ATORVASTATIN CALCIUM- atorvastatin calcium tablet
H.J. Harkins Company Inc.

Indications and Usage

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously with diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin calcium tablets are indicated to:

Reduce the risk of myocardial infarction
Reduce the risk of stroke
Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

Reduce the risk of myocardial infarction
Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin calcium tablets are indicated to:

Reduce the risk of non-fatal myocardial infarction
Reduce the risk of fatal and non-fatal stroke
Reduce the risk for revascularization procedures
Reduce the risk of hospitalization for CHF
Reduce the risk of angina

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb);
As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
For the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet;
To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥ 190 mg/dL or

b. LDL-C remains ≥ 160 mg/dL and:

there is a positive family history of premature cardiovascular disease or

two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

Dosage and Administration

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of therapy and response (see current NCEP Guidelines). After initiation and/or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

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

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy [see current NCEP Pediatric Panel Guidelines, Clinical Pharmacology (12), and Indications and Usage (1.2)]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin calcium tablets; thus, dosage adjustment in patients with renal dysfunction is not necessary [see Warnings and Precautions, Skeletal Muscle (5.1), Clinical Pharmacology, Pharmacokinetics (12.3)].

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

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin calcium tablets should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin calcium tablets should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium is employed. In patients taking the HIV protease inhibitor nelfinavir, or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin calcium tablets should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose

necessary of atorvastatin calcium tablets is employed [see Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)].

Dosage Forms and Strengths

Atorvastatin calcium tablets of 10 mg are white to off-white capsule shaped, biconvex, film coated tablets debossed ‘RDY’ on one side and ‘121’on other side.

Atorvastatin calcium tablets of 20 mg are white to off-white capsule shaped, biconvex, film coated tablets debossed ‘RDY’ on one side and ‘122’ on other side.

Atorvastatin calcium tablets of 40 mg are white to off-white capsule shaped, biconvex, film coated tablets debossed ‘RDY’ on one side and ‘123’ on other side.

Contraindications

4.1 Active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin calcium may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of atorvastatin calcium use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN CALCIUM 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 this drug, atorvastatin calcium should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

4.4 Nursing mothers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin calcium treatment should not breastfeed their infants [see Use in Specific Populations (8.3)].

Warnings and Precautions

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calciumand with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

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 serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing atorvastatin. Atorvastatin calcium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin calcium and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see Drug Interactions (7)). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also Dosage and Administration (2.6), Drug Interactions (7), Clinical Pharmacology (12.3)].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	
Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

*Use with caution and with the lowest dose necessary (12.3)

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see Drug Interactions (7.11)]

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

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40,

and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin calcium.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin calcium 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 atorvastatin calcium, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin calcium.

Atorvastatin calcium should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin calcium [see Contraindications (4.1)].

5.3 Endocrine Function

Increased in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin calcium.

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

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin calcium 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin calcium 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo

groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see Adverse Reactions (6.1)].

CLOSE

Adverse Reactions

The following serious adverse reactions are discussed in greater detail in other sections of the label:

Rhabdomyolysis and myopathy [see Warnings and Precautions (5.1)]

Liver enzyme abnormalities [see Warnings and Precautions (5.2)]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the atorvastatin calcium placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin calcium vs. 7311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin calcium that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin calcium in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6%), and urinary tract infection (5.7%).

Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin calcium (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patients treated with any dose of atorvastatin calcium and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6	8.5	3.7	9.3	3.1	5.9
Urinary tractinfection	5.7	6.9	6.4	8	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6	3.3	4.3
Nausea	4	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse Reaction ≥ 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include: Body as a whole: malaise,

pyrexia; Digestive system: abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; Musculoskeletal system: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; Metabolic and nutritional system: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; Nervous system: nightmare; Respiratory system: epistaxis; Skin and appendages: urticaria; Special senses: vision blurred, tinnitus; Urogenital system: white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

In ASCOT [see Clinical Studies (14.1)] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin calcium 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin calcium was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)

In CARDS [see Clinical Studies (14.1)] involving 2,838 subjects (age range 39 to 77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1% other) with type 2 diabetes treated with atorvastatin calcium 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)

In TNT [see Clinical Studies (14.1)] involving 10,001 subjects (age range 29 to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1% Asians, 2% other) with clinically evident CHD treated with atorvastatin calcium 10 mg daily (n=5006) or atorvastatin calcium 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)

In IDEAL [see Clinical Studies (14.1)] involving 8,888 subjects (age range 26 to 80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin calcium 80 mg/day (n=4439) or simvastatin 20 to 40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin calcium 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4 to 10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see Warnings and Precautions (5.5)].

In a post-hoc analysis, atorvastatin calcium 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between

groups (17 atorvastatin calcium vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin calcium vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium 80 mg/day group vs. 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin calcium 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin calcium 80 mg group (5%) than in the placebo group (4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of atorvastatin calcium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with atorvastatin calcium therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, pancreatitis and interstitial lung disease.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see Warnings and Precautions (5.1)]

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10 to 17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was generally similar to that of placebo [see Clinical Studies (14.6)and Use in Special Populations, Pediatric Use (8.4)].

Drug Interactions

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) [see Warnings and Precautions, Skeletal Muscle (5.1)and Clinical Pharmacology (12.3)].

7.1 Strong Inhibitors of Cytochrome P450 3A4

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

Clarithromycin:Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin calcium alone [see Clinical Pharmacology (12.3)]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin calcium dose exceeds 20 mg [see Warnings and Precautions, Skeletal Muscle (5.1)and Dosage and Administration (2.6)].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin calcium alone [see Clinical Pharmacology (12.3)]. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin calcium should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin calcium should not exceed 20 mg and should be used with caution [see Warnings and Precautions, Skeletal Muscle (5.1)andDosage and Administration (2.6)]. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of atorvastatin calcium should not exceed 40 mg andclose clinicalmonitoring is recommended.

Itraconazole:Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium 40 mg and itraconazole 200 mg [see Clinical Pharmacology (12.3)]. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin calcium dose exceeds 20 mg [see Warnings and Precautions, Skeletal Muscle (5.1)and Dosage and Administration (2.6)].

7.2 Grapefruit Juice

Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

7.3 Cyclosporine

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin calcium alone [see Clinical Pharmacology (12.3)]. The co-administration of atorvastatin calcium with cyclosporine should be avoided [see Warnings and Precautions, Skeletal Muscle (5.1)].

7.4 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of atorvastatin calcium with gemfibrozil should be avoided [see Warnings and Precautions (5.1)].

7.5 Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, atorvastatin calcium should be administered with caution when used concomitantly with other fibrates [see Warnings and Precautions (5.1)].

7.6 Niacin

The risk of skeletal muscle effects may be enhanced when atorvastatin calcium is used in combination with niacin; a reduction in atorvastatin calcium dosage should be considered in this setting [see Warnings and Precautions (5.1)].

7.7 Rifampin or other Inducers of Cytochrome P450 3A4

Concomitant administration of atorvastatin calcium with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin calcium with rifampin is recommended, as delayed administration of atorvastatin calcium after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin

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

7.9 Oral Contraceptives

Co-administration of atorvastatin calcium and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see Clinical Pharmacology (12.3)]. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin calcium.

7.10 Warfarin

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

7.11 Colchicine

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

Use in Specific Populations

8.1 Pregnancy

Pregnancy Category X

Atorvastatin calcium is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m2) [see Contraindications, Pregnancy (4.3)].

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. Atorvastatin calcium should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking atorvastatin calcium, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring atorvastatin calcium treatment should be advised not to nurse their infants [see Contraindications (4)].

8.4 Pediatric Use

Safety and effectiveness in patients 10 to 17 years of age 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 calcium had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. Doses greater than 20 mg have not been studied in this patient population. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10 to 17 years) (6.3); and Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age) (2.2)]. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin calcium therapy [see Contraindications, Pregnancy (4.3) and Use in Specific Populations, Pregnancy (8.1)]. Atorvastatin calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients [see Clinical Studies, Homozygous Familial Hypercholesterolemia (14.5)].

8.5 Geriatric Use

Of the 39,828 patients who received atorvastatin calcium in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin calcium should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

Atorvastatin calcium is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see Contraindications (4)and Pharmacokinetics (12.3)].

Overdosage

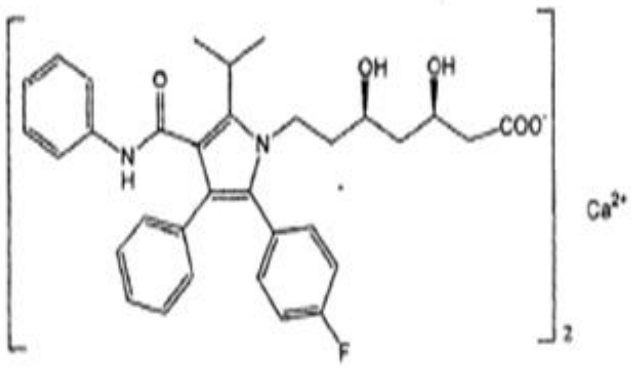
There is no specific treatment for atorvastatin calcium overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin calcium clearance.

Description

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1). The molecular formula of

atorvastatin calcium is C66H68CaF2N4O10and its molecular weight is 1155.36. Its structural formula is:



Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in dimethyl sulphoxide, slightly soluble in alcohol, very slightly soluble in water, in pH 7.4 phosphate buffer and in acetonitrile and practically insoluble in aqueous solutions of pH 4 and below.

Atorvastatin calcium tablets for oral administration contain 10, 20 and 40 mg atorvastatin and the following inactive ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains isopropyl alcohol, methylene chloride and coloring agent opadry OY-58900 white contains polyethylene glycol, titanium dioxide and hypromellose.

Clinical Pharmacology

12.1 Mechanism of Action

Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium also reduces LDL production and the number of LDL particles. Atorvastatin calcium reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

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

Atorvastatin calcium reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

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

12.2 Pharmacodynamics

Atorvastatin calcium, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see Dosage and Administration (2)].

12.3 Pharmacokinetics

Absorption:Atorvastatin calcium is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin calcium is given with or without food. Plasma atorvastatin calcium concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see Dosage and Administration (2)].

Distribution:Mean volume of distribution of atorvastatin calcium is approximately 381 liters. Atorvastatin calcium 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 calcium is likely to be secreted in human milk [see Contraindications, Nursing Mothers (4.4)and Use in Specific Populations, Nursing Mothers (8.3)].

Metabolism:Atorvastatin calcium is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin calcium. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin calcium metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin calcium in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see Drug Interactions (7.1)]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

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

following oral administration.

Specific Populations

Geriatric:Plasma concentrations of atorvastatin calcium are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see Use in Specific Populations, Geriatric Use (8.5)].

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

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

Renal Impairment:Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin calcium; thus, dose adjustment in patients with renal dysfunction is not necessary [see Dosage and Administration, Dosage in Patients with Renal Impairment (2.5), Warnings and Precautions, Skeletal Muscle (5.1)].

Hemodialysis:While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin calcium since the drug is extensively bound to plasma proteins.

Hepatic Impairment:In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin calcium are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see Contraindications (4.1)].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen Atorvastatin
Dose (mg) Change in AUC& Change in Cmax&
#Cyclosporine 5.2 mg/kg/day, stable dose 10 mg QD for 28 days ↑ 8.7 fold ↑10.7 fold
#Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days 10 mg, SD ↑ 9.4 fold ↑ 8.6 fold
#Telaprevir 750 mg q8h, 10 days 20 mg, SD ↑ 7.88 fold ↑ 10.6 fold
#, ‡Saquinavir 400 mg BID/ ritonavir 400mg BID,
15 days 40 mg QD for 4 days ↑ 3.9 fold ↑ 4.3 fold
#Clarithromycin 500 mg BID, 9 days 80 mg QD for 8 days ↑ 4.4 fold ↑ 5.4 fold
#Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days 10 mg QD for 4 days ↑3.4 fold ↑2.25 fold
#Itraconazole 200 mg QD, 4 days 40 mg SD ↑ 3.3 fold ↑ 20%
#Fosamprenavir 700 mg BID/ritonavir 100 mg BID,
14 days 10 mg QD for 4 days ↑ 2.53 fold ↑2.84 fold
#Fosamprenavir 1400 mg BID, 14 days 10 mg QD for 4 days ↑ 2.3 fold ↑ 4.04 fold
#Nelfinavir 1250 mg BID, 14 days 10 mg QD for 28 days ↑ 74% ↑ 2.2 fold
#Grapefruit Juice, 240 mL QD * 40 mg, SD ↑ 37% ↑ 16%
Diltiazem 240 mg QD, 28 days 40 mg, SD ↑ 51% No change
Erythromycin 500 mg QID, 7 days 10 mg, SD ↑ 33% ↑ 38%
Amlodipine 10 mg, single dose 80 mg, SD ↑ 15% ↓ 12 %
Cimetidine 300 mg QID, 2 weeks 10 mg QD for 2 weeks ↓ Less than 1% ↓ 11%
Colestipol 10 mg BID, 28 weeks 40 mg QD for 28 weeks Not determined ↓ 26%**
Maalox TC® 30 mL QD, 17 days 10 mg QD for 15 days ↓ 33% ↓ 34%
Efavirenz 600 mg QD, 14 days 10 mg for 3 days ↓ 41% ↓ 1%
#Rifampin 600 mg QD, 7 days (co-administered) † 40 mg SD ↑ 30% ↑ 2.7 fold
#Rifampin 600 mg QD, 5 days (doses separated) † 40 mg SD ↓ 80% ↓ 40%
#Gemfibrozil 600mg BID, 7 days 40mg SD ↑ 35% ↓ Less than 1%
#Fenofibrate 160mg QD, 7 days 40mg SD ↑ 3% ↑ 2%
Boceprevir 800 mg TID, 7 days 40 mg SD ↑ 2.30 fold ↑2.66 fold

& 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).

See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).

** Single sample taken 8-16 h post dose.

† Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

‡ 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.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
Drug/Dose (mg)		Change in AUC	Change in Cmax
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	# Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg - ethinyl estradiol 35µg		
		↑ 28% ↑ 19%	↑ 23% ↑ 30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mgBID/ritonavir 100 mg BID, 14 days	No change	No change

See Section 7 for clinical significance.

Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0 to 24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

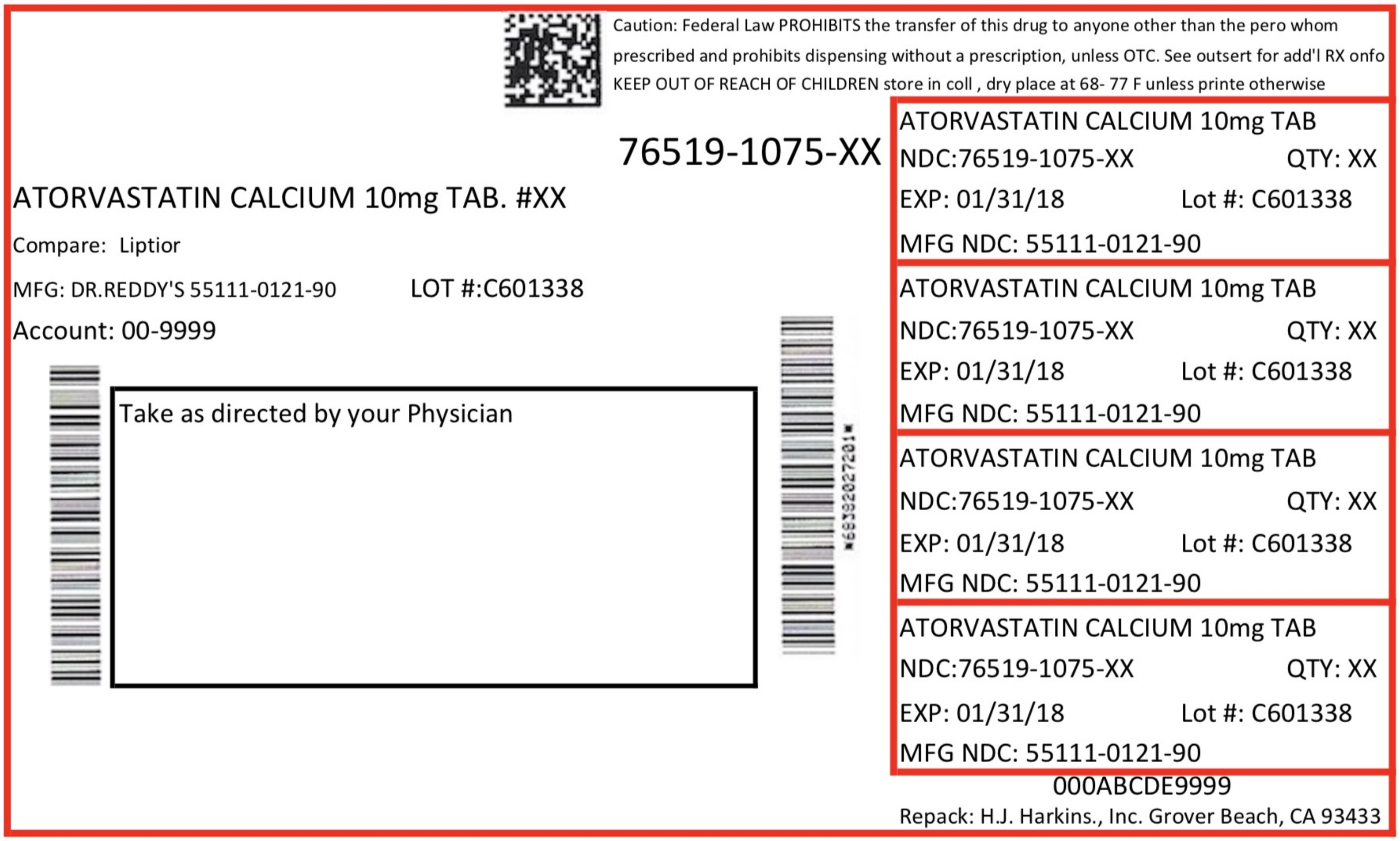
A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0 to 24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day

of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Package Label. Prinicipal Display Panel



ATORVASTATIN CALCIUM

atorvastatin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:76519-1075
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ATORVASTATIN CALCIUM (UNII: 48A5M73Z4Q) (ATORVASTATIN - UNII:A0JWA85V8F)	ATORVASTATIN	10 mg

Product Characteristics			
Color	white	**Score**	score with uneven pieces
Shape	CAPSULE	**Size**	10mm

Flavor		**Imprint Code**	RDY;121
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76519-1075-3	30 in 1 CONTAINER; Type 0: Not a Combination Product	11/20/2017	
2	NDC:76519-1075-9	90 in 1 CONTAINER; Type 0: Not a Combination Product	11/20/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091650	11/20/2017	

Labeler - H.J. Harkins Company Inc. (147681894)

Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company Inc.		147681894	relabel(76519-1075) , repack(76519-1075) , manufacture(76519-1075)

Revised: 11/2017 H.J. Harkins Company Inc.