azole antifungals).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Transporter Inhibitors

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin.

Erythromycin/Clarithromycin

Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride

Co-administration of atorvastatin (40mg) with diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

Cimetidine

No clinically significant interactions were seen.

Itraconazole

Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC.

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).

Inducers of cytochrome P450 3A

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacids

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

Antipyrene

Because atorvastatin does not affect the pharmacokinetics of antipyrene, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol

Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

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.

Azithromycin

Co-administration of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

Oral Contraceptives

Co-administration with an oral contraceptive containing norethindrone and ethinyl estradiol increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin

No clinically significant interactions were seen.

Amlodipine

Co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

Colchicine

Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Fusidic Acid

Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Other Concomitant Therapy

Atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

Statement on Usage During Pregnancy and Lactation

Atorvastatin is contraindicated in pregnancy. Women of childbearing potential should use adequate contraceptive measures. Atorvastatin 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 to the fetus.

Atorvastatin is contraindicated while breast-feeding. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin should not breast-feed.

Adverse Effects / Undesirable Effects

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient.

Most frequent adverse effects associated with atorvastatin therapy

Infections and infestations: nasopharyngitis

Metabolism and nutrition disorders: hyperglycemia

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis

Gastrointestinal disorders : nausea, diarrhea, dyspepsia, flatulence

Musculoskeletal and connective tissue disorders : arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling

Investigations: liver function test abnormal, blood creatine phosphokinase increased

Additional adverse effects reported with atorvastatin therapy

Psychiatric disorders: nightmare

Eye disorders: vision blurred

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: abdominal discomfort, eructation

Hepatobiliary disorders: hepatitis, cholestasis

Skin and subcutaneous tissue disorders: urticaria

Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain

General disorders and administration site conditions: malaise, pyrexia

Investigations: white blood cells urine positive

Not all effects listed above have been causally associated with atorvastatin therapy.

Pediatric Patients

Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections.

Additional undesirable effects have been reported in post-marketing experience

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: allergic reactions (including anaphylaxis)

Injury, poisoning and procedural complications: tendon rupture

Metabolism and nutrition disorders: weight gain

Nervous system disorders: hypoesthesia, amnesia, dizziness, dysgeusia

Gastrointestinal disorders: Pancreatitis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, bullous rashes

Musculoskeletal and connective tissue disorders: rhabdomyolysis, immune mediated necrotizing myopathy, back pain

General disorders and administration site conditions: chest pain, peripheral edema, fatigue.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been

reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Increases in HbA1c and fasting serum glucose levels have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

Overdose and Treatment

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, 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 atorvastatin clearance.

Storage Conditions

Store below°C

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]