

ATORVAS TABLETS

(Atorvastatin Calcium Tablets)

COMPOSITION

Each film coated tablet contains:

Atorvastatin Calcium
equivalent to Atorvastatin..... 10 mg

Each film coated tablet contains:

Atorvastatin Calcium
equivalent to Atorvastatin..... 20 mg

Each film coated tablet contains:

Atorvastatin Calcium
equivalent to Atorvastatin..... 40 mg

PRODUCT DESCRIPTION

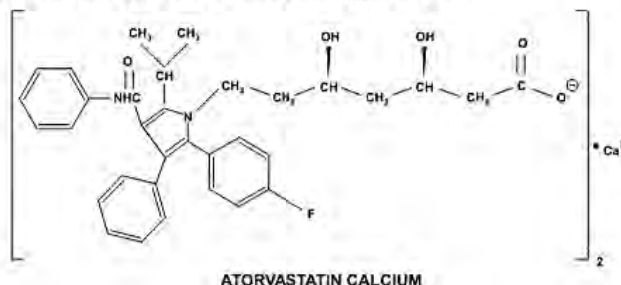
Atorvas Tablet 10mg : White to off-white, film-coated, capsule shaped, biconvex tablets debossed with 'RX 12' on one side and score-line on the other side.

Atorvas Tablet 20mg : White to off-white, film-coated, capsule shaped, biconvex tablets debossed with 'RX 828' on one side and score-line on the other side.

Atorvas Tablet 40mg : White to off-white, film-coated, oval shaped tablets debossed with 'RX 829' on one side and a score-line on the other side.

DESCRIPTION

ATORVAS TABLETS contain atorvastatin calcium. Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin 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. It is chemically designated as [R-(R*,R*)]-2-(4-Fluorophenyl)-[β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The molecular formula of atorvastatin calcium is (C₃₃H₃₄FN₂O₅)₂Ca and molecular weight is 1155.36. The structural formula of atorvastatin calcium is given below.



PHARMACOLOGY

• Mechanism of Action

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. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, 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 to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1.

Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

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

• Pharmacokinetics

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) 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.

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is $\geq 98\%$ bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

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 cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic 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

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥ 65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction 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: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease.

INDICATIONS

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.

DOSAGE AND ADMINISTRATION

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 80mg 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 10mg 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 - In a compassionate-use study of patients with homozygous familial hypercholesterolemia, most patients responded to 80mg of atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).

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.

PRECAUTIONS

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures.

• 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 other underlying medical problems (see **INDICATIONS**).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Children aged 10-17 years

In patients aged <18 years efficacy and safety have not been studied for treatment periods >52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

• Warnings

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g. semiannually) thereafter. Liver enzyme changes generally occur in the first 3 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, reduction of 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. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see **CONTRAINDICATIONS**).

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times 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 report promptly 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, or azole antifungals. 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 or 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. 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.

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).

• Contraindications

Active liver disease or unexplained persistent elevations of serum transaminases.
Hypersensitivity to any component of this medication.

Pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures

• Drug Interactions

The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, azole antifungals, or niacin. This increase in risk may also occur when combining these drugs with atorvastatin.

Phenazone (antipyrine) is a non-specific model for evaluation of drug metabolism by the hepatic microsomal enzyme system. Administration of multiple doses of atorvastatin with phenazone showed little or no detectable effect on the pharmacokinetics of phenazone in healthy subjects (no change in the clearance of phenazone but the formation clearance of 4-hydroxyphenazone increased by 20% and that of norphenazone by 8%).

More specific in vitro studies using human hepatic microsomes and cells expressing human cytochrome P450 isozymes show that atorvastatin, like other HMG-CoA reductase inhibitors, is metabolized by cytochrome P450 3A4 indicating the possibility of an interaction with drugs also metabolized by this isozyme. When combining atorvastatin with other drugs which are the substrate of this isozyme (e.g. immunomodulators, many antiarrhythmic agents, some calcium channel antagonists and some benzodiazepines) the possibility of a change in the plasma drug levels of either drug should be considered. In clinical studies in which atorvastatin was administered with antihypertensives (including ACE inhibitors, beta-blockers, calcium channel antagonists, and diuretics) or hypoglycemic agents no clinically significant interactions were seen.

Based on experience with other HMG-CoA reductase inhibitors caution should also be exercised when atorvastatin is administered with inhibitors of cytochrome P450 3A4 (e. g. certain macrolide antibiotics and azole antifungals). Increases and decreases in plasma phenytoin levels have been reported, but the relationship with atorvastatin is unknown.

Inhibitors of P-glycoprotein: Atorvastatin and atorvastatin metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. cyclosporine) can increase the bioavailability of atorvastatin and thereby increase the risk of dose-related side effects such as myopathy.

Gemfibrozil/fibric acid derivatives: The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse event has been described when fibrates are co-administered with HMG-CoA reductase inhibitors. The risk of atorvastatin induced myopathy may therefore be increased with concomitant use of fibric acid derivatives. Pre-clinical data suggest that gemfibrozil may also interact with atorvastatin by inhibiting its glucuronidation. Co-administration of atorvastatin with fibrates (especially gemfibrozil) should only be undertaken with caution.

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. Patients taking digoxin should be monitored appropriately.

Macrolide antibiotics:

Erythromycin, clarithromycin: Coadministration of atorvastatin and erythromycin (500 mg QID), or clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin.

Azithromycin: Coadministration of atorvastatin (10 mg OD) and azithromycin (500 mg OD) did not alter the plasma concentrations of atorvastatin.

Oral contraceptives: Administration of atorvastatin with an oral contraceptive containing norethisterone and ethinyl estradiol produced increases in plasma concentrations of norethisterone and ethinyl estradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Amlodipine: Atorvastatin pharmacokinetics were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state.

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 administered together than when either drug was given alone.

Antacid: Administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides decreased atorvastatin plasma concentrations approximately 35%; however, LDLC reduction was not altered.

Warfarin: Administration of atorvastatin with warfarin caused a minimal decrease in prothrombin time (mean $\pm$ SE of 1.7 ± 0.4 seconds) during the first 4 days of dosing with 80 mg atorvastatin. Dosing continued for 15 days and prothrombin time returned to normal by the end of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.

Cimetidine: An interaction study with cimetidine and atorvastatin was conducted, and no interaction was seen.

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 ortho-hydroxy metabolite. However, large quantities of grapefruit juice (over 1.2L 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.

Protease inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with an approximately two-fold increase in plasma concentrations of atorvastatin. Consideration should be given to starting atorvastatin at a lower dose when co-administered with a protease inhibitor.

• **Adverse reactions**

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in $\geq 2\%$ of patients and the events in plain type occurred in $< 2\%$ of patients.

Body as a Whole: Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis.

Nervous System: Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: Urinary tract infection, hematuria, albuminuria, urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction Reports

Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following:

anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis and fatigue.

OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, 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

Store below 30°C, protected from moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

JAUHKAN UBAT DARI KANAK-KANAK

SUPPLY

Blister strips of 10's, Box of 10's, Box of 3 x 10's, Box of 10 x 10's

Date of revision : February 2017

Manufactured by:

RANBAXY (MALAYSIA) SDN. BHD.

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