

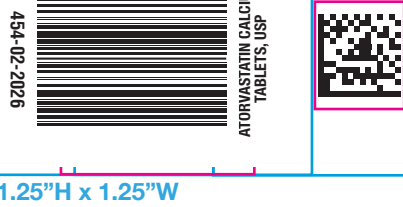
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS, USP.

INDICATIONS AND USAGE
Atorvastatin calcium tablets are an HMG-CoA reductase inhibitor (statin) indicated (1):

- To reduce the risk of:
o Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD.
o MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD.
o Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD.
o As an adjunct to diet to reduce low-density lipoprotein (LDL-C) in:
o Adults with primary hyperlipidemia.
o Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
o As an adjunct to other LDL-C-lowering therapies to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).
o As an adjunct to diet for the treatment of adults with:
o Primary dysbetalipoproteinemia.
o Hypertiglyceridemia.

DRUG INTERACTIONS
Take orally once daily with or without food (2.1).

- See full prescribing information for details regarding concomitant use of atorvastatin calcium tablets with other drugs or grapefruit juice that increase the risk of myopathy and rhabdomyolysis (2.5, 7.1).
o Rifampin: May reduce atorvastatin plasma concentrations. Administer simultaneously with atorvastatin calcium tablets (7.2).
o Oral Contraceptives: May increase plasma levels of norethindrone and ethinyl estradiol; consider this effect when selecting an oral contraceptive (7.3).
o Digoxin: May increase digoxin plasma levels; monitor patients appropriately (7.3).
o Pregnancy: May cause fetal harm (8.1).
o Lactation: Breastfeeding not recommended during treatment with atorvastatin calcium tablets (8.2).

ADVERSE REACTIONS
Most common adverse reactions (incidence >5%) are nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

DRUG FORMS AND STRENGTHS
Tablets: 10 mg, 20 mg, 40 mg, and 80 mg of atorvastatin (3).

CONTRAINDICATIONS
Acute liver failure or decompensated cirrhosis (4).

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- Hypersensitivity to atorvastatin or any excipient in atorvastatin calcium tablets (4).
o Myopathy and Rhabdomyolysis: Risk factors include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher atorvastatin calcium dosage. Discontinue atorvastatin calcium tablets if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue atorvastatin calcium tablets in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing atorvastatin calcium tablets dosage. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever (2.5, 5.1, 7.1, 8.5, 8.6).
o Immune-Mediated Necrotizing Myopathy (IMNM): Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use. Discontinue atorvastatin calcium tablets if IMNM is suspected (5.2).
o Hepatic Dysfunction: Increases in serum transaminases have occurred, some persistent. Rare reports of fatal and non-fatal hepatic failure have occurred. Consider testing liver enzymes before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue atorvastatin calcium tablets (5.3).

ADVERSE REACTIONS
Most common adverse reactions (incidence >5%) are nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

DRUG INTERACTIONS
Take orally once daily with or without food (2.1).

- See full prescribing information for details regarding concomitant use of atorvastatin calcium tablets with other drugs or grapefruit juice that increase the risk of myopathy and rhabdomyolysis (2.5, 7.1).
o Rifampin: May reduce atorvastatin plasma concentrations. Administer simultaneously with atorvastatin calcium tablets (7.2).
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ADVERSE REACTIONS
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Acute liver failure or decompensated cirrhosis (4).

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with statins, including atorvastatin calcium. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

5.5 Increased Risk of Hemorrhagic Stroke in Patients on Atorvastatin Calcium Tablets 80 mg with Recent Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial where 2,365 adult patients, without CHD who had a stroke or TIA within the preceding 6 months, were treated with atorvastatin calcium 80 mg, a higher incidence of hemorrhagic stroke was seen in the atorvastatin calcium 80 mg group compared to placebo (55, 2.3% atorvastatin calcium 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 non-fatal hemorrhagic stroke was significantly higher in the atorvastatin calcium 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 calcium group [see Adverse Reactions (6.1)]. Consider the risk/benefit of use of atorvastatin calcium 80 mg in patients with recent hemorrhagic stroke.

6 ADVERSE REACTIONS
The following important adverse reactions are described below and elsewhere in the labeling:

- Myopathy and Rhabdomyolysis [see Warnings and Precautions (5.1)]
o Immune-Mediated Necrotizing Myopathy [see Warnings and Precautions (5.2)]
o Hepatic Dysfunction [see Warnings and Precautions (5.3)]
o Increases in HbA1c and Fasting Serum Glucose Levels [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

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

In the atorvastatin calcium placebo-controlled clinical trial database of 16,066 patients (8755 Atorvastatin Calcium vs. 7,311 placebo; age range 10 years to 93 years, 39% female, 91% White, 3% Black or African American, 2% Asian, 4% other) with a median treatment duration of 53 weeks, the most common adverse reactions in patients treated with atorvastatin calcium 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%).

Table 1 summarizes adverse reactions reported in > 2% at a rate greater than placebo in patients treated with Atorvastatin Calcium (n=8,755), from seventeen placebo-controlled trials.

Table 1: Adverse Reactions Occurring in > 2% in Patients Atorvastatin Calcium-Treated with Any Dose and Greater than Placebo

Table with 7 columns: Adverse Reaction, % Placebo (N=7,311), % 10 mg (N=3,908), % 20 mg (N=188), % 40 mg (N=604), % 80 mg (N=4,055), % Any dose (N=8,755). Rows include: Nasopharyngitis, Arthralgia, Diarrhea, Pain in extremity, Urinary tract infection, Dyspepsia, Nausea, Musculoskeletal pain, Muscle spasms, Myalgia, Insomnia, Pharyngolaryngeal pain.

Other adverse reactions reported in placebo-controlled trials include: Body as a Whole: malaise, pyrexia. Digestive System: abdominal discomfort, eructation, flatulence, hepatitis, cholelithiasis. 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. Elevations in Liver Enzyme Tests.

Persistent elevations in serum transaminases, defined as more than 3 times the ULN and occurring on 2 or more occasions, 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 10mg, 20mg, 40mg, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver enzyme tests 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 liver enzyme elevations continued treatment with a reduced dose of atorvastatin calcium.

Treating to New Targets Study (TNT) [see Clinical Studies (14.1)] 10,001 patients (age range 29-78 years, 19% female; 94% White, 3% Black or African American, 1% Asian, 2% other) with clinically evident CHD were treated with atorvastatin calcium 10 mg daily (n=5006) or atorvastatin calcium 80 mg daily (n=4995). In the high-dose atorvastatin calcium group, there were more patients with serious adverse reactions (1.8%) and discontinuations due to adverse reactions (0.9%) as compared to the low-dose group (1.4%, 0.1%, respectively).

In a 26-week controlled study in pediatric patients with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% White, 1.6% Black or African American, 1.6% Asian, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 mg to 20 mg daily, as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels, was generally similar to that of placebo [see Use in Specific Populations (8.4) and Clinical Studies (14.6)].

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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.

Gastrointestinal Disorders: pancreatitis. General Disorders: fatigue. Hepatobiliary Disorders: fatal and non-fatal hepatic failure. Immune System Disorders: anaphylaxis. Injury: tendon rupture. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, myositis.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use.

Nervous System Disorders: dizziness, peripheral neuropathy.

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

There have been rare reports of new-onset or exacerbation of myasthenia gravis, including ocular myasthenia, and reports of recurrence when the same or a different statin was administered.

Psychiatric Disorders: depression. Respiratory Disorders: interstitial lung disease. Skin and Subcutaneous Tissue Disorders: angioneurotic edema, bullous rash (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis).

7 DRUG INTERACTIONS
7.1 Drug Interactions that May Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin Calcium Tablets

Atorvastatin calcium is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp, or BCRP). Atorvastatin calcium plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters. Table 2 includes a list of drugs that may increase exposure to atorvastatin calcium and may increase the risk of myopathy and rhabdomyolysis when used concomitantly and instructions for preventing or managing them [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

Table 2: Drug Interactions that May Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin Calcium Tablets

Table with 2 columns: Cyclosporine or Gemfibrozil, Clinical Impact. Rows include: Atorvastatin plasma levels were significantly increased with concomitant administration of cyclosporine and gemfibrozil; Concomitant use of cyclosporine or gemfibrozil with atorvastatin calcium is not recommended.

Anti-Viral Medications

Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin calcium with many anti-viral medications, which are inhibitors of CYP3A4 and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2) [see Clinical Pharmacology (12.3)]. Cases of myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir plus sofosbuvir with atorvastatin calcium.

Concomitant use of ledipasvir plus sofosbuvir with atorvastatin calcium is not recommended.

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Table 4: Atorvastatin Calcium Tablets Effects on Other Drugs

Table with 2 columns: Oral Contraceptives, Clinical Impact. Rows include: Co-administration of atorvastatin calcium and an oral contraceptive increased plasma concentrations of norethindrone and ethinyl estradiol; Consider this when selecting an oral contraceptive for patients taking atorvastatin calcium.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

Discontinue atorvastatin calcium when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. Atorvastatin calcium decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol.

Therefore, atorvastatin calcium may cause fetal harm when administered to pregnant patients because of the mechanism of action [see Clinical Pharmacology (12.1)]. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational cohort studies with atorvastatin calcium use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage [see Data]. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats or rabbits orally administered atorvastatin at doses that resulted in up to 30 times and 20 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 80 mg, based on body surface area (mg/m<sup>2</sup>). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development delay were observed at doses > 6 times the MRHD [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

A Medicaid cohort linkage study of 1,152 statin-exposed pregnant women compared to 886,998 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The alcohol risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were no statistically significant increases in the rate of organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain factors such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Animal Data

A Medicaid cohort linkage study of 1,152 statin-exposed pregnant women compared to 886,998 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The alcohol risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were no statistically significant increases in the rate of organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain factors such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Atorvastatin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. 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 at the MRHD based on surface area (mg/m<sup>2</sup>). In the rat, the maternal toxic dose of 300 mg/kg resulted in increased post-implantation loss and decreased fetal body weight. At the maternally toxic doses of 50 mg/kg/day and 100 mg/kg/day in rabbits, there was increased post-implantation loss, and at 100 mg/kg/day fetal body weights were decreased.

In a study in pregnant rats administered 20 mg/kg/day, 100 mg/kg/day, or 225 mg/kg/day from gestation day 7 through to lactation day 20 (weaning), there was decreased survival at birth, postnatal day 4, weaning, and post-weaning in pups of mothers dosed with 225 mg/kg/day. A dose at which maternal toxicity was observed. Pup body weight was decreased through postnatal day 21 at 100 mg/kg/day, and through postnatal day 91 at 225 mg/kg/day. Pup development was delayed (rotor performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human exposure at the MRHD, based on AUC.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma.

8.2 Lactation
Risk Summary

There is no information about the presence of atorvastatin in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, it has been shown that another drug in this class passes into human milk. Studies in rats have shown that atorvastatin and/or its metabolites are present in the breast milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk [see Data]. Statins, including atorvastatin calcium, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant.

Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with atorvastatin calcium [see Use in Specific Populations (8.1), Clinical Pharmacology (12.1)].

Data

Following a single oral administration of 10 mg/kg of radioactive atorvastatin to lactating rats, the concentration of total radioactivity was determined. Atorvastatin and/or its metabolites were measured in the breast milk and pup plasma at a 2:1 ratio (milk:plasma).

8.4 Pediatric Use

The safety and effectiveness of atorvastatin calcium as an adjunct to diet to reduce LDL-C have been established in pediatric patients 10 years of age and older with HeFH. Use of atorvastatin calcium for this indication is based on a trial without a concurrent control group in 8 pediatric patients 10 years of age and older with HeFH [see Clinical Studies (14)].

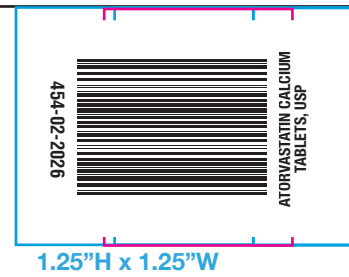
The safety and effectiveness of atorvastatin calcium have not been established in pediatric patients younger than 10 years of age with HeFH or HoFH, or in pediatric patients with other types of hyperlipidemia (other than HeFH or HoFH).

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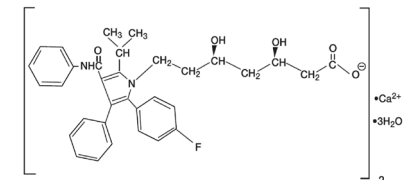
4-fold greater in patients with Childs-Pugh A disease. C<sub>max</sub> and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease. Atorvastatin calcium is contraindicated in patients with acute liver failure or decompensated cirrhosis [see Contraindications (4)].

10 OVERDOSAGE No specific antidotes for atorvastatin calcium are known. Contact Poison Control (1-800-222-1222) for latest recommendations. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin calcium clearance.

11 DESCRIPTION

Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Atorvastatin calcium, USP is [R-(R',R'')]-2-[4-(fluorophenyl)-8,8-dihydroxy-5-(1-methylethyl)-3-phenyl-4-(phenylamino)carboxyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C<sub>33</sub>H<sub>44</sub>FNO<sub>7</sub>)<sub>2</sub>Ca<sub>2</sub>•3H<sub>2</sub>O, and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium, USP is a white to off-white crystalline powder. Atorvastatin calcium, USP is freely soluble in methanol and insoluble in aqueous solutions of pH 4 and below.

Atorvastatin calcium tablets, USP for oral administration contain 10 mg, 20 mg, 40 mg, or 80 mg atorvastatin and the following inactive ingredients: lactose monohydrate, NF; colloidal silicon dioxide, NF; copovidone, NF; croscarmellose sodium, NF; magnesium stearate, NF; mannitol, USP; silicified microcrystalline cellulose, NF; sodium bicarbonate, USP; sodium carbonate anhydrous, NF; sodium lauryl sulfate, NF; hypromellose, polyethylene glycol, tac, titanium dioxide, and iron oxide yellow.

This product meets the requirements of USP Dissolution Test-2.

12 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-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. 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.

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 C<sub>max</sub> 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 C<sub>max</sub> and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution

Mean volume of distribution of atorvastatin 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.

Elimination

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.

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 hours 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 C<sub>max</sub> and 30% for AUC) in healthy elderly subjects (age >65 years) than in young adults.

Pediatric

Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population PK model with data including pediatric HEFH patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.

Gender

Plasma concentrations of atorvastatin calcium in females differ from those in males (approximately 20% higher for C<sub>max</sub> and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin calcium between males and females.

Renal Impairment

Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin calcium [see Use in Specific Populations (8.6)]. 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. C<sub>max</sub> and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C<sub>max</sub> and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see Use in Specific Populations (8.7)].

Drug Interactions

Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Table 5: Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Table with 4 columns: Co-administered drug and dosage regimen, Atorvastatin Dosage (mg), Ratio of AUC, Ratio of C<sub>max</sub>.

Table with 4 columns: Atorvastatin Dosage, Co-administered drug and dosage regimen, Ratio of AUC, Ratio of C<sub>max</sub>.

Table 6: Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Table with 4 columns: Atorvastatin Dosage, Co-administered drug and dosage regimen, Ratio of AUC, Ratio of C<sub>max</sub>.

Table 7: Overview of Efficacy Results in TNT

Table with 5 columns: Endpoint, Atorvastatin 10 mg (N=5,006), Atorvastatin 80 mg (N=4,995), HR<sup>a</sup> (95%CI).

14 CLINICAL STUDIES

Prevention of Cardiovascular Disease

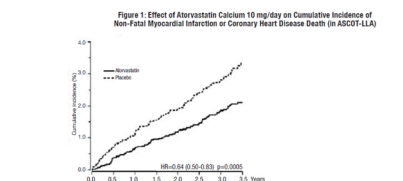
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 patients with hypertension, 40-80 years of age (mean of 63 years; 19% female; 95% White, 3% Black or African American, 1% South Asian, 1% other), without a previous myocardial infarction and with total cholesterol (TC) levels <251 mg/dL. Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81%), age >55 years (85%), smoking (33%), diabetes (24%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14%), peripheral vascular disease (5%), left ventricular hypertrophy (14%), prior cerebrovascular event

(10%), specific ECG abnormality (14%), proteinuria/albuminuria (62%). In this double-blind, placebo-controlled trial, patients were treated with anti-hypertensive therapy (goal BP <140/90 mm Hg for patients without diabetes, <130/80 mm Hg for patients with diabetes) and allocated to either atorvastatin calcium 10 mg daily (n=5,168) or placebo (n=5,137), 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 calcium on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium group)] with a relative risk reduction of 36% [based on an incidence of 1.9% for atorvastatin calcium vs. 3.0% for placebo, p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin calcium was seen regardless of baseline LDL levels.

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



Atorvastatin calcium also significantly decreased the relative risk for revascularization procedures by 42% (incidences of 1.4% for atorvastatin calcium and 2.5% for placebo). Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium on cardiovascular disease (CVD) endpoints was assessed in 2,838 subjects (94% white, 2% Black or African American, 2% South Asian, 1% other; 68% male), ages 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL <160 mg/dL and triglycerides (TG) <600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the trial. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin calcium 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HDL-C 7.7 mg/dL, median LDL-C 120 mg/dL, median TC 207 mg/dL, median TG 151 mg/dL, median HDL-C 52 mg/dL.

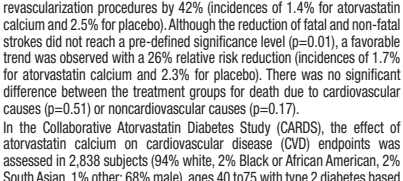
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium group vs. 127 events in the placebo group) with a relative risk reduction of 37% (HR 0.63, 95% CI (0.48, 0.83), p<0.001 (see Figure 2)). An effect of atorvastatin calcium was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin calcium significantly reduced the rate of stroke by 48% (21 events in the atorvastatin calcium group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium group vs. 64 events in the placebo group), HR 0.58, 95% CI (0.39, 0.86) (p=0.007). There was no significant difference between treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin calcium group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of Atorvastatin Calcium 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In the Treating to New Targets Study (TNT), the effect of atorvastatin calcium 80 mg/day vs. atorvastatin calcium 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% White, 81% male, 38% >65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MACE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TG, TC, TG, HDL, and HDL cholesterol levels at 12 weeks were 75 mg/dL, 145 mg/dL, 128 mg/dL, 98 mg/dL, and 47 mg/dL, during treatment with 80 mg of atorvastatin calcium and 99 mg/dL, 177 mg/dL, 152 mg/dL, 129 mg/dL, and 48 mg/dL, during treatment with 10 mg of atorvastatin calcium.

Treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of MACE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p<0.0002 (see Figure 3 and Table 7). The overall risk reduction was consistent regardless of age (<65, >65) or sex.

Figure 3: Effect of Atorvastatin Calcium 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

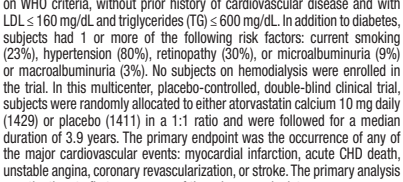


Table with 5 columns: Endpoint, Atorvastatin Calcium 10 mg (N=5,168), Atorvastatin Calcium 20 mg (N=5,137), HR (95%CI).

Table 8: Dose Response in Patients with Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)

Table with 6 columns: Dose, N, TC, LDL-C, Apo B, TG, HDL-C.

Table 9: Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Table with 6 columns: Treatment (Daily Dosage), N, Total-C, LDL-C, Apo B, TG, HDL-C.

Table 10: Combined Patients with Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

Table with 5 columns: Placebo (N=12), Atorvastatin Calcium 10 mg (N=37), Atorvastatin Calcium 20 mg (N=13), Atorvastatin Calcium 80 mg (N=14).

15 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myopathy and Rhabdomyolysis

Advise patients that atorvastatin calcium may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication or consuming large quantities of grapefruit juice and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever [see Warnings and Precautions (5.1), Drug Interactions (7.1)].

Hepatic Dysfunction

Inform patients that atorvastatin calcium may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice [see Warnings and Precautions (5.3)].

Increases in HbA1c and Fasting Serum Glucose Levels

Inform patients that increases in HbA1c and fasting serum glucose levels may occur with atorvastatin calcium. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices [see Warnings and Precautions (5.4)].

Pregnancy

Advise pregnant patients and patients who may become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if atorvastatin calcium should be discontinued [see Use in Specific Populations (8.1)].

Lactation

Advise patients that breastfeeding is not recommended during treatment with atorvastatin calcium [see Use in Specific Populations (8.2)].

Missed Doses

If a dose is missed, advise patients not to take the missed dose and resume with the next scheduled dose.

Manufactured by: ScieGen Pharmaceuticals, Inc.

Hauppauge, NY 11788 USA

Distributed by: Radha Pharmaceuticals, Inc.

Hauppauge, NY 11788 USA

Dispense the Patient Information available at: https://radhapharm.com/medication-guide/

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apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia are shown in the table below (Table 11).

Table 11: Open-Label Crossover Trial of 16 Patients with Dysbetalipoproteinemia

Table with 4 columns: Median % Change (min, max), Atorvastatin Calcium 80 mg, Atorvastatin Calcium 10 mg.

HEFH in Adults and Pediatric Patients

In a trial without a concurrent control group, 29 patients (mean age of 22 years, median age of 24 years, 31% <18 years) with HEFH received maximum daily doses of 20 mg to 80 mg of atorvastatin calcium. The mean LDL-C reduction in this trial was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

HEFH in Pediatric Patients

In a double-blind, placebo-controlled trial followed by an open-label phase, 187 males and post-menarchal females 10 years to 17 years of age (mean age 14.1 years; 31% female; 92% White, 1.6% Black or African American, 1.6% Asian, 4.8% other) with heterozygous familial hypercholesterolemia (HEFH) or severe hypercholesterolemia, were randomized to atorvastatin calcium (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium for 26 weeks. Inclusion in the trial required 1) a baseline LDL-C level >190 mg/dL or 2) a baseline LDL-C level >160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 219 mg/dL (range: 139 mg/dL to 365 mg/dL) in the atorvastatin calcium group compared to 230 mg/dL (range: 160 mg/dL to 325 mg/dL) in the placebo group. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >130 mg/dL. The number of atorvastatin calcium-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 78 (56%).

Atorvastatin calcium significantly decreased plasma levels of total-C, LDL-C, TG, and apolipoprotein B during the 26-week double-blind phase (see Table 12).

Table 12: Lipid-altering Effects of Atorvastatin Calcium in Adolescent Males and Females with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Intention-to-Treat Population)

Table with 6 columns: Dosage, N, Total-C, LDL-C, HDL-C, TG, Apolipoprotein B.

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the atorvastatin calcium group compared to 226.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

Atorvastatin was also studied in a three year open-label, uncontrolled trial that included 163 patients with HEFH who were 10 years to 15 years old (62 males and 81 females). All patients had a clinical diagnosis of HEFH confirmed by genetic analysis (if not already confirmed by family history). Approximately 98% were White, and less than 1% were Black, African American or Asian. Mean LDL-C at baseline was 232 mg/dL. The starting atorvastatin dosage was 10 mg once daily and doses were adjusted to achieve a target of <130 mg/dL LDL-C. The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous clinical trials in both adult and pediatric placebo-controlled trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

Atorvastatin Calcium Tablets, USP are supplied as follows:

Table with 4 columns: Strength, How Supplied, NDC, Tablet Description.

Storage

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Dispense in a light, child-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myopathy and Rhabdomyolysis

Advise patients that atorvastatin calcium may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication or consuming large quantities of grapefruit juice and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever [see Warnings and Precautions (5.1), Drug Interactions (7.1)].

Hepatic Dysfunction

Inform patients that atorvastatin calcium may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice [see Warnings and Precautions (5.3)].

Increases in HbA1c and Fasting Serum Glucose Levels

Inform patients that increases in HbA1c and fasting serum glucose levels may occur with atorvastatin calcium. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices [see Warnings and Precautions (5.4)].

Pregnancy

Advise pregnant patients and patients who may become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if atorvastatin calcium should be discontinued [see Use in Specific Populations (8.1)].

Lactation

Advise patients that breastfeeding is not recommended during treatment with atorvastatin calcium [see Use in Specific Populations (8.2)].

Missed Doses

If a dose is missed, advise patients not to take the missed dose and resume with the next scheduled dose.

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