Natrapharm

Atorvastatin calcium

Atorvast-Natrapharm®

20mg film-coated tablet
40mg film-coated tablet
80mg film-coated tablet
Antihyperlipidemic

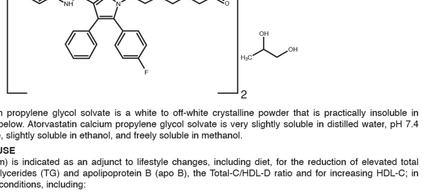
FORMULATION:
Each film-coated tablet contains:
Atorvast-Natrapharm 20 mg: Atorvastatin calcium propylene glycol solvate.....22mg (equivalent to Atorvastatin 20mg)
Atorvast-Natrapharm 40 mg: Atorvastatin calcium propylene glycol solvate.....44mg (equivalent to Atorvastatin 40mg)
Atorvast-Natrapharm 80 mg: Atorvastatin calcium propylene glycol solvate.....88mg (equivalent to Atorvastatin 80mg)

PHARMACEUTICAL INFORMATION
Drug Substance
Proper Name: Atorvastatin Calcium Propylene Glycol Solvate

Chemical Name: (*3R,5R*)-7-[2-(4-Flurophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-yl)-3,5-dihydroxy-1-heptanoic acid,calcium salt (2:1), propylene glycol solvate

Molecular formula and molecular weight: $C_{66}H_{76}CaF_2N_4O_{12}$ and 1231.45 g/mol

Structural Formula:



Description: Atorvastatin calcium propylene glycol solvate is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium propylene glycol solvate is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

INDICATIONS AND CLINICAL USE
Atorvastatin (atorvastatin calcium) is indicated as an adjunct to lifestyle changes, including diet, for the reduction of elevated total cholesterol (total-C), LDL-C, triglycerides (TG) and apolipoprotein B (apo B), the Total-C/HDL-D ratio and for increasing HDL-C; in hyperlipidemic and dyslipidemic conditions, including:

- Primary hypercholesterolemia (Type IIa);
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia,regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV);
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, Atorvastatin should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.
- 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 still present:
  a. LDL-C remains ≥4.9 mmol/L (190 mg/dL) or
  b. LDL-C remains ≥4.1 mmol/L (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.

Prior to initiating therapy with Atorvastatin, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

LDL-C (mmol/L) = total-C - [(0.37 x (TG) + HDL-C)]
LDL-C (mg/dL) = total-C - [(0.2 x (TG) + HDL-C)]

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

Patients with high or very high triglyceride levels, i.e. >2.2 mmol/L (200 mg/dL) or >5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with Atorvastatin.

In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis (see WARNINGS AND PRECAUTIONS, Muscle Effects, Pharmacokinetic Interactions and DRUG INTERACTIONS).

Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small dense LDL particles and low HDL-cholesterol), insulin resistance with or without glucose intolerance, raised blood pressure and prothrombic and proinflammatory states).

When drugs are prescribed attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibers) should always be maintained and reinforced.

Prevention of Cardiovascular Disease
Atorvastatin is indicated to reduce the risk of myocardial infarction in adult hypertensive patients without clinically evident coronary heart disease, but with at least three additional risk factors for coronary heart disease such as age ≥55 years, male sex, smoking, type 2 diabetes, left ventricular hypertrophy, other specified abnormalities on ECG, microalbuminuria or proteinuria, ratio of plasma total cholesterol to HDL-cholesterol ≥6, or premature family history of coronary heart disease.

Atorvastatin is also indicated to reduce the risk of myocardial infarction and stroke in adult patients with type 2 diabetes mellitus and hypertension without clinically evident coronary heart disease, but with other risk factors such as age ≥55 years, retinopathy, albuminuria or smoking.

Atorvastatin is indicated to reduce the risk of myocardial infarction in patients with clinically evident coronary heart disease.

CONTRAINDICATIONS
Hypersensitivity to any component of this medication (for a complete listing of the components, see DOSAGE FORMS, COMPOSITION AND PACKAGING).

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS AND PRECAUTIONS).

Pregnancy and nursing women: Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. If the patient becomes pregnant while taking Atorvastatin, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see PRECAUTIONS - Use in Pregnancy, Use in Nursing Mothers).

WARNINGS AND PRECAUTIONS
General
Before instituting therapy with Atorvastatin (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of Atorvastatin or any other lipid-lowering agents.

Pharmacokinetic Interactions
The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme (see WARNINGS AND PRECAUTIONS, Muscle effects, and DRUG INTERACTIONS).

Muscle Effects
Effects on skeletal muscle such as myalgia, myopathy and rarely, rhabdomyolysis have been reported in patients treated with atorvastatin.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported with atorvastatin and with other HMG-CoA reductase inhibitors.

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine kinase (CK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. Atorvastatin therapy should be discontinued if markedly elevated CK levels are measured or myopathy is diagnosed or suspected.

Pre-disposing Factors for Myopathy/Rhabdomyolysis: Atorvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate, or niacin
- Hypothyroidism
- Alcohol abuse
- Excessive physical exercise
- Age > 65 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of active ingredient may occur.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of drugs that interfere with metabolism of atorvastatin via CYP 3A4, such as cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. Concomitant use of strong inhibitors of CYP 3A4 with atorvastatin should be used with caution. If such use must be instituted, lower starting and maintenance doses of atorvastatin should be considered and patients should be monitored closely for musculoskeletal effects (see Pharmacokinetic Interactions; DRUG INTERACTIONS, Drug-Drug Interactions; DETAILED PHARMACOLOGY, Human Pharmacokinetics).

In cases where co-administration of Atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10mg. Temporary suspension of atorvastatin during fusidic acid therapy is recommended (see DRUG INTERACTIONS, Drug-Drug Interactions).

Although patients with renal impairment are known to be predisposed to the development of rhabdomyolysis with administration of HMG-CoA reductase inhibitors (also known as statins), those with a history of renal impairment may also be predisposed to the development of rhabdomyolysis. Such patients merit close monitoring for skeletal muscle effects.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as sepsis, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Cardiovascular

Hemorrhagic Stroke in Patients with Recent Stroke or Transient Ischemic Attack (TIA)
A post-hoc analysis of a clinical study in 4,731 patients without coronary heart disease (CHD) who had a stroke or TIA within the preceding six months revealed a 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. The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1-6 months) stroke or TIA.

Effect on Ubiquinone (CoQ10) Levels
Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see REFERENCES).

Endocrine and Metabolism

Endocrine Function
HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, 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.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Effect on Lipoprotein (a)
In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy (see REFERENCES).

Patients with Severe Hypercholesterolemia
Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors** (see WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, Muscle Effects; DRUG INTERACTIONS; DOSAGE AND ADMINISTRATION).

Hepatic/Biliary/Pancreatic

Hepatic Effects
In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received atorvastatin. When the dosage of atorvastatin was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of atorvastatin without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

Atorvastatin, as well as other HMG-CoA reductase inhibitors, should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of atorvastatin; if such a condition should develop during therapy, the drug should be discontinued.

Ophthalmologic

Effect on the Lens
Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Renal

Renal Insufficiency
Plasma concentrations and LDL-C lowering efficacy of atorvastatin was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of Atorvastatin should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS AND PRECAUTIONS, Muscle Effects; DRUG INTERACTIONS). Refer also to DOSAGE AND ADMINISTRATION.

Sensitivity/Resistance

Hypersensitivity
An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, Atorvastatin should be discontinued if hypersensitivity is suspected.

Special Populations

Use in Pregnancy: Atorvastatin is contraindicated during pregnancy (see CONTRAINDICATIONS).

Use in Nursing Mothers: In rats, milk concentrations of atorvastatin are similar to those in plasma. 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.

Pediatric Use: Safety and effectiveness of atorvastatin in patients 10-17 years of age (N=140) with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and post-menarchal girls. Patients treated with atorvastatin had a safety and tolerability profile generally similar to that of placebo. Doses greater than 20 mg have not been studied in this patient population.

Safety and effectiveness of atorvastatin in pediatric patients has not been determined in the prevention of myocardial infarction.

Atorvastatin had no effect on growth or sexual maturation in boys and in girls. The effects on menstrual cycle were not assessed [see PHARMACOLOGY, Clinical Studies section; ADVERSE REACTIONS, Pediatric Patients; and DOSAGE AND ADMINISTRATION for Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)].

Adolescent females should be counselled on appropriate contraceptive methods while on Atorvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, Use in Pregnancy). Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.

Doses of atorvastatin up to 80 mg/day for 1 year have been evaluated in 8 pediatric patients with homozygous familial hypercholesterolemia (see Clinical Studies - Heterozygous Familial Hypercholesterolemia in pediatric patients).

Geriatric Use: Treatment experience in adults 70 years or older (N=221) with doses of atorvastatin up to 80 mg/day has demonstrated that the safety and effectiveness of the atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see DETAILED PHARMACOLOGY, Human Pharmacokinetics; REFERENCES).

Elderly patients may be more susceptible to myopathy (see WARNINGS - Muscle Effects - Predisposing Factors for Myopathy/Rhabdomyolysis).

ADVERSE REACTIONS
Adverse reactions with atorvastatin have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin versus 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinue due to adverse reactions compared to 4.0% of the patients on placebo.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of atorvastatin and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

Table 1: Associated Adverse Events Reported in ≥1 % of Patients in Placebo-Controlled Clinical Trials

	Atorvastatin % (n=8755)	Placebo % (n=7311)
Gastrointestinal disorders:		
Diarrhea	6.8	6.3
Dyspepsia	4.6	4.3
Nausea	4.0	3.5
Constipation	3.9	4.3
Flatulence	1.2	1.0
General disorders and administration site conditions:		
Asthenia	1.1	1.1
Infections and Infestations:		
Nasopharyngitis	8.3	8.2
Metabolism and nutrition disorders:		
Liver function test abnormal*	4.1	2.0
Blood creatine phosphokinase increased	1.9	1.8
Hyperglycemia	5.9	5.5
Musculoskeletal and connective tissue disorders:		
Arthralgia	6.9	6.5
Pain in extremity	6.0	5.9
Musculoskeletal Pain	3.8	3.6
Muscle spasms	3.6	3.0
Myalgia	3.5	3.1
Joint swelling	1.3	1.2
Nervous system disorders		
Headache	6.5	6.7
Respiratory, thoracic and mediastinal disorders:		
Pharyngolaryngeal pain	2.3	2.1
Epistaxis	1.2	1.1

*alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, liver function test abnormal and transaminases increased.

The following additional adverse events were reported in placebo-controlled clinical trials during atorvastatin therapy: Muscle cramps, myositis, muscle fatigue, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, cholestasis, anorexia, vomiting, abdominal discomfort, alopecia, pruritus, rash, urticaria, erectile dysfunction, nightmare, vision blurred, tinnitus, eructation, neck pain, malaise, pyrexia and white blood cells urine positive.

In summary, the adverse events occurring at a frequency <1% are listed below:
General disorders and administration site conditions: malaise; pyrexia
Gastrointestinal disorders: abdominal discomfort, eructation
Hepatobiliary disorders: hepatitis, cholestasis
Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain
Psychiatric disorders: nightmare
Skin and subcutaneous tissue disorders: urticaria
Eye disorders: vision blurred
Ear and labyrinth disorders: tinnitus
Investigations: white blood cells urine positive

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (ages 10-17 years):
In a 26-week controlled study in boys and postmenarchal girls (n=187, where 140 patients received atorvastatin), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was similar to that of placebo. The adverse events reported in ≥1% of patients were as follows: abdominal pain, depression and headache (see DETAILED PHARMACOLOGY, Clinical Studies and PRECAUTIONS, Pediatric Use).

Laboratory Changes and Adverse Events
The criteria for clinically significant laboratory changes were >3 X the upper limit of normal (ULN) for liver enzymes, and >5 X ULN for creatine kinase. A total of 8 unique subjects met one or more of these criteria during the double-blind phase. Hence, the incidence of patients who experienced abnormally high enzymatic levels (AST/ALT and creatine kinase) was >4% (8/187).

Five atorvastatin and one placebo subjects had increases in CK >5 X ULN during the double-blind phase; two of the five atorvastatin treated subjects had increases in CK >10 X ULN.

There were 2 subjects who had clinically significant increases in ALT.

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory Tests: Increases in serum transaminase levels and serum glucose have been noted in clinical trials (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions
The following adverse events have also been reported during post-marketing experience with atorvastatin, regardless of causality assessment:

Rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS AND PRECAUTIONS, Muscle Effects, Renal Insufficiency and DRUG INTERACTIONS).

Isolated reports: Gynecomastia, thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), fatigue, back pain, chest pain, malaise, dizziness, amnesia, peripheral edema, weight gain, abdominal pain, insomnia, hypoesthesia, tinnitus, tendon rupture, and dysgeusia.

Opthalmologic observations: see WARNINGS AND PRECAUTIONS.

Cases of erectile dysfunction have been reported in association with the use of statins.

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares;
- Mood related disorders, including depression;
- Very rare cases of interstitial lungs disease, especially with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

DRUG INTERACTIONS
Overview
Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also WARNINGS AND PRECAUTIONS, Special Populations; Renal Insufficiency; Patients with Severe Hypercholesterolemia; Geriatric Use).

Concomitant Therapy with Other Lipid Metabolism Regulators: Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates, and lipid-modifying doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see WARNINGS-Muscle Effects). Therefore, combined drug therapy should be approached with caution; lower starting and maintenance doses of atorvastatin should be considered.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P- 450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), protease inhibitors, or the antidepressant, nefazodone, have the potential to increase plasma concentrations of HMG CoA reductase inhibitors, including atorvastatin (see Drug-Drug Interactions, REFERENCES). Concomitant use of strong inhibitors of CYP 3A4 with atorvastatin should be used with caution. If such use must be instituted, lower starting and maintenance doses of atorvastatin should be considered and patients should be monitored closely for musculoskeletal effects (see WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, Muscle Effects, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; REFERENCES).

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 (see DETAILED PHARMACOLOGY, Human Pharmacokinetics).

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 resulted in a mean increase in C_{max} and AUC of atorvastatin of 12 and 190%, respectively. In contrast, a delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction (approximately 80%) in atorvastatin plasma concentrations.

Drug-Drug Interactions
The drugs listed in this table are based on either drug interactions studies, case reports, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated). Interactions with other drugs have not been established.

Table 2: Established or Potential Drug -Drug Interactions

Proper name	Effect	Clinical comment
Bile Acid Sequestrants	Patients with mild to moderate HC: ↑ LDL-C reduction (-45%) when atorvastatin 10mg and colestipol 20g were coadministered than when either drug was administered alone (-35% for atorvastatin and -22% for colestipol). Patients with severe HC: LDL-C reduction was similar (-53%) when atorvastatin 40mg and colestipol 20g were coadministered when compared to that with atorvastatin 80 mg alone. ↓ plasma concentration (~26%) when atorvastatin 40mg plus colestipol 20g were co-administered compared with atorvastatin 40mg alone. However, the combination drug therapy was less effective in lowering TG than atorvastatin monotherapy in both types of hypercholesterolemic patients.	When atorvastatin is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of atorvastatin may be impaired by the resin.
Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (nicotinic acid)	↑ in the risk of myopathy during treatment with other drugs in this class, including atorvastatin, with concurrent administration with a fibric acid derivative.	Although there is limited experience with the use of atorvastatin given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered (see WARNINGS AND PRECAUTIONS, Muscle Effects and REFERENCES).
Coumarin Anticoagulants	No clinically significant effect on prothrombin time.	Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy. (see REFERENCES)
Digoxin	In healthy subjects, digoxin PK at steady-state were not significantly altered by coadministration of digoxin 0.25mg and atorvastatin 10 mg daily. ↑ in digoxin steady-state concentrations by ~20% following coadministration of digoxin 0.25mg and atorvastatin 80mg daily (see DETAILED PHARMACOLOGY, Human Pharmacokinetics).	Patients taking digoxin should be monitored appropriately.
Antihypertensive Agents: Amlodipine Quinapril	In healthy subjects, atorvastatin PK were not altered by the coadministration of atorvastatin 80mg and amlodipine 10mg at steady state. No apparent changes in BP or HR. Steady-state quinapril dosing of 80 mg QD did not significantly affect the PK profile of atorvastatin tablets 10 mg QD.	see DETAILED PHARMACOLOGY - Human Pharmacokinetics
Oral Contraceptives and Hormone Replacement Therapy	↑ plasma concentrations (AUC levels) of norethindone by ~30% and ethinyl estradiol by ~20% following coadministration of atorvastatin with an oral contraceptive containing 1mg norethindone and 35 µg ethinyl estradiol. In clinical studies, atorvastatin was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.	These increases should be considered when selecting an oral contraceptive.
Antacids	↓ in plasma concentrations of atorvastatin by ~35% following administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension. LDL-C reduction was not altered; TG-lowering effect of atorvastatin may be affected.	

Cimetidine	No effect on plasma concentrations or LDL-C lowering efficacy of atorvastatin ↓ in TG-lowering effect of atorvastatin from 34% to 26%.	
Diltiazem Hydrochloride	Steady-state diltiazem increases the exposure, based on $AUC_{(ATS)ss}$, of a single dose of atorvastatin by approximately 50%.	
Antipyrine	Atorvastatin had no effect on the PK of antipyrine.	Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). Interactions with other drugs metabolized via the same cytochrome isozymes are not expected.
Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin)	In healthy adults, coadministration of atorvastatin (10mg QD) and azithromycin (500mg QD) did not significantly alter the plasma concentrations of atorvastatin.	See WARNINGS AND PRECAUTIONS, Muscle Effects; DETAILED PHARMACOLOGY - Human Pharmacokinetics
Clarithromycin and erythromycin are both CYP3A4 inhibitors	↑ plasma concentration by ~40% with erythromycin (500mg QID) and ~80% with clarithromycin (500mg BID) when coadministered with atorvastatin (10mg QD)	
Protease Inhibitors	↑ plasma concentrations of atorvastatin when atorvastatin 10 mg QD is coadministered with nelfinavir mesylate 1250 mg BID. ↑AUC by 74% and ↑ C_{max} by 122% ↑ AUC by 5.9 fold and ↑ C_{max} by 4.7 fold with atorvastatin 20mg QD and Lopinavir 400mg / Ritonavir 100mg BID* ↑ AUC by 3.9 fold and ↑ C_{max} by 4.3 fold with atorvastatin 40mg QD and Ritonavir 400mg / Saquinavir 400mg BID*	Concomitant use of strong inhibitors of CYP 3A4 with atorvastatin should be used with caution. If such use must be instituted, lower starting and **maintenance doses of atorvastatin should be considered and patients should be monitored closely for musculoskeletal effects**
Cyclosporine	Concomitant administration of atorvastatin 10mg and cyclosporine 5.2mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin.	Concomitant use should be used with caution. In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10mg. See **WARNINGS and PRECAUTIONS** - Muscle Effects; **DETAILED PHARMACOLOGY** - Human Pharmacokinetics
Itraconazole	Concomitant administration of atorvastatin 20-40mg and itraconazole 200mg daily resulted in a 2.5-3.3-fold increase in atorvastatin AUC.	Concomitant use of strong inhibitors of CYP 3A4 with atorvastatin should be used with caution. If such use must be instituted, lower starting and maintenance doses of atorvastatin should be considered and patients should be monitored closely for musculoskeletal effects (see DETAILED PHARMACOLOGY - Human Pharmacokinetics).
Efavirenz	↓ AUC by 41% and ↓ C_{max} by 1% with atorvastatin 10mg and Efavirenz 600mg daily.	
Rifampin	Co-administration*: ↑ AUC by 30% and ↑ C_{max} by 2.7 fold co-administered atorvastatin 40mg single dose and Rifampin 600mg daily. Separate administration* ↓ in AUC by 80% and ↓ C_{max} by 40% with atorvastatin 40mg single dose and Rifampin 600mg daily. (doses separated)	Due to the dual interaction mechanism of rifampin, 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.
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.	Temporary suspension of atorvastatin treatment should be considered (see WARNINGS AND PRECAUTIONS - Muscle Effects).

Legend: HC = hypercholesterolemia; TG = triglycerides; PK = pharmacokinetics; BP = Blood Pressure; HR = Heart Rate; AUC = Area under the curve

* Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

Drug-Food Interactions
Coadministration of grapefruit juice has the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including atorvastatin. The equivalent of 1.2 Litres per day resulted in a 2.5 fold increase in AUC of atorvastatin. Consumption of excessive grapefruit juice with atorvastatin is not recommended.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug/Laboratory Test Interactions
Atorvastatin may elevate serum transaminase and creatine kinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with Atorvastatin, cardiac and noncardiac fractions of these enzymes should be determined.

DOSAGE AND ADMINISTRATION
Patients should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin, and should continue on this diet during treatment with Atorvastatin. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with Atorvastatin, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

Primary Hypercholesterolemia and Combined (Mixed) Dyslipidemia, Including Familial Combined Hyperlipidemia

The recommended starting dose of Atorvastatin is 10 or 20 mg once daily, depending on patient's LDL-C reduction required. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of Atorvastatin is 10 to 80 mg once daily. Doses can be given at any time of the day with or without food, and should preferably be given in the evening. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Adjustments of dosage, if necessary, should be made at intervals of 2 to 4 weeks. The maximum dose is 80 mg/day.

The dosage of Atorvastatin should be individualized according the baseline LDL-C, total-C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest dose needed to achieve LDL-C desired level. Lipid levels should be monitored periodically and, if necessary, the dose of Atorvastatin adjusted based on desired lipid levels recommended by guidelines.

Severe Dyslipidemias
In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS AND PRECAUTIONS, Pharmacokinetics Interactions, Muscle Effects; DRUG INTERACTIONS).

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)
In this population, the recommended starting dose of Atorvastatin is 10 mg/day; the maximum recommended dose is 20mg/day (doses greater than 20 mg/day have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see INDICATIONS AND CLINICAL USE and PHARMACOLOGY, Clinical Studies). Adjustments should be made at intervals of 4 weeks or more.

Prevention of Cardiovascular Disease
Clinical trials conducted that evaluated atorvastatin in the primary prevention of myocardial infarction used a dose of 10 mg atorvastatin once daily. For secondary prevention of myocardial infarction, optimal dosing may range from 10 mg to 80 mg atorvastatin once daily, to be given at the discretion of the prescriber, taking into account the expected benefit and safety considerations relevant to the patient to be treated.

Concomitant Therapy
See DRUG INTERACTIONS.

Dosage in Patients with Renal Insufficiency
See WARNINGS AND PRECAUTIONS.

OVERDOSAGE
There is no specific treatment for atorvastatin over dosage. 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 (See **ADVERSE REACTIONS**).

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY
Mechanism of Action
Atorvastatin is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3- hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of 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 Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

Atorvastatin reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. Atorvastatin also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDL-C and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. Some studies have also shown that the total (TC):HDL-C ratio (TC:HDL-C) is the best predictor of coronary artery disease. In contrast, increased levels of HDL-C are associated with decreased cardiovascular risk. Drug therapies that reduce levels of LDL-C or decrease TG while simultaneously increasing HDL-C have demonstrated reductions in rates of cardiovascular mortality and morbidity.

Pharmacodynamics
The lowering of total cholesterol, LDL-C and ApoB have been shown to reduce the risk of cardiovascular events and mortality.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase. In both subjects and in patients with homozygous and heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia, and dysbetalipoproteinemia, atorvastatin has been shown to reduce levels of total cholesterol (total-C), LDL-C, apo B and total TG, and raises HDL-C levels.

Epidemiologic and clinical studies have associated the risk of coronary artery disease (CAD) with elevated levels of total-C, LDL-C and decreased levels of HDL-C. These abnormalities of lipoprotein metabolism are considered as major contributors to the development of the disease. Like LDL cholesterol-enriched lipoproteins, including VLDL, 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 (metabolic syndrome). Clinical studies have also shown that serum triglycerides can be an independent risk factor for CAD. CAD risk is especially increased if the hypertriglyceridemia is due to increased intermediate density lipoproteins (IDL) or associated with decreased HDL or increased LDL-C. In addition, high TG levels are associated with an increased risk of pancreatitis. Although epidemiological and preliminary clinical evidence link low HDL-C levels and high triglyceride levels with coronary artery disease and atherosclerosis, the independent effect of raising HDL or lowering TG on the risk of coronary and cerebrovascular morbidity and mortality has not been demonstrated in prospective, well controlled outcome studies. Other factors, e.g. interactions between lipids/lipoproteins and endothelium, platelets and macrophages, have also been incriminated in the development of human atherosclerosis and of its complications. Regardless of the intervention used (low fat/ low-cholesterol diet, partial ileal bypass surgery or pharmacologic therapy), effective treatment of hypercholesterolemia/ dyslipidemia has consistently been shown to reduce the risk of CAD.

Atorvastatin reduces LDL-C and the number of LDL particles, lowers Very Low Density Lipoprotein-Cholesterol (VLDL-C) and serum triglyceride, reduces the number of apo B containing particles, and also increases HDL-C. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolemia, a condition that rarely responds to any other lipid-lowering medication. In addition to the above effects, atorvastatin reduces IDL-C and apolipoprotein E (apo E) in patients with dysbetalipoproteinemia (Type III).

In patients with type II hyperlipidemia, atorvastatin improved endothelial dysfunction. Atorvastatin significantly improved flow-mediated endothelium-dependent dilatation induced by reactive hyperemia, as assessed by brachial ultrasound ($p<0.01$).

Pharmacokinetics
Absorption: Atorvastatin is rapidly absorbed after oral administration; maximal plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets are 95-99% bioavailable compared to solutions. The absolute bioavailability (parent drug) of atorvastatin is approximately 12% 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 first-pass metabolism in the liver. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, as assessed by Cmax and AUC respectively, LDL-C reduction and HDL-C elevation are similar when atorvastatin is given with and without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following drug administration in the evening compared with morning dosing. However, LDL-C reduction and HDL-C elevation are the same regardless of the time of drug administration.

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥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.

Metabolism: Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives by cytochrome P-450 3A4 (CYP 3A4) and to various beta-oxidation products. In vitro, inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation. Atorvastatin and its metabolites are eliminated by biliary excretion.

Excretion: Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life for inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations and Conditions
Pediatrics: Assessment of pharmacokinetic parameters such as Cmax, AUC and bioavailability of atorvastatin in pediatric patients (>10 to <17 years old, postmenarche) was not performed during the 6-month, placebo-controlled trial referred to earlier (see Clinical Studies - Heterozygous Familial Hypercholesterolemia in Pediatric Patients and PRECAUTIONS - Pediatric Use).

Geriatrics: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age 65 years or older) compared with younger individuals. LDL-C reduction, however, is comparable to that seen in younger patient populations.

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

Race: Plasma concentrations of atorvastatin are similar in black and white subjects.

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

Renal Insufficiency: Plasma concentrations and LDL-C lowering efficacy of atorvastatin are similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of atorvastatin should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS AND PRECAUTIONS, Muscle Effects; DRUGS INTERACTIONS; DOSAGE AND ADMINISTRATION).

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:
Atorvast-Natrapharm is available in dosage strengths of 20 mg, 40 mg and 80 mg Atorvastatin.

PACKAGING:
Alu-alu blister pack x 10's (Box of 10's and 100's)

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Registration Number: 20mg (DR-XY40121), 40mg (DR-XY40120), 80mg (DR-XY40119)
Date of First Authorization: 20mg, 40mg, 80mg (October 2011)
Revision Date: January 2022

Store at temperatures not exceeding 30°C. Dispense in a tight container. Protect from moisture.

Manufactured by:
Apotex,Inc.
150 Signet Drive,
Toronto, Ontario, Canada

Imported and Repacked for:
Natrapharm, Inc.
The Patriot Building,
SLEX, Sucat, Parañaque City

Repacked by:
Lloyd Laboratories, Inc.
No. 10 Lloyd Ave.,
First Bulacan Industrial City
City of Malolos, Bulacan

IMPORTANT: PLEASE READ

This leaflet is part III of a three-part "Product Monograph" published when atorvastatin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about atorvastatin. Contact your doctor or pharmacist if you/your child have any questions about the drug. Please read this information carefully.

ABOUT THIS MEDICATION: PLEASE READ

What the medication is used for:
Your doctor has prescribed these pills to help lower your cholesterol or other fats in the blood (such as triglycerides) and to prevent cardiovascular disease such as heart attacks. High levels of cholesterol and other fats can cause heart disease by clogging the blood vessels that feed blood and oxygen to the heart.

Children 10-17 years old with heterozygous familial hypercholesterolemia (high cholesterol inherited from one of the parents) and a family history of cardiovascular disease or 2 or more risk factors of cardiovascular disease, as determined by your doctor, can also benefit from taking atorvastatin.

Atorvastatin is just part of the treatment your doctor will plan with you/your child to help keep you healthy. Depending on your/your child's health and lifestyle, your doctor may recommend:

- a change in diet to control weight and reduce cholesterol, reduce intake of saturated fats and increase fiber
- exercise that is right for you/your child
- quitting smoking or avoiding smoky places
- giving up alcohol or drinking less

Follow your doctor's instructions carefully.

What it does:
Atorvastatin belongs to the class of medicines known as "statins", more specifically called HMG-CoA reductase inhibitors. HMG-CoA reductase is an enzyme involve in regulating cholesterol levels in your body. Statins are used along with changes to exercise and diet to help control the amount of cholesterol produced by the body.

Atorvastatin can help your body:

- Decrease LDL (bad) cholesterol, triglyceride levels and other lipids/fats in the blood.
- Increase HDL (good) cholesterol.
- Decrease the Total Cholesterol HDL-Cholesterol Ratio (TC:HDL-C Ratio). This ratio represents the balance between bad and good cholesterol.

Atorvastatin also reduces the risk of heart attacks and strokes in people with multiple risk factors for coronary heart disease such as high blood pressure and diabetes. When used by people who have suffered a heart attack in the past, atorvastatin reduces the risk of having another heart attack.

Atorvastatin is only available by prescription after seeing a doctor.

When it should not be used:
Do not take Atorvastatin if you/your child:

- Are/is allergic to any ingredient of this medication (see what the medicinal ingredient is and what the important non medicinal ingredients are).
- Have active liver disease or unexplained increases in liver enzymes.
- Are/is pregnant or breast-feeding.

What the medicinal ingredient is:
atorvastatin calcium propylene glycol solvate.

What the important nonmedicinal ingredients are:
Atorvastatin tablets contains: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide.

What dosage forms it comes in:
Tablets are available in 4 strengths: 10 mg, 20 mg, 40 mg and 80 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Tell your doctor if you/your child have any muscle pain, tenderness, soreness or weakness during treatment with atorvastatin.

Before using this medicine:
Before taking atorvastatin, tell your doctor or pharmacist if you/your child:

- are/is pregnant, intend to become pregnant. Cholesterol compounds are essential elements for the development of a fetus. Cholesterol-lowering drugs can harm the fetus. Females of child-bearing age should discuss with their doctor the potential hazards to the fetus and the importance of the birth control methods. Atorvastatin should not be used by pregnant women. If you/your child become pregnant, discontinue use immediately and discuss with your doctor.
- are/is breast-feeding or intend to breast-feed. This medicine may be present in breast milk.
- have thyroid problems
- have had a stroke or a mini stroke (TIA)
- regularly drink *three or more* alcoholic drinks daily
- are taking any other cholesterol lowering medication such as fibrates (gemfibrozil, fenofibrate), niacin or ezetimibe
- have a family history of muscular disorders
- had any past problems with the muscles (pain, tenderness), after using an HMG-CoA reductase inhibitor ("statin") such as atorvastatin(Atorvast-Natrapharm), fluvastatin (Lescol®), lovastatin (Mevacor®), pravastatin (Pravacol®), rosuvastatin (Crestor®) or simvastatin (Zocor®) or have developed an allergy or intolerance to them
- have kidney or liver problems
- have diabetes (as the dosage of atorvastatin may need to be adjusted)
- have undergone surgery or other tissue injury
- do excessive physical exercise

Atorvastatin was studied in boys and girls (girls who already started their period) 10-17 years at a dose of 10 and 20mg. Atorvastatin has not been studied in pre-pubertal patients or patients younger than 10 years of age. Adolescent girls should discuss with their doctor the potential hazards to the fetus and importance of birth control while on atorvastatin therapy.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interaction with other drugs is possible. Tell your doctor or pharmacist if you are taking any other medications, including prescription, non-prescription and natural health products. In particular, these drugs may interact with atorvastatin:

- corticosteriods (cortisone-like medicines)
- cyclosporine (SANDIMMUNE®)
- gemfibrozil (LOPID®)
- fenofibrate (LIPIDIL MICRO® or bezafibrate (BEZALIP®)
- lipid-lowering doses of naicin (nicotinic acids)
- erythromycin, clarithromycin or azole antifungal agents (ketoconazole or itraconazole)
- nefazodone (SERZONE®)
- INDINAVIR SULFATE (CRIXIVAN®), nelfinavir mesylate (VIRACEPT®), ritonavir (NORVIR®), saquinavir mesylate (INVIRASE™), lopinavir/ritoavir (e.g. KALETRA®)
- fusidic acid (e.g. FUSIDIN)
- digoxin
- diltiazem
- efavirenz, rifampin
- antacids (frequent use) and atorvastatin should be taken 2 hours apart
- grapefruit juice - especially if ingesting upwards of 1.2 liters of grapefruit juice at once

PROPER USE OF THIS MEDICATION

We often cannot see or feel the problems that high cholesterol causes until a lot of time has passed. That's why it is important to take these pills just as prescribed. You/your child and your doctor will be watching you/your child's cholesterol levels to get them down to a safe range. Here are some important tips.

- Follow the plan that you/your child and your doctor make for diet, exercise and weight control.
- Take atorvastatin as a single dose. It does not matter if atorvastatin is taken with food or without food, but it should not be taken with grapefruit juice. Your doctor will usually tell you/your child to take it in the evenings.
- Do not change the dose unless directed by a doctor.
- If you/your child get sick, have an operation, or need medical treatment, inform your doctor or pharmacist that you/your child are taking atorvastatin.
- If you/your child have to take any other medicine - prescription or non-prescription - while taking atorvastatin, talk to your doctor or pharmacist first.
- If you/your child have to see a different doctor for any reason, be sure to inform him/her that you/your child are/is taking atorvastatin.
- Atorvastatin was prescribed for you/your child only. Don't give these pills to anyone else.

Usual dose:
Adults: The recommended starting dose of atorvastatin is 10 or 20 mg once daily, depending on your required LDL-C reduction. Patients who need a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg once daily. The maximum dose is 80 mg/day.

The recommended dose of atorvastatin is 10 to 80mg/day for people who have already suffered heart attack.

Children (10-17 years old): the recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control center, even if there are no symptoms.

Missed Dose:
if you/your child miss take a pill, take it as soon as possible. But if it is almost time for the next dose, skip the missed dose and just take the next dose. Don't take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most people do not have any problems with side effects when taking this medicine. However, all medicines can cause unwanted side effects. Check with your doctor or pharmacist promptly if any of the following persist or become troublesome:

- constipation/diarrhea/gas
- depression (in children)
- headache
- skin rash
- stomach pain or upset
- vomiting or throwing up

Very rarely, a few people may suffer from jaundice, (which may be manifested by yellowing of the skin and eyes), from a liver condition called hepatitis (inflammation of the liver).

Possible side effects reported with some statins:

- breathing problems including persistent cough and/or shortness of breath or fever.
- cases of erectile dysfunction (difficulty to achieve or maintain an erection)
- sleep disturbances (difficulty sleeping or staying asleep), including insomnia and nightmares
- mood related disorders including depression

This is not a complete list of side effects. If you/your child notice anything unusual or any unexpected effects while taking atorvastatin, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT DO ABOUT THEM

Symptom/Effect		Talk with your doctor or pharmacist		Stop taking the drug and seek emergency medical assistance
		Only if severe	In all cases	
Rare	Muscle pain that you cannot explain		√	
	Muscle tenderness or weakness		√	
	Generalized weakness, especially if you don't feel well		√	
	Brownish or discoloured urine		√	

HOW TO STORE IT

Always keep medicine well out of the reach of children.

Keep atorvastatin at room temperature (15-30°C), away from warm and damp places, like the bathroom or kitchen.

REPORTING SUSPECTED SIDE EFFECTS

You can report any adverse event or questionable efficacy observed in the use of pharmaceutical products to the National Pharmacovigilance Center or Pharmacovigilance units Tel. No.: (02)807-8511 c/o The ADR Unit.

You may also report any suspected adverse reactions associated with the use of the same product to Natrapharm, Inc. through the following:

- Email details to jssandiego@natrapharm.com
- Fax details to (02)821-7383
- Or call us at (02)821-7382

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

The leaflet can also be found at
http://www.apotex.ca/products.

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