PRODUCT MONOGRAPH

Pr APO-ATORVASTATIN

(Atorvastatin Calcium tablets)

10 mg, 20 mg, 40 mg and 80 mg

(Atorvastatin as Atorvastatin Calcium Propylene Glycol Solvate)

LIPID METABOLISM REGULATOR

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Pr APO-ATORVASTATIN
Atorvastatin Calcium Tablets
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets: 10 mg, 20 mg, 40 mg and 80 mg atorvastatin	calcium acetate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium carbonate, titanium dioxide

INDICATIONS AND CLINICAL USE

APO-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), apolipoprotein B (apo B), the Total-C/HDL-C 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, APO-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 APO-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 APO-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
APO-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.

APO-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.

APO-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). APO-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 APO-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 APO-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 APO-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, myositis, 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. APO-ATORVASTATIN therapy should be discontinued if markedly elevated CK levels are measured or myopathy is diagnosed or suspected.

Pre-disposing Factors for Myopathy/Rhabdomyolysis: APO-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, nefazodone, colchicine, hepatitis C protease inhibitors telaprevir, boceprevir, HIV protease inhibitor fosamprenavir and each of the following HIV protease inhibitor combinations: saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir and fosamprenavir plus ritonavir. The combined therapy with APO-ATORVASTATIN and cyclosporine, gemfibrozil, telaprevir or tipranavir plus ritonavir should be avoided. APO-ATORVASTATIN dose restriction or caution is recommended for combined therapy with other CYP 3A4 inhibitors (see Pharmacokinetic Interactions; DRUG INTERACTIONS, Drug-Drug Interactions; DETAILED PHARMACOLOGY, Human Pharmacokinetics).

The concurrent use of atorvastatin and fusidic acid should be avoided, therefore, temporary suspension of atorvastatin during fusidic acid therapy is advised (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.

APO-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).

APO-ATORVASTATIN therapy should be discontinued if markedly elevated CPK levels

occur or myopathy is diagnosed or suspected.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy associated with statin use. IMNM is characterized by:

- proximal muscle weakness and elevated creatine kinase, which persist despite discontinuation of statin treatment
- muscle biopsy showing necrotizing myopathy without significant inflammation
- improvement with immunosuppressive agents.

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 80mg 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 to 6 months) stroke or TIA.

Effect on Ubiquinone (CoQ_{10})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.

Increases in fasting glucose and HbA1c levels have been reported with inhibitors of HMG-CoA reductase as a class. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The benefit of treatment continues to outweigh the

small increased risk. Periodic monitoring of these patients is recommended.

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. **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.**

Liver function tests should be performed before the initiation of treatment, and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with APO-ATORVASTATIN, promptly interrupt therapy. If an alternate etiology is not found, do not restart APO-ATORVASTATIN.

APO-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 APO-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, APO-ATORVASTATIN should be discontinued if hypersensitivity is suspected.

Special Populations

Use in Pregnancy:
APO-ATORVASTATIN is contraindicated during pregnancy (see CONTRAINDICATIONS).

There are no data on the use of atorvastatin during pregnancy. APO-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. If the patient becomes pregnant while taking APO-ATORVASTATIN, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer.

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 APO-ATORVASTATIN should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness of atorvastatin in patients 10 to 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 postmenarchal 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 to 17 years of age)].

Adolescent females should be counselled on appropriate contraceptive methods while on APO-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 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 Lipitor versus 7311 placebo) patients treated for a median period of 53 weeks , 5.2% of patients on atorvastatin discontinued 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 to 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 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, ADVERSE REACTIONS).

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).

There have been rare reports of immune-mediated necrotizing myopathy with statins (see WARNINGS AND PRECAUTIONS – Muscle Effects)s.

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

Ophthalmologic 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 lung disease, especially with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Endocrine disorders: Increases in fasting glucose and HbA1c levels have been reported with APO-ATORVASTATIN.

There have been rare post-marketing 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 non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

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 (see WARNINGS, Muscle Effects; DRUG INTERACTIONS, Drug-Drug Interactions, Table 2 - Established or Potential Drug-Drug Interactions).

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Interaction may occur when APO-ATORVASTATIN is administered with inhibitors of cytochrome P450 3A4 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. Concomitant administration can lead to increased plasma concentrations of atorvastatin. Therefore, special caution should be exercised when atorvastatin is used in combination with such medicinal agents and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed (see WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, Muscle Effects, Renal Insufficiency and Endocrine Function; DRUG INTERACTIONS, Drug-Drug Interactions, Table 2 – Established or Potential Drug-Drug Interactions; 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.

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 10 mg and colestipol 20 g 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 40 mg and colestipol 20 g were coadministered when compared to that with atorvastatin 80 mg alone. ↓ plasma concentration (~26%) when atorvastatin 40 mg plus colestipol 20 g were co-administered compared with atorvastatin 40 mg 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.

Proper name	Effect	Clinical comment
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.	The concomitant therapy with APO-ATORVASTATIN and gemfibrozil should be avoided. The benefits and risks of combined therapy with APO-ATORVASTATIN and fenofibrate, bezafibrate and niacin should be carefully considered; lower starting and maintenance doses of atorvastatin should be 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 0.25 mg and atorvastatin 10 mg daily. ↑ in digoxin steady-state concentrations by ~20% following coadministration of digoxin 0.25 mg and atorvastatin 80 mg daily (see DETAILED PHARMACOLOGY, Human Pharmacokinetics).	Patients taking digoxin should be monitored appropriately.
<u>Antihypertensive Agents</u>: Amlodipine Quinapril	In healthy subjects, atorvastatin PK were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state. No apparent changes in BP or HR. In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no clinical significant change in the AUC (average of 18% increase) or C_{max} or T_{max} of atorvastatin. 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 Close monitoring is required.
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 1 mg norethindone and 35 mcg 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.

Proper name	Effect	Clinical comment
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.	This decrease in exposure should be considered when prescribing atorvastatin with antacids.
Cimetidine	No effect on plasma concentrations or LDL-C lowering efficacy of atorvastatin ↓ in TG-lowering effect of atorvastatin from 34% to 26%	This decrease in TG-lowering should be considered when prescribing atorvastatin with cimetidine.
Diltiazem Hydrochloride	Steady-state diltiazem increases the exposure, based on AUC_{LASTs}, 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). Clarithromycin and erythromycin are both CYP3A4 inhibitors	In healthy adults, coadministration of atorvastatin (10mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. ↑ plasma concentration by ~40% with erythromycin (500 mg QID) and ~80% with clarithromycin (500 mg BID) when coadministered with atorvastatin (10 mg QD)	See WARNINGS AND PRECAUTIONS, Muscle Effects; DETAILED PHARMACOLOGY - Human Pharmacokinetics
Protease Inhibitors (nelfinavir mesylate, lopinavir/ritonavir, tipranavir/ritonavir, telaprevir, boceprevir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, fosamprenavir)	↑ 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 8.4 fold and ↑C_{max} by 7.6 fold with atorvastatin 10mg SD and Tipranavir 500mg	The dose of APO-ATORVASTATIN used in combination with nelfinavir should not exceed 40 mg daily. The concomitant therapy with APO-ATORVASTATIN and the combination of lopinavir plus ritonavir should be used with caution and lowest APO-ATORVASTATIN dose necessary. (See Warnings and Precautions, Muscle Effect) The concomitant therapy with APO-ATORVASTATIN and the

Proper name	Effect	Clinical comment
	BID / Ritonavir 200mg BID, 7 days. Atorvastatin 10 mg SD had no effect on the PK of Tripanavir 500mg BID / Ritonavir 200 mg BID, 7 days* ↑ AUC by 6.9 fold and ↑C_{max} by 9.6 fold with atorvastatin 20mg SD and Telaprevir 750mg q8h, 10 days* ↑ AUC by 2.30 fold and ↑ C_{max} by 2.66 fold with atorvastatin 40mg SD and Boceprevir 800 mg TID, 7 days* ↑ AUC by 2.9 fold and ↑C_{max} by 3.3 fold with atorvastatin 40mg QD for 4 days and Ritonavir 400mg BID, 15 days / Saquinavir 400mg BID*† ↑AUC by 2.4 fold and ↑C_{max} by 1.3 fold with atorvastatin 10mg QD for 4 days and Darunavir 300mg BID/ Ritonavir 100 mg BID, 9 days* ↑ AUC by 1.5 fold and ↑C_{max} by 1.8 fold with atorvastatin 10mg QD for 4 days and Fosamprenavir 700 mg BID/ritonavir 100mg BID,14 days* ↑ AUC by 1.3 fold and ↑C_{max} by 3.0 fold with atorvastatin 10mg QD for 4 days and Fosamprenavir 1400 mg BID, 14 days*. Atorvastatin 10mg QD for 4 days had the following effect on the PK of Fosamprenavir 1400 mg BID, 14 days: ↓AUC by 0.27 fold and ↓C_{max} by 0.18 fold* Atorvastatin 10mg QD, 4 days had noeffect on the PK of Fosamprenavir 700mg BID/ Ritonavir 100 mg BID, 14 days*	combination of tipranavir plus ritonavir or APO-ATORVASTATIN and telaprevir should be avoided. The dose of APO-ATORVASTATIN should be restricted to 20 mg daily when used in combination with boceprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir alone or fosamprenavir plus ritonavir. † The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used
Cyclosporine	Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin.	Concomitant use should be avoided. 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.	The dose of APO-ATORVASTATIN used in combination with itraconazole should not exceed 20 mg daily (see DETAILED PHARMACOLOGY – Human Pharmacokinetics).
Efavirenz	↓ AUC by 41 %and ↓ C_{max} by 1% with atorvastatin 10mg and Efavirenz 600mg daily.	This decrease in exposure should be considered when prescribing atorvastatin with efavirenz.
Rifampin	<u>Co-administration*:</u> Ratios of AUC and C_{max} are 1.12 and 2.9,	Due to the dual interaction mechanism of rifampin (cytochrome

Proper name	Effect	Clinical comment
	respectively, for co-administered atorvastatin 40mg single dose and 7 day Rifampin 600mg daily vs. atorvastatin 40mg single dose alone. Separate administration* ↓ in AUC by 80% and ↓ C_{max} by 40% with atorvastatin 40mg single dose and Rifampin 600mg daily (doses separated)	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.
Fusidic Acid	Although interaction studies with atorvastatin and fusidic acid have not been conducted, rhabdomyolysis resulting in fatal outcome has been reported in patients receiving a combination of statins, including atorvastatin, and fusidic acid. The mechanism of this interaction is not known. .	The concurrent use of atorvastatin and fusidic acid should be avoided. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. Statin therapy may be re-introduced at least seven days after the last dose of fusidic acid. Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. (see WARNINGS AND PRECAUTIONS – Muscle Effects).
Colchicine	Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administrated with colchicine.	Caution should be exercised when prescribing atorvastatin with colchicine. (See Warnings and Precautions, Muscle Effect).

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

APO-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 APO-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 APO-ATORVASTATIN, and should continue on this diet during treatment with APO-ATORVASTATIN. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with APO-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 APO-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 APO-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 to 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 APO-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 APO-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, Pharmacokinetic Interactions, Muscle Effects; DRUG INTERACTIONS).

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

In this population, the recommended starting dose of APO-ATORVASTATIN is 10 mg/day; the maximum recommended dose is 20 mg/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

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

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 (see ADVERSE REACTIONS)

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 increases in proportion to atorvastatin dose. Atorvastatin tablets are 95 to 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 C_{max} 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 C_{max} 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 C_{max}, 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 C_{max} 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 C_{max} 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 C_{max} 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; DRUG INTERACTIONS; DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Store at controlled room temperature 15°C to 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

APO-ATORVASTATIN 10 mg: Each tablet contains 11 mg atorvastatin calcium propylene glycol solvate, equivalent to 10 mg free acid. White, oval, biconvex film-coated tablets. Engraved “APO” on one side, “A10” on the other side.

APO-ATORVASTATIN 20 mg: Each tablet contains 22 mg atorvastatin calcium propylene glycol solvate, equivalent to 20 mg free acid. White, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV20” on the other side.

APO-ATORVASTATIN 40 mg: Each tablet contains 44 mg atorvastatin calcium propylene glycol solvate, equivalent to 40 mg free acid. White, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV40” on the other side.

APO-ATORVASTATIN 80 mg: Each tablet contains 88 mg atorvastatin calcium propylene glycol solvate, equivalent to 80 mg free acid. White, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV80” on the other side.

Tablet Composition

Each tablet contains either 11 mg (or 22 mg, 44 mg or 88 mg) Atorvastatin Calcium Propylene Glycol Solvate, equivalent to 10 mg, 20 mg, 40 mg and 80 mg free acid respectively, as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium acetate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium carbonate, titanium dioxide.

APO-ATORVASTATIN is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

Packaging

10 mg: Available in bottles of 90, 100, 500, and 1000 tablets, blisters of 30.
20 mg: Available in bottles of 90, 100, 500, and 1000 tablets, blisters of 30.
40 mg: Available in bottles of 90, 100, 500, and 1000 tablets, blisters of 30.
80 mg: Available in bottles of 90, 100 and 500 tablets, blisters of 30.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

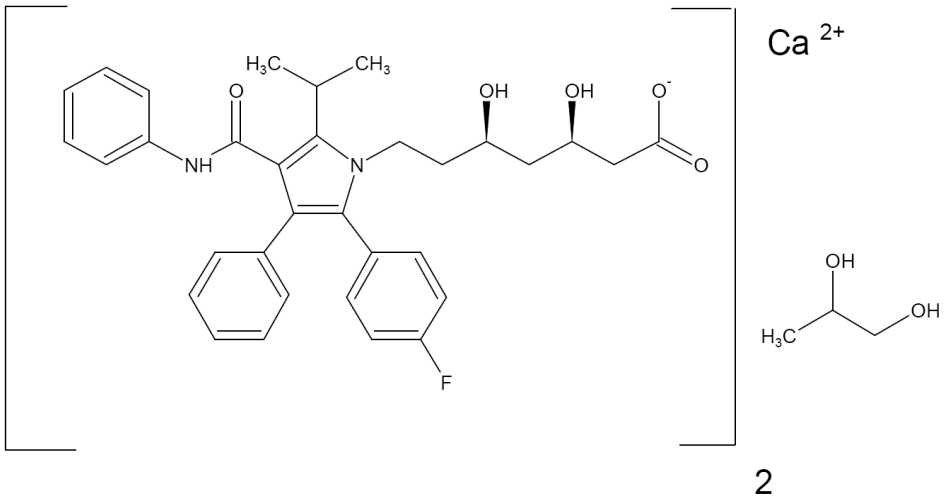
Drug Substance

Proper name: Atorvastatin Calcium Propylene Glycol Solvate

Chemical name: (3*R*,5*R*)-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: $C_{69}H_{76}CaF_2N_4O_{12}$ 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.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative crossover bioavailability study was performed on 17 healthy male volunteers under fasting conditions. The rate and extent of absorption of atorvastatin was measured and compared following a single oral dose of APO-ATORVASTATIN (atorvastatin calcium) or LIPITOR® tablets. The results from measured data are summarized in table 3.

Table 3:

Summary Table of the Comparative Crossover Bioavailability Data
Atorvastatin
(A single 80 mg dose: 1 x 80 mg)
From Measured Data/Fasting Conditions
uncorrected for potency

Geometric Least Square Mean[#]
Arithmetic Mean (CV%)

Parameter	APO-ATORVASTATIN	Lipitor®†	% Ratio of Geometric Means[#]	90% Confidence Interval[#]
AUC_t (ng•h/mL)	156.685 164.034 (34)	142.528 152.427 (40)	109.9	99.7 – 121.2
AUC_{inf} (ng•h/mL)	160.672 168.401 (35)	146.909 157.053 (41)	109.4	99.4 – 120.4
C_{max} (ng/mL)	38.400 41.003 (38)	34.428 38.583 (51)	111.5	94.9 – 131.0
T_{max}[§] (h)	1.76 (62)	0.82 (41)		
T_{half}[§] (h)	9.66 (14)	9.92 (15)		

[§] Expressed as the arithmetic means (CV%) only.

[#] Based on the least squares estimate.

[†] Lipitor® tablets (Pfizer Canada Inc.) were purchased in Canada.

Hypercholesterolemia

Atorvastatin has been shown to significantly improve lipid profiles in a variety of dyslipidemic conditions. Atorvastatin has been shown to be highly effective in reducing total and LDL-cholesterol, and triglycerides and apolipoprotein B in patients with primary hypercholesterolemia, familial and non-familial hypercholesterolemia, and mixed hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus (NIDDM). In patients with hypertriglyceridemia (Type IV), Atorvastatin (10 to 80 mg daily) reduced TG (25 to 56%) and LDL-C levels (23 to 40%). Atorvastatin has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels > 11 mmol/L), i.e. types I and V.

In 2 multicenter, placebo-controlled, double-blind dose-response studies in patients with mild to moderate hypercholesterolemia (Fredrickson types IIa and IIb), atorvastatin given as a single daily dose over 6 weeks reduced total-C, LDL-C, apo B, and TG; HDL was increased (Table 4). A therapeutic response was evident within 2 weeks, and the maximum response was usually achieved within 2 to 4 weeks.

Table 4: Dose-Response in Patients with Mild to Moderate Hypercholesterolemia (Fredrickson Types IIa and IIb) (Mean Percent Change from Baseline)[a]

Atorvastatin Dose (mg/day)	N	Total-C	LDL-C	Apo B	TG	HDL-C
Placebo	21	+4	+4	+3	+10	-3
10	22	-29	-39	-32	-19	+6
20	20	-33	-43	-35	-26	+9
40	21	-37	-50	-42	-29	+6
80	23	-45	-60	-50	-37	+5

[a] Results are pooled from 2 dose-response studies

In a pooled data set from 24 controlled clinical trials in patients with primary hypercholesterolemia (type IIa) and mixed (combined) dyslipidemia (type IIb), atorvastatin increased HDL C by 5% to 8% from baseline at each dose tested (10, 20, 40, and 80 mg QD) (Table 5). In patients with HDL C <0.9 mmol/L (a condition often observed in persons with the metabolic syndrome) [see **INDICATIONS AND CLINICAL USE**], atorvastatin raised HDL-C 7% to 14%. These changes were independent of the dose administered. Atorvastatin also decreased total-C/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C ratios from baseline in a dose dependent manner (Table 5). Atorvastatin (10, 20, 40 and 80 mg QD) increased HDL-C levels from baseline for both men and women.

Table 5: Adjusted[a] Mean Percent Changes from Baseline in HDL-C, Total-C/HDL-C, LDL-C/HDL-C, Non-HDL-C/HDL-C, and HDL ≤ C 0.9 mmol/L for Patients[b] With Mild to Moderate Hypercholesterolemia (Fredrickson Types IIa and IIb)

Atorvastatin Dose (mg/day)	N (all patients)	HDL-C	Total-C/ HDL-C	LDL-C/ HDL-C	Non HDL-C/ HDL-C	HDL-C (baseline ≤ 0.9mmol/L) (N)
Placebo	250	+0.2**	+2.8**	+3.8**	+3.5**	+6.2* (17)
10	1871	+6.4	-29.3†	-37.0†	-35.5†	+13.8 (248)
20	147	+7.8	-36.0†	-44.1†	-43.0†	+8.3 (20)
40	115	+7.1	-38.9†	-49.6†	-47.1†	+8.6 (8)
80	318	+5.0	-43.5†	-55.3†	-52.4†	+7.1 (58)

[a] Least squares means from ANCOVA model with study, treatment and baseline
[b] Data pooled from 24 controlled studies
† significant linear dose trend
** significantly different from atorvastatin 10 mg ($p<0.01$)
* significantly different from atorvastatin 10 mg ($p<0.05$)

In another multicenter, placebo controlled, double blind trial in patients with hypertriglyceridemia, atorvastatin lowered triglycerides in a dose related manner, without causing a redistribution of triglycerides into various lipoprotein fractions (Table 6).

Table 6: Efficacy in Patients with Hypertriglyceridemia (Mean Percent Change from Baseline)

Atorvastatin Dose (mg/day)	N	VLDL-C	Total-C	VLDL-TG	LDL-C	TG	HDL-C	Apo B
Placebo	12	-2.0	+0.3	-6.6	+1.4	-5.3	+2.4	+2.7
5	11	-34.0*	-19.9*	-28.7	-12.7*	-27.3	+7.1	-15.4*
20	12	-46.0*	-33.1*	-35.7*	-31.1*	-33.7*	+10.6	-32.7*
80	11	-54.2*	-41.3*	-43.6*	-36.1*	-42.4*	+11.8*	-38.7*

* Significantly different from placebo, $p<0.05$

Comparison of pooled data by Fredrickson types shows similar reductions for Type IIa and IIb patients in total-C, LDL-C and apo B; however, Type IIb patients, and Types IV patients experience a greater percent decrease in VLDL-C and TG levels (Table 7).

Table 7: Efficacy in Patients by Fredrickson Type[a] (Mean Percent Change from Baseline)

	Atorvastatin 10 mg/day		
Lipid Parameter	Type IIa (N=935)	Type IIb (N=550)	Type IV (N=29)
LDL-C	-36	-35	-26
Apo B	-28	-28	-25
Total-Cl	-27	-27	-25

TG	-14	-24	-29
VLDL-C	-15	-28	-41
HDL-C	+6	+10	+13
Apo B/HDL-C	-31	-34	-33
Non-HDL-C/HDL-C	-37	-38	-38

[a] Pooled dataset

In a pilot study of 8 patients with homozygous familial hypercholesterolemia, the mean decrease in LDL-C with 80 mg/day atorvastatin was 30% for patients not on plasmapheresis, and 31% for patients who continued plasmapheresis. A LDL-C lowering of 35% was observed in receptor defective patients (n=6) and of 19% in receptor negative patients (n=2). All patients also experienced decreases in total-C, apo B, LDL-C/HDL-C and non-HDL-C/HDL-C ratios (Table 8).

Table 8: Patients with Homozygous FH
(Mean Percent Change from Baseline After 8 Weeks)

Lipid Parameter	Atorvastatin 80 mg/day		
	All patients (N=8)	Patients Not on Plasmapheresis (N=3)	Patients on Plasmapheresis (N=5)
Total-C	-29	-29	-29
LDL-C	-31	-30	-31
Apo B	-28	-17	-34
TG	-20	-41	-8
LDL-C/HDL-C Ratio	-23	-19	-25
Non-HDL-C/HDL-C Ratio	-22	-19	-24

In an open label study, 69 patients (2 to 61 years of age) with homozygous familial hypercholesterolemia, and 92 patients with severe hypercholesterolemia who had ≤15% response to maximum combination therapy, received atorvastatin 10 to 80 mg/day. Most patients began atorvastatin treatment with 40 mg/day, but severely debilitated and very young patients began treatment with 10 mg/day. Atorvastatin was titrated at 4-week intervals to ≤80 mg/day. The mean reduction in LDL-C for 69 patients diagnosed with homozygous familial hypercholesterolemia was 22%. Table 9 shows the mean percent change in lipid parameters. In 2 receptor-negative patients mean LDL-C reduction was 19%. Six patients had less than a 10% response to treatment.

Table 9: Patients with Homozygous FH or Severe Nonresponsive Hypercholesterolemia
(Mean Percent Change from Baseline after 8 Weeks)

Lipid Parameter	Atorvastatin 80 mg/day	
	Homozygous FH (N=69[a])	Severe Unresponsive Hypercholesterolemia (N=92)
Total-C	-21%	-34%
LDL-C	-22%	-39%
TG	-9%	-29%

HDL-C	+3%	+6%

[a] Data available from 68 patients

In a 1-year study in patients with heterozygous familial hypercholesterolemia, atorvastatin monotherapy (80 mg/day) was compared with combination therapy of colestipol (10 g BID) plus atorvastatin (40 mg/day). The 2 treatments produced similar effects on total-C, LDL-C, TG, VLDL-C, apo B and HDL-C; however, atorvastatin monotherapy was more effective than atorvastatin plus colestipol in decreasing TG levels (Table 10).

Table 10: Efficacy in Patients with Heterozygous Familial Hypercholesterolemia (Mean Percent Change from Baseline after 52 Weeks)

Lipid Parameter	**Atorvastatin 80 mg/day** (N=189)	**Atorvastatin 40 mg/day Plus Colestipol 10 g BID** (N=124)
Total-C	-44	-42
LDL-C	-53	-53
VLDL-C	-33	-17
HDL-C	+7	+9
TG	-33[a]	-17
Non-HDL/HDL-C Ratio	-53	-52
Apo B	-46	-45

[a] Significantly different from atorvastatin plus colestipol ($p<0.05$), ANCOVA

A comparison of results in patients with heterozygous familial and non-familial hypercholesterolemia shows similar magnitudes of reductions in LDL-C, apo B and non-HDL-C/HDL-C ratio, in both patient populations (Table 11).

Table 11: Efficacy in Heterozygous FH and Non FH Patients[†] (Mean Percent Change from baseline)

Lipid Parameter	**Phenotype**	**Atorvastatin**	
		10 mg/day	**80 mg/day**
LDL-C	Heterozygous FH	-36 (N=140)	-53 (N=154)
	Non FH	-36 (N=1215)	-52 (N=166)
Apo B	Heterozygous FH	-27 (N=134)	-46 (N=153)
	Non FH	-28 (N=1149)	-46 (N=144)
Non-HDL-C/HDL-C Ratio	Heterozygous FH	-37 (N=140)	-53 (N=132)
	Non FH	-37 (N=1215)	-54 (N=166)

[†] Data from several studies

Comparison of results in patients with and without familial combined hyperlipidemia (FCH) demonstrated that atorvastatin lowered LDL-C, apo B, total-C, VLDL-C, TG, and the nonHDL-C/HDL-C ratio to a similar extent in both patient populations (Table 12).

Table 12: Efficacy in Patients With and Without FCH[†], [a]
(Mean Percent Change from Baseline)

Lipid Parameter	Atorvastatin 10 mg/day	
	FCH (N=78-84)	Non-FCH (N=1084-1224)
Total-C	-26%	-27%
LDL-C	-34%	-36%
TG	-21%	-17%
HDL-C	+8%	+7%
Apo B	-26%	-28%
VLDL-C	-25%	-18%
Non-HDL-C/HDL-C Ratio	-36%	-37%
LDL-C/Apo B Ratio	-9%	-11%

[†] Data from several studies

[a] The following criteria were used to define patients with FCH: first degree relative with lipid disorder, TG>250 mg/dL (>2.8 mmol/L), VLDL >45 mg/dL (>1.16 mmol/L), HDL <35 mg/dL (<0.9 mmol/L) (men) or <45 mg/dL (<1.16 mmol/L) (women).

In an open-label, randomised, cross-over study in patients with dysbetalipoproteinemia (Type III), atorvastatin 80 mg/day resulted in a significantly greater reduction in serum lipids than either atorvastatin 10 mg/day or gemfibrozil 1200 mg/day (Table 13).

Table 13: Efficacy in Patients with Type III Hyperlipoproteinemia
(Familial Dysbetalipoproteinemia)
Mean Percent Change from Baseline

Lipid parameter	Atorvastatin 10 mg/day (N=15)	Atorvastatin 80 mg/day (N=16)	Gemfibrozil 1200 mg/day (N=16)
Total-C	-40	-57 [a]	-34
LDL-C	+20 [a]	-6 [a]	+86
TG	-40 [a]	-56	-52
VLDL-C	-32	-59 [a]	-35
IDL-C	-28 [a]	-50 [a]	-13
IDL-C + VLDL-C	-34	-58 [a]	-33
HDL-C	+3	+13	+11
Apo B (total)	-47	-66 [a]	-53
Apo-C III	-16	-31	-12
Apo-E	-27	-41 [a]	-24

[a] significantly different from gemfibrozil, p<0.05 (ANOVA)

In a 6-month, double-blind, study in patients with hyperlipidemia and non-insulin dependent diabetes mellitus (NIDDM), atorvastatin (10 or 20 mg/day) lowered total cholesterol by 27%, LDL-C by 34%, apo B by 30%, TG by 24%, and increased HDL-C by 12% (Table 14).

Table 14: Efficacy in Patients with NIDDM (Mean Percent Change From Baseline)

Lipid Parameter	Atorvastatin 10 or 20 mg/day (N=84)
Total-C	-27
LDL-C	-34
VLDL-C	-35
TG	-24
VLDL-TG	-26
HDL-C	+12
Apo B	-30

In three, double-blind, multicenter studies in patients with mild to moderate hypercholesterolemia, the number of patients meeting NCEP target LDL-C levels on atorvastatin was assessed over a 1-year period. After 16 weeks, between 46 to 74% of patients receiving 10 mg/day atorvastatin reached target LDL-C levels. The efficacy of atorvastatin (10 or 20 mg/day) was maintained over 52 weeks, with between 50 to 78% of patients achieving their LDL-C target levels.

The effect of atorvastatin was evaluated in comparative clinical trials with lovastatin, simvastatin and pravastatin. For information on these results please refer to REFERENCES.

In a 1-year study in postmenopausal women with primary hyperlipidemia, atorvastatin monotherapy (10 mg/day) was compared with estradiol monotherapy (1 mg/day) and with combination therapy of atorvastatin 10 mg/day plus estradiol 1 mg/day (Table 15). Atorvastatin monotherapy (10 mg/day) was significantly more effective in lowering total-C, LDL-C, VLDL--C, TG, apo B and non-HDL-C/HDL-C ratio than estradiol monotherapy (1 mg/day). For combination therapy (atorvastatin plus estradiol), reductions in total-C, LDL-C, VLDL-C, Lp(a), apo B and non HDL-C/HDL-C ratio were similar compared with atorvastatin monotherapy. However, HDL-C levels were significantly higher for combination therapy compared with atorvastatin monotherapy. TG levels were lower with atorvastatin monotherapy compared with combination therapy. Adverse reactions were similar in type and incidence following combination therapy (atorvastatin plus estradiol) compared with estradiol monotherapy.

Table 15: Efficacy in Post-menopausal Women (Mean Percent Change from Baseline after 52 Weeks)

Lipid Parameter	Atorvastatin 10 mg/day (N=38)	Estradiol 1 mg/day (N=16)	Atorvastatin 10 mg/day Plus Estradiol (1 mg/day) (N=21)

TOTAL-C	-29	-1 [a]	-27
LDL-C	-40	-5 [a]	-42
VLDL-C	-32	+13 [a]	-20
HDL-C	+8	+11	+20 [a]
TG	-27	+5 [a]	-13 [a]
non-HDL/HDL-C Ratio	-43	-12 [a]	-48
Apo B	-34	-3 [a]	-34

[a]Significantly different from atorvastatin monotherapy ($p<0.05$), ANCOVA

In a comparative study with niacin in patients with hypercholesterolemia and mixed hyperlipidemia (Fredrickson types IIa and IIb) and hypertriglyceridemia (Frederickson Type IV), atorvastatin (10 mg/day) had greater cholesterol-lowering efficacy (greater decreases in LDL-C, apo B, LDL-apo B), while niacin (3 g/day) had greater triglyceride-lowering efficacy (greater decreases in TG, VLDL-TG, HDL-TG, VLDL-apo B). Atorvastatin was better tolerated by patients compared with niacin (Table 16).

Table 16: Atorvastatin versus Niacin (Mean Percent Change from Baseline)

Parameter	Fredrickson Types IIa and IIb		Fredrickson Type IV	
	Atorvastatin 10 mg (N=43)	Niacin 3 g/day (N=39)	Atorvastatin 10 mg (N=11)	Niacin 3 g/day (N=12)
LDL-C	-33*	-8	-15*	+14
Apo B	-30*	-16	-23*	-3
Total-C	-28*	-11	-26*	0
TG	-16	-29*	-36	-29
HDL-C	+4	+27*	+4	+25
VLDL-C	-28	-39	-43	-36
Non-HDL-C/HDL-C	-34	-32	-34	-19
Apo B/HDL	-32	-31	-28	-18

* Significant difference between treatments, ANCOVA $p<0.05$.

In a comparative study with fenofibrate in patients with combined hyperlipidemia or hypertriglyceridemia, atorvastatin (20 mg/day) was more effective in lowering LDL-C, apo B and total cholesterol levels compared to fenofibrate (100 mg TID). Treatment with atorvastatin also resulted in clinically significant reductions in TG and VLDL-C, and increases in HDL-C levels, although not to the same extent as was seen with fenofibrate. Atorvastatin therapy resulted in a better reduction of the non-HDL-C/HDL-C ratio, which may be a good indicator of overall lipid-regulating benefit. Atorvastatin was also better tolerated compared with fenofibrate (Table 17).

Table 17: Atorvastatin versus Fenofibrate (Mean Percent Change From Baseline After 24 Weeks)

Parameter	Fredrickson Types IIa and IIb		Fredrickson Type IV	
	Atorvastatin 20 mg (N=36)	Fenofibrate 300 mg (N=33)	Atorvastatin 20 mg (N=9)	Fenofibrate 300 mg (N=8)
LDL-C	-39*	-7	-28*	+27
Apo B	-36*	-17	-27	-9

Total-C	-34*	-14	-26	-13
TG	-27	-39	-34	-57*
HDL-C	+9	+22*	+8	+30*
VLDL-C	-39	-50	-36	-73*
Non-HDL-C/HDL-C	-44*	-32	-36	-35

* Significant difference between treatments, ANCOVA $p<0.05$.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients:

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10 to 17 years of age (mean 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks after that, all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥4.9 mmol/L (190 mg/dL) or 2) a baseline ≥4.1 mmol/L (160 mg/dL) and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative.

Table 18: Effect of atorvastatin on LDL-C, TC and TG in a controlled trial of 6 months duration in adolescent boys and postmenarchal girls 10-17 years of age (N=187) with heterozygous familial hypercholesterolemia at a dose of 10 and 20 mg.

N	Age	Dose	% Change		
			LDL-C	TC	TG
22	10-13	10 mg	-37.85	-29.3	-9.2
40	14-17	10 mg	-38.2	-29.4	-6.9
33	10-13	20 mg	-42.1	-34.0	-13.3
43	14-17	20 mg	-40.3	-33.0	-18.3

The mean baseline LDL-C value was 5.7 mmol/L (218.6 mg/dL) (range: 3.6-10.0 mmol/L [138.5 to 385.0 mg/dL]) in the atorvastatin group compared to 5.9 mmol/L (230.0 mg/dL) (range: 4.1 to 8.4 mmol/L [160.0 to 324.5 mg/dL]) in placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >3.4 mmol/L (130 mg/dL). The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 18, and Table 19).

Table 19: Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

Dosage	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12	-34

The mean achieved LDL-C value was 3.8 mmol/L (130.7 mg/dL) (range: 1.8 to 6.3 mmol/L [70.0 to 242.0 mg/dL]) in the atorvastatin group compared to 5.9 mmol/L (228.5 mg/dL) (range: 3.9 to 10.0 mmol/L [152.0 to 385.0 mg/dL]) in the placebo group during the 26 week double-blind phase. The safety and tolerability profile of atorvastatin 10 to 20 mg daily was similar to that of placebo.

In this controlled study, there was no effect on growth or sexual maturation in boys and in girls, as measured by Tanner staging during 26 weeks. The proportion of subjects who had an increase in Tanner stage between baseline and week 26 of the double-blind phase was similar for the atorvastatin and placebo groups (28% and 31%, respectively; P = 0.7). No specific documentation of menstrual cycle was recorded. Atorvastatin had no effect on plasma levels of LH, FSH, cortisol, testosterone and dehydroepiandrosterone. Effect of treatment on cognitive function was not captured during the course of this study.

Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children.

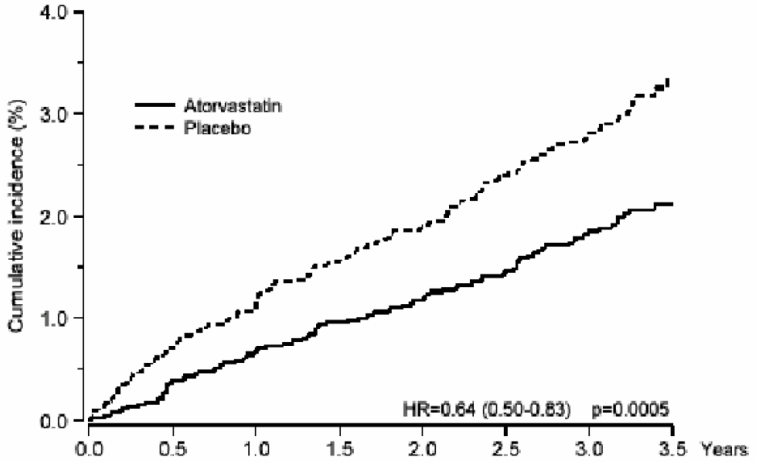
Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤6.5 mmol/L. Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age ≥55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL ≥6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the atorvastatin group) or nonfatal MI (108 events in the placebo group vs 60 events in the atorvastatin group)] with an absolute risk reduction of 1.1% and a relative risk reduction of 36% (based on incidences of 1.9% for atorvastatin vs 3.0% for placebo), p=0.0005 (see Figure 1)]. This risk reduction yields a Number Needed to Treat of 311 patients per year. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



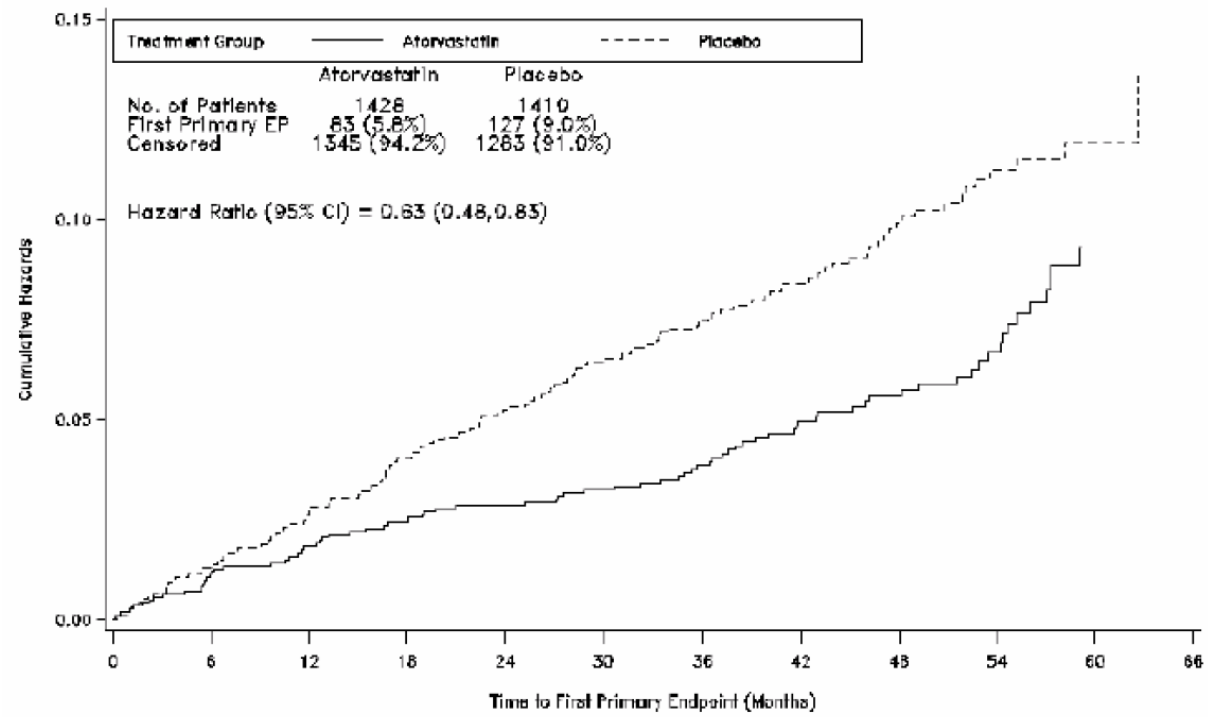
In the Collaborative AtoRvastatin Diabetes Study (CARDS), the effect of atorvastatin on coronary heart disease (CHD) and non-CHD endpoints was assessed in 2838 men (68%) and women (32%), ages 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 4.14 mmol/L and TG ≤ 6.78 mmol/L. In addition to type 2 diabetes, subjects had one or more of the following CHD risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), microalbuminuria (9%) or macroalbuminuria (3%). In this multicenter, placebo-controlled, double blind clinical trial of primary prevention of fatal and nonfatal cardiovascular and cerebrovascular disease in subjects with type 2 diabetes and 1 other CHD risk factor, patients were randomly allocated to either atorvastatin 10 mg daily (1429) or placebo (1411) in a 1:1 ratio.

Patients were followed for a median duration of 3.9 years. Due to significant treatment benefits ($p<0.0005$, one-sided, in favor of atorvastatin) seen early in the study, the study was stopped by the CARDS Steering Committee two years earlier than anticipated.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 3.10 mmol/L; median TC 5.35 mmol/L; median TG 1.70 mmol/L; median HDL-C 1.34 mmol/L.

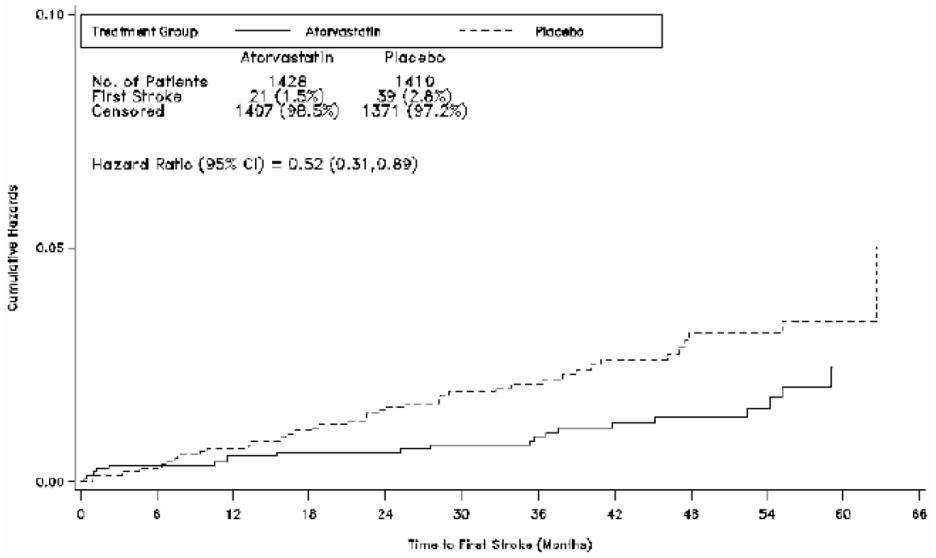
The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.
Treatment with atorvastatin was associated with a statistically significant 37% relative risk reduction (RRR), or 3.2% absolute risk reduction (ARR) in the rate of major cardiovascular events. Efficacy analysis showed that 83 (5.8%) of atorvastatin treated patients and 127 (9.0%) of placebo treated patients experienced their first primary clinical endpoint. Comparison of the time to the first primary endpoint in the two groups yielded the hazard ratio (HR) of 0.63 with 95% CI 0.48, 0.83 and p=0.001 in favour of atorvastatin. The number needed to treat (NNT) for one year to prevent one case experiencing the primary clinical endpoint, based on the ARR 3.2% yields 125 patients. The effect of atorvastatin was seen regardless of age, sex, or baseline lipid levels.

Figure 2. Time to Occurrence of First Primary Endpoint



When cardiovascular events were evaluated separately, atorvastatin significantly reduced the relative risk of stroke by 48% (ARR of 1.3%). There were 21 cases of stroke (1.5%) in the atorvastatin group vs 39 cases (2.8%) in the placebo group, HR 0.52, 95% CI 0.31, 0.89, p=0.016. To prevent one case of stroke 307 patients are needed to be treated for one year.

Figure 3. Time to Occurrence of First Stroke



Relative risk of myocardial infarction was reduced by 42%, or ARR by 1.8%, with 38 cases (2.7%) in the atorvastatin group vs 64 cases (4.5%) in the placebo group, HR 0.58, 95% CI 0.39, 0.86, p = 0.007. To prevent one case of myocardial infarction 222 patients have to be treated for one year.

No significant risk reduction was observed in the time to first CABG, PTCA or other coronary revascularization procedure, time to first unstable angina or time to acute CHD death. No significant reduction was observed in time to death due to all causes (61 deaths in the atorvastatin group vs 82 deaths in the placebo group, HR 0.73, 95% CI 0.52, 1.01, p=0.059), cardiovascular causes, or non-cardiovascular causes.

DETAILED PHARMACOLOGY

(I) Human Pharmacology

Human Pharmacokinetics

Pharmacokinetic interaction studies have been conducted in healthy subjects with 3 macrolide antibiotics: erythromycin and clarithromycin (both of which inhibit CYP 3A4), and with azithromycin. Coadministration of atorvastatin with erythromycin or clarithromycin, resulted in moderately increased atorvastatin plasma levels but atorvastatin plasma levels were not altered by azithromycin. Twelve healthy subjects were administered atorvastatin 10 mg on days 1 and 15; erythromycin 500 mg QID was administered from days 8 to 19. Erythromycin increased atorvastatin C_{max} and AUC approximately 40%. In a second study, atorvastatin 10 mg was administered daily for 8 days; clarithromycin (500 mg BID) or azithromycin (500 mg QD) was coadministered from days 6 to 8 (N=12/treatment). Coadministration with clarithromycin increased atorvastatin AUC ~80% and C_{max} ~50%, but atorvastatin plasma levels were not significantly altered by coadministration with azithromycin.

Steady-state, open-label, pharmacokinetic studies with digoxin have been performed in healthy subjects with both low and high doses of atorvastatin. Atorvastatin (10 mg or 80 mg QD; N=11 and N=12, respectively), was administered from days 1 to 20 and digoxin (0.25 mg QD) from days 11 to 20. At steady-state, atorvastatin 10 mg daily had no significant effect on steady-state digoxin pharmacokinetics. However, following co-administration with atorvastatin 80 mg QD, the mean steady-state digoxin AUC and C_{max} increased 15% and 20%, respectively. Patients taking digoxin should be monitored appropriately.

The effect of amlodipine on the pharmacokinetics of atorvastatin was assessed at steady-state in a randomized, open-label, placebo-controlled, crossover study in healthy male subjects (N=16). Atorvastatin (80 mg QD) was administered with amlodipine (10 mg QD) or placebo from days 1 8. Following a 14 day washout, the alternate combination was administered from days 22 to 29. At steady-state, the coadministration of maximum doses of atorvastatin and amlodipine did not significantly alter the pharmacokinetics of atorvastatin and there were no apparent changes in blood pressure or heart rate.

The effect of quinapril on the pharmacokinetics of atorvastatin was assessed in a randomized, open-label study in healthy volunteers (N=22). Single doses of atorvastatin (10 mg) were administered on days 1 to 14, and single doses of quinapril (80 mg) were administered on days 1 to 7 or days 8 to 14. The mean T_{max} value for atorvastatin during steady state quinapril administration was shortened by 1.25 hours compared to that of atorvastatin administered alone but with no change in absorption/AUC or C_{max}. No significant changes in blood pressure or heart rates were observed.

Concomitant administration of atorvastatin 20 to 40 mg and itraconazole 200 mg daily resulted in a 2.5 to 3.3-fold increase in atorvastatin AUC.

Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin.

(II) **Animal Pharmacology**

The hypolipidemic potential of atorvastatin was evaluated in normocholesterolemic animals, models of diet-induced hypercholesterolemia and a model of LDL receptor deficiency.

In LDL receptor deficient mice, atorvastatin lowered plasma total and LDL-C levels 14% to 49% over the dose range of 10 to 300 mg/kg after 2 weeks. Atorvastatin lowered plasma cholesterol in chow-fed rats irrespective of whether the compound was admixed in the diet or administered by oral gavage. In chow-fed guinea pigs, a model in which LDL is the major lipoprotein, atorvastatin given at 3, 10, or 30 mg/kg by gavage daily for 2 weeks, dose-dependently decreased plasma total cholesterol 34% to 57%.

The ability of atorvastatin to lower plasma total and lipoprotein cholesterol levels was also evaluated in two rabbit models of hypercholesterolemia. In the endogenous hypercholesterolemic rabbit model (where most of the plasma cholesterol is transported in LDL), administration of atorvastatin in the diet at 1, 3, and 10 mg/kg for 6 to 7 weeks lowered plasma total cholesterol 38% to 54%. The efficacy of atorvastatin was due to a 56% decrease in LDL production and 47% reduction in apo B. In the cholesterol-fed rabbit model (where hypercholesterolemia is mostly due to the accumulation of beta-migrating VLDL), atorvastatin administered at 2.5 mg/kg in a 0.5% cholesterol, 3% peanut oil, 3% coconut oil diet for 2 weeks reduced plasma total, VLDL-C, and LDL-C levels 35%, 44%, and 21%, respectively.

In cholestyramine-primed dogs, oral administration of atorvastatin for 3 weeks dose-dependently lowered plasma total cholesterol 15% to 41% over the dose range of 0.3 to 10 mg/kg. In miniature pigs fed a diet where 34% of calories were derived from fat, supplemented with 400 mg cholesterol/day, atorvastatin given at 3 mg/kg in gelatin capsules for 3 weeks reduced plasma total and LDL-C 15% and 27%, respectively. These decreases were associated with a 23% to 29% reduction in plasma VLDL and LDL apo B levels and apo B pool sizes and a 21% and 26% decrease in VLDL-apo B and LDL-apo B production rates, respectively.

Atorvastatin reduced plasma TG levels up to 39% in male and female LDL receptor deficient mice at doses of 10**,** 30, 100, and 300 mg/kg and the changes were unrelated to dose and not associated with changes in TG production rates. In chow-fed rats, atorvastatin decreased plasma TG levels 30% when administered in the diet at 100 mg/kg; however, upon oral gavage administration TG levels were reduced 33% and 75% at 25 and 100 mg/kg, respectively. In the sucrose-fed rat, a model of hypertriglyceridemia due to enhanced VLDL-TG production, atorvastatin reduced plasma TG levels 26% to 53% at 1 to 30 mg/kg and TG secretion rates 43% and 66% at 10 and 30 mg/kg, respectively. Changes in plasma TG levels were also noted in guinea pigs, rabbits, and miniature swine.

In intact, oleate-treated HEP-G2 cells, a human hepatocyte cell line, atorvastatin reduced the oleate-stimulated secretion of apo B by 21% and decreased the amount of intracellular apo B remaining within the cells by 25%. Atorvastatin increased the intracellular degradation of apo B and impaired the translocation of apo B into the lumen of the endoplasmic reticulum (ER) in permeabilized HEP-G2 cells; this was associated with a decrease in the amount of apo B particles present in the microsomal fraction.

Following a single oral dose to rats, atorvastatin inhibited sterol synthesis (assessed by [^{14}C]acetate incorporation into lipids); the dose of atorvastatin that inhibited sterol synthesis by 50% (ED_{50}) ranged from 0.61 to 3.4 mg/kg. The duration of inhibition for atorvastatin was similar to other HMG-CoA reductase inhibitors; however, atorvastatin more consistently inhibited sterol synthesis an average of 34% over the first 8 hours postdose. Atorvastatin and its metabolites were relatively equipotent in inhibition of HMG-CoA reductase (as assessed by measuring the incorporation of radiolabelled HMG-CoA into mevalonate).

Antiatherosclerotic Potential of Atorvastatin

The antiatherosclerotic potential of atorvastatin was determined in rabbit models of atherosclerotic lesion progression and regression. A common feature of the models is that atherosclerotic lesions were induced by a combination of hypercholesterolemia and chronic endothelial denudation of the arteries.

Atherosclerotic lesion development was assessed in the thoracic aorta and chronically denuded iliac-femoral artery of hypercholesterolemic New Zealand White rabbits fed a 0.5% cholesterol, 3% peanut oil, 3% coconut oil diet either alone or containing 2.5 mg/kg atorvastatin, lovastatin, pravastatin, or simvastatin for 8 weeks. The lipid content of the iliac-femoral artery was unaffected by treatment; however, atorvastatin significantly reduced the thoracic aortic cholesterol ester content by 55% and free cholesterol content 45%. Atorvastatin significantly decreased the cross-sectional area of the iliac-femoral lesion by 69% and monocyte-macrophage content by 71%. In the descending thoracic aorta, a site of spontaneous, diet-induced atherosclerotic lesions, atorvastatin significantly reduced the percentage of grossly discernible atherosclerotic lesions.

The ability of atorvastatin to blunt the development of complex atherosclerotic lesions and promote regression of a lipid-enriched lesion was assessed in an additional rabbit model of atherosclerosis. In rabbits after a 15-week lesion induction phase consisting of feeding a 0.5% cholesterol, 3% peanut oil, 3% coconut oil diet for 9 weeks and a 0% cholesterol, 3% peanut oil, 3% coconut oil diet for 6 weeks to nearly normalize plasma cholesterol levels in all treatment groups, 5 mg/kg atorvastatin administration for 8 weeks in the chow/fat diet reduced the cholesterol ester enrichment of the iliac-femoral artery and thoracic aorta by 27% to 41% without changing the gross extent of thoracic aortic lesions and incidence of fibrous plaques. Atorvastatin also reduced the cholesterol ester content of the iliac-femoral artery by 37% relative to initiation of drug intervention, ie, a group of animals necropsied prior to drug treatment. Morphometric analysis of the iliac-femoral artery revealed that atorvastatin reduced the lesion cross-sectional area by 40% and monocyte-macrophage content by 60%.

TOXICOLOGY

Acute Toxicity

The acute toxicity of atorvastatin following single doses was evaluated in mice, rats and dogs by oral and intravenous routes, and the results are summarized below:

Table 20. Acute Oral and Intravenous Toxicity Studies with Atorvastatin

Species	Sex	Route	Dose Range (mg/kg)	Results
Mouse	Male/Female	Oral	200-5000	No Deaths
Mouse	Male/Female	IV	0.4-4	No Deaths
Rat	Male/Female	Oral	200-5000	No Deaths
Rat	Male/Female	IV	0.4-4	No Deaths
Dog	Male/Female	Oral	10-400	No Deaths
Dog	Male/Female	IV	0.4-4	No Deaths

The acute toxicity of atorvastatin in rodents and dogs is low. Oral median lethal doses in mice and rats are greater than 5000 mg/kg.

Subacute and Chronic Toxicity Studies

The target organs affected by atorvastatin in multiple dose toxicity studies in rats (2 weeks to 52 weeks), and dogs (2 weeks to 104 weeks) are summarized in the table below. The spectrum of effects observed is not unexpected in view of the magnitude of the dose levels used, potency of atorvastatin in inhibiting mevalonate synthesis and the essential role of HMG-CoA reductase in maintaining cellular homeostasis.

Table 21. Atorvastatin: Target Organs Affected in Animal Studies

Rat	Dog
Liver	Liver
Stomach (non-glandular)	Gallbladder

Skeletal Muscle	Skeletal Muscle Intestine Brain/Optic Nerve*

* Occurred after administration of high, intolerable doses (280 mg/kg)

The following table summarizes the significant adverse changes observed during long-term toxicology studies in rats (52 weeks) and dogs (104 weeks):

Table 22. Atorvastatin: Significant Adverse Changes in Chronic Studies

Species/Results	Minimal Toxic Dose (mg/kg/day)	No-Effect Dose (mg/kg/day)
RAT		
Hepatocellular atypia	70	5
Bile Duct hyperplasia[1]	125	70
Nonglandular stomach acanthosis	125	70
DOG		
Death[2]	120	40
Hepatocellular granulomata[3]	10	ND
Hepatocellular necrosis[3]	120	40
Gallbladder edema/hemorrhage[3]	120	40
Bile duct hyperplasia[3]	120	10
Intestinal ulcers and single cell necrosis[3]	120	40
Skeletal muscle (tongue) necrosis[2]	120	40

[1] Present only at Week 26; not observed at Week 52.

[2] Findings occurred in Week 7 or 9.

[3] Findings occurred at Week 52 or in moribund dogs, were less pronounced after a 12-week withdrawal period (Week 64), and were not observed after 104 weeks of dosing.

ND = Not determined

The results of the long-term toxicology studies with atorvastatin indicated that similar to other HMG-CoA reductase inhibitors, the liver is the primary target organ. This is expected since the liver is the primary site of the pharmacologic action of atorvastatin and it is subject to the greatest drug exposure following oral administration. In both the rat and dog studies, the hepatic changes diminished with time (i.e. effects were less pronounced at the end of the 52-week and 104-week studies) suggesting an adaptive response.

Brain hemorrhage, optic nerve degeneration, lenticular opacities and testicular degeneration were not seen in dogs treated for 104-weeks with atorvastatin up to 120 mg/kg/day.

Carcinogenicity and Genotoxicity Studies

Atorvastatin was not carcinogenic in rats given 10, 30 or 100 mg/kg/day for 2 years. The 100 mg/kg dose is 63-fold higher than the maximum recommended human dose of 80 mg (1.6 mg/kg, based on a 50 kg human) and AUC (0 to 24 hr) values were 8 to 16-fold higher.

In a 2-year study in mice given 100, 200 or 400 mg/kg/day, incidences of hepatocellular adenoma in males and hepatocellular carcinoma in females were increased at 400 mg/kg. This dose is 250 times the maximum recommended human dose on a mg/kg basis and systemic exposure based on AUC (0 to 24 hr) was 6 to 11 times higher. There was no evidence of treatment-related increases in tumor incidences at the lower doses of 100 and 200 mg/kg/day (i.e. up to 125 times the maximum recommended human dose on a mg/kg basis and systemic exposures of 3 times higher based on AUC (0 to 24 hr).

Atorvastatin did not demonstrate mutagenic or clastogenic potential in four *in vitro* tests with and without metabolic activation or in one *in vivo* assay. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test.

Reproductive and Teratogenicity Studies

No adverse effects on fertility or reproduction were observed in male rats given doses of atorvastatin up to 175/mg/kg/day or in female rats given doses up to 225 mg/kg/day. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg basis. Atorvastatin did not cause any adverse effects on sperm or semen parameters, or in reproductive organ histopathology in dogs given doses of 10, 40 or 120 mg/kg for 2 years. Atorvastatin was not teratogenic in either rats or rabbits.