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ATORVASTATIN CALCIUM TABLETS, USP



#### 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.

#### ATORVASTATIN CALCIUM TABLETS, oral use

Initial U.S. Approval: 1996

#### INDICATIONS AND USAGE

Atorvastatin calcium tablet is an HMG-CoA reductase inhibitor (statin) indicated (1):

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

#### DOSE AND ADMINISTRATION

- Take orally once daily with or without food (2.1).
- Assess LDL-C when clinically appropriate as early as 4 weeks after initiating atorvastatin calcium tablets, and adjust dosage if necessary (2.1).
- Adults (2.2):
  - Recommended starting dosage is 10 mg or 20 mg once daily; dosage range is 10 mg to 80 mg once daily.
  - Patients requiring LDL-C reduction  $\geq 45\%$  may start at 40 mg once daily.
- Pediatric Patients Aged 10 Years of Age and Older with HeFH:
  - Recommended starting dosage is 10 mg once daily; dosage range is 10 mg to 20 mg once daily (2.3).
- Pediatric Patients Aged 10 Years of Age and Older with HoFH:
  - Recommended starting dosage is 10 mg to 20 mg once daily; dosage range is 10 mg to 80 mg once daily (2.4).
- See full prescribing information for atorvastatin calcium tablets dosage modifications due to drug interactions (2.5).

#### DOSE FORMS AND STRENGTHS

Tablets: 10 mg, 20 mg, 40 mg, and 80 mg of atorvastatin (3).

#### CONTRAINDICATIONS

- Acute liver failure or decompensated cirrhosis (4).

#### FULL PRESCRIBING INFORMATION: CONTENTS

##### 1 INDICATIONS AND USAGE

##### 2 DOSAGE AND ADMINISTRATION

##### 2.1 Important Dosage Information

##### 2.2 Recommended Dosage in Adult Patients

##### 2.3 Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HeFH

##### 2.4 Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HoFH

##### 2.5 Dosage Modifications Due to Drug Interactions

##### 3 DOSAGE FORMS AND STRENGTHS

##### 4 CONTRAINDICATIONS

##### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Myopathy and Rhabdomyolysis

##### 5.2 Immune-Mediated Necrotizing Myopathy

##### 5.3 Hepatic Dysfunction

##### 5.4 Increases in HbA1c and Fasting Serum Glucose Levels

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

##### 6 ADVERSE REACTIONS

##### 6.1 Clinical Trials Experience

##### 6.2 Postmarketing Experience

##### 7 DRUG INTERACTIONS

##### 7.1 Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin Calcium Tablets

##### 7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets

##### 7.3 Atorvastatin Calcium Tablets Effects on Other Drugs

##### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

##### 8.2 Lactation

##### 8.3 Fertility

##### 8.4 Geriatric Use

##### 8.5 Renal Impairment

##### 8.6 Hepatic Impairment

##### 10 DESCRIPTION

##### 11 DESCRIPTION

##### 12 CLINICAL PHARMACOLOGY

##### 12.1 Mechanism of Action

##### 12.2 Pharmacodynamics

##### 12.3 Pharmacokinetics

##### 13 NONCLINICAL TOXICOLOGY

##### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

##### 14 CLINICAL STUDIES

##### 14.1 HOW SUPPLIED/STORAGE AND HANDLING

##### 15 PATIENT COUNSELING INFORMATION

##### 15.1 Contraindications

##### 15.2 Warnings and Precautions

##### 15.3 Drug Interactions

##### 15.4 Pregnancy, Lactation, and Fertility

##### 15.5 Geriatric Use

##### 15.6 Renal Impairment

##### 15.7 Hepatic Impairment

##### 15.8 Hemorrhagic Stroke

##### 15.9 Myopathy and Rhabdomyolysis

##### 15.10 Immune-Mediated Necrotizing Myopathy

##### 15.11 Hepatic Dysfunction

##### 15.12 Increases in HbA1c and Fasting Serum Glucose Levels

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

##### 15.14 Adverse Reactions

##### 15.15 Clinical Trials Experience

##### 15.16 Postmarketing Experience

##### 15.17 Drug Interactions

##### 15.18 Atorvastatin Calcium Tablets Effects on Other Drugs

##### 15.19 Pregnancy, Lactation, and Fertility

##### 15.20 Geriatric Use

##### 15.21 Renal Impairment

##### 15.22 Hepatic Impairment

##### 15.23 Hemorrhagic Stroke

##### 15.24 Myopathy and Rhabdomyolysis

##### 15.25 Immune-Mediated Necrotizing Myopathy

##### 15.26 Hepatic Dysfunction

##### 15.27 Increases in HbA1c and Fasting Serum Glucose Levels

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

##### 15.29 Adverse Reactions

##### 15.30 Clinical Trials Experience

##### 15.31 Postmarketing Experience

##### 15.32 Drug Interactions

##### 15.33 Atorvastatin Calcium Tablets Effects on Other Drugs

##### 15.34 Pregnancy, Lactation, and Fertility

##### 15.35 Geriatric Use

##### 15.36 Renal Impairment

##### 15.37 Hepatic Impairment

##### 15.38 Hemorrhagic Stroke

##### 15.39 Myopathy and Rhabdomyolysis

##### 15.40 Immune-Mediated Necrotizing Myopathy

##### 15.41 Hepatic Dysfunction

##### 15.42 Increases in HbA1c and Fasting Serum Glucose Levels

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

##### 15.44 Adverse Reactions

##### 15.45 Clinical Trials Experience

##### 15.46 Postmarketing Experience

##### 15.47 Drug Interactions

##### 15.48 Atorvastatin Calcium Tablets Effects on Other Drugs

##### 15.49 Pregnancy, Lactation, and Fertility

##### 15.50 Geriatric Use

##### 15.51 Renal Impairment

##### 15.52 Hepatic Impairment

##### 15.53 Hemorrhagic Stroke

##### 15.54 Myopathy and Rhabdomyolysis

##### 15.55 Immune-Mediated Necrotizing Myopathy

##### 15.56 Hepatic Dysfunction

##### 15.57 Increases in HbA1c and Fasting Serum Glucose Levels

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

##### 15.59 Adverse Reactions

##### 15.60 Clinical Trials Experience

##### 15.61 Postmarketing Experience

##### 15.62 Drug Interactions

##### 15.63 Atorvastatin Calcium Tablets Effects on Other Drugs

##### 15.64 Pregnancy, Lactation, and Fertility

##### 15.65 Geriatric Use

##### 15.66 Renal Impairment

##### 15.67 Hepatic Impairment

##### 15.68 Hemorrhagic Stroke

##### 15.69 Myopathy and Rhabdomyolysis

##### 15.70 Immune-Mediated Necrotizing Myopathy

##### 15.71 Hepatic Dysfunction

##### 15.72 Increases in HbA1c and Fasting Serum Glucose Levels

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

##### 15.74 Adverse Reactions

- Hypersensitivity to atorvastatin or any excipient in atorvastatin calcium tablets (4).

#### WARNINGS AND PRECAUTIONS

- 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).
- 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).
- 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  $\geq 5\%$ ) are nasopharyngitis, upper respiratory tract infection, and urinary tract infection (6.1). To report SUSPECTED ADVERSE REACTIONS, contact ScieGen Pharmaceuticals, Inc., at 1-855-724-3436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

#### DRUG INTERACTIONS

- 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).
- Rifampin:** May reduce atorvastatin plasma concentrations. Administer simultaneously with atorvastatin calcium tablets (7.2).
- Oral Contraceptives:** May increase plasma levels of norethindrone and ethinyl estradiol; consider this effect when selecting an oral contraceptive (7.3).
- Digoxin:** May increase digoxin plasma levels; monitor patients appropriately (7.3).

#### USE IN SPECIFIC POPULATIONS

- Pregnancy:** May cause fetal harm (8.1).
- Lactation:** Breastfeeding not recommended during treatment with atorvastatin calcium tablets (8.2).

#### See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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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 higher in the atorvastatin calcium 80 mg group compared to placebo (5.2, 3% atorvastatin calcium vs. 3.1, 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.

#### ADVERSE REACTIONS

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

- Myopathy and Rhabdomyolysis (see Warnings and Precautions (5.1) and Immune-Mediated Necrotizing Myopathy (see Warnings and Precautions (5.2))
- Hepatic Dysfunction (see Warnings and Precautions (5.3))
- 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 (975 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 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%).

Table 1 summarizes adverse reactions reported in  $\geq 2\%$  and 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 $\geq 2\%$ in Patients Atorvastatin Calcium - Treated with any Dose and Greater than Placebo

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)
Nasopharyngitis	8.2	12.9	5.3	7.0	4.2	8.3
Arthralgia	6.5	8.9	11.7	10.6	4.3	6.9
Diarrhea	6.3	7.3	6.4	14.1	5.2	6.8
Pain in extremity	5.9	8.5	3.7	9.3	3.1	6.0
Urinary tract infection	5.6	6.9	6.4	8.0	4.1	5.7
Dyspepsia	4.3	5.9	3.2	6.0	3.3	4.7
Nausea	3.5	3.7	3.7	7.1	3.8	4.0
Musculoskeletal pain	3.6	5.2	3.2	5.1	2.3	3.8
Muscle spasms	3.0	4.6	4.8	5.1	2.4	3.6
Myalgia	3.1	3.6	5.9	8.4	2.7	3.5
Insomnia	2.9	2.8	1.1	5.3	2.8	3.0
Pharyngolaryngeal pain	2.1	3.9	1.6	2.8	0.7	2.3

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: transaminase increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia

Nervous System: nightmares

Respiratory System: epistaxis

Skin and Appendages: urticaria

Sense Organs: 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 treated with 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.

**Trials in New Targets Study (NT)**

In 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 (9.9%) as compared to the low-dose group (1.4%; 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations ( $\geq 3$  x ULN twice within 4-10 days) occurred in 1.3% of individuals with the atorvastatin calcium group and 0.2% of individuals with atorvastatin calcium 10 mg. Elevations of CK ( $> 10$  x ULN) were higher in the high-dose atorvastatin calcium group (0.3%) compared to the low-dose atorvastatin calcium group (0.1%).

**Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)**

In SPARCL, 4,731 patients (age range 21-82 years, 40% female; 93% White, 3% Black or African American, 1% Asian, 3% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months were 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 ( $\geq 3$  x ULN twice within 4-10 days) in the atorvastatin calcium group (0.9%) compared to placebo (0.1%). Elevations of CK ( $> 10$  x ULN) were rare, but were higher in the atorvastatin calcium group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 6.1% of subjects in the atorvastatin calcium group and 3.9% of subjects in the placebo group.

In a post-hoc analysis, atorvastatin calcium 80 mg reduced the incidence of ischemic stroke (2.3% vs. 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 calcium group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Patients who entered the trial with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke (16% Atorvastatin calcium vs. 4% placebo).

**Adverse Reactions from Clinical Studies of atorvastatin calcium in Pediatric Patients with HeFH**

In a 26-week controlled study in pediatric patients with HeFH (ages 10 years to 17 years) (n=140; 31% female; 52% White, 16% Black or African American, 15% Asian, 4.8% other), safety and tolerability profile of atorvastatin calcium 10 mg to 20 mg daily, as well as 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.

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ATORVASTATIN CALCIUM TABLETS, USP

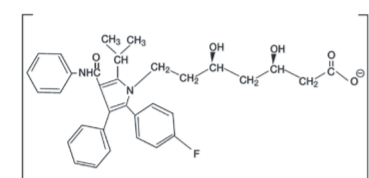
4-fold greater in patients with Childs-Pugh A disease.  $C_{max}$  and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease. Atorvastatin calcium is contraindicated in patients with acute liver failure or decompensated cirrhosis (see Contraindications (4)).

#### 10 OVERDOSE

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)-6,8-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[phenylamino]carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is  $(C_{28}H_{37}FNO_6)_2Ca \cdot 3H_2O$  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 carbonate, USP; sodium carbonate anhydrous, NF; sodium lauryl sulfate, NF; hypromellose, polyethylene glycol, talc, 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

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 inhibitor activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by  $C_{max}$  and AUC, LDL-C reduction is similar whether atorvastatin calcium is given with or without food. Plasma atorvastatin calcium concentrations are lower (approximately 30% for  $C_{max}$  and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

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 para-hydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and para-hydroxylated 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 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  $C_{max}$  and 30% for AUC) in healthy elderly subjects (age >65 years) than in young adults.

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  $C_{max}$  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.  $C_{max}$  and AUC are each 4-fold greater in patients with Childs-Pugh A disease.  $C_{max}$  and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (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

Co-administered drug and dosage regimen	Atorvastatin		
	Dosage (mg)	Ratio of AUC <sup>a</sup>	Ratio of C <sub>max</sub> <sup>a</sup>
Cyclosporin 5.2 mg/kg/day, stable dose	10 mg QD <sup>b</sup> for 28 days	8.69	10.66
Tiripranavir 500 mg BID/tiripranavir 200 mg BID, 7 days	10 mg SD <sup>c</sup>	9.36	8.58

Atorvastatin	Co-administered drug and dosage regimen	Ratio of AUC	Ratio of C <sub>max</sub>
80 mg QD <sup>d</sup> for 15 days	Amipyrine, 600 mg SD <sup>e</sup>	1.03	0.89
80 mg QD <sup>d</sup> for 10 days	* Digoxin 0.25 mg QD <sup>f</sup> , 20 days	1.15	1.20
40 mg QD <sup>d</sup> for 22 days	Oral contraceptive QD <sup>g</sup> , 2 months - norethindrone 1mg - ethinyl estradiol 35µg	1.28 1.19	1.23 1.30
10 mg SD <sup>c</sup>	Tiripranavir 500 mg BID/ ritonavir 200 mg BID, 7 days	1.08	0.96
10 mg QD <sup>d</sup> for 4 days	Fosamprenavir 1400 mg BID, 14 days	0.73	0.82
10 mg QD <sup>d</sup> for 4 days	Fosamprenavir 700 mg BID/ ritonavir 100 mg BID, 14 days	0.99	0.94

<sup>a</sup> See Section 7 for clinical significance.  
<sup>b</sup> Once daily  
<sup>c</sup> Single dose  
<sup>d</sup> Three times daily  
<sup>e</sup> Four times daily  
<sup>f</sup> Every 8 hours

<sup>g</sup> Represents ratio of treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).  
<sup>h</sup> See Sections 5.1 and 7 for clinical significance.  
<sup>i</sup> Greater increases in AUC (ratio of AUC up to 2.5) and/or C<sub>max</sub> (ratio of C<sub>max</sub> up to 1.71) have been reported with excessive grapefruit consumption (> 750 mL to 1.2 liters per day).  
<sup>j</sup> Ratio based on a single sample taken 8 to 16 h post dose.

<sup>k</sup> 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.  
<sup>l</sup> 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.

<sup>m</sup> Once daily  
<sup>n</sup> Single dose  
<sup>o</sup> Three times daily  
<sup>p</sup> Four times daily  
<sup>q</sup> Every 8 hours

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

Atorvastatin	Co-administered drug and dosage regimen	Ratio of AUC	Ratio of C <sub>max</sub>
80 mg QD <sup>d</sup> for 15 days	Amipyrine, 600 mg SD <sup>e</sup>	1.03	0.89
80 mg QD <sup>d</sup> for 10 days	* Digoxin 0.25 mg QD <sup>f</sup> , 20 days	1.15	1.20
40 mg QD <sup>d</sup> for 22 days	Oral contraceptive QD <sup>g</sup> , 2 months - norethindrone 1mg - ethinyl estradiol 35µg	1.28 1.19	1.23 1.30
10 mg SD <sup>c</sup>	Tiripranavir 500 mg BID/ ritonavir 200 mg BID, 7 days	1.08	0.96
10 mg QD <sup>d</sup> for 4 days	Fosamprenavir 1400 mg BID, 14 days	0.73	0.82
10 mg QD <sup>d</sup> for 4 days	Fosamprenavir 700 mg BID/ ritonavir 100 mg BID, 14 days	0.99	0.94

<sup>a</sup> See Section 7 for clinical significance.  
<sup>b</sup> Once daily  
<sup>c</sup> Single dose  
<sup>d</sup> Three times daily  
<sup>e</sup> Four times daily  
<sup>f</sup> Every 8 hours

#### 13 NONCLINICAL TOXICOLOGY

##### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day, 2 rats from two groups in the high-dose females; in one, there was a fibrosarcoma, 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 mg/kg/day, 200 mg/kg/day, 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.

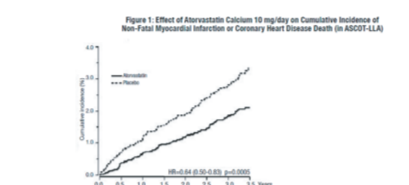
In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects on fertility. Studies in male rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was oligospermia and aspermia in the epididymis 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 mg/kg 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, sperm head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10 mg/kg, 40 mg/kg, or 120 mg/kg for two years.

##### 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  $\geq 251$  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  $\geq 6$  (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=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin 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. 80 events in the atorvastatin calcium group)) with a relative risk reduction of 36% (based on incidences 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.



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-C  $\geq 160$  mg/dL and triglycerides (TG)  $\geq 500$  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 assigned 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 HbA1c 7.7%; 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 risk 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 the 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 (0.73 vs. 0.96 deaths per 100 patient-years).

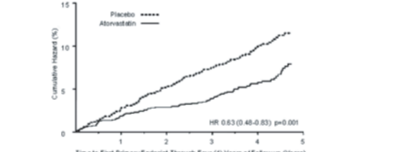


Figure 2: Effect of Atorvastatin Calcium 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS

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, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73 mg/dL, 145 mg/dL, 128 mg/dL, 98 mg/dL, and 47 mg/dL, respectively. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 48 weeks were 73 mg/dL, 145 mg/dL, 128 mg/dL, 98 mg/dL, and 47 mg/dL, respectively. 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)

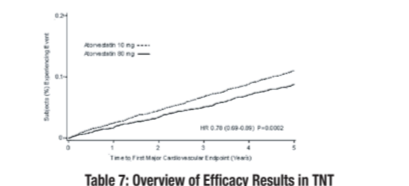


Table 7: Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5,006)	Atorvastatin 80 mg (N=4,995)	HR <sup>a</sup> (95%CI)
<b>PRIMARY ENDPOINT</b>	n (%)	n (%)	
First major cardiovascular endpoint	548 (10.9)	434 (8.7)	0.78 (0.69, 0.89)
<b>Components of the Primary Endpoint</b>			
CHD death	127 (2.5)	101 (2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308 (6.2)	243 (4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155 (3.1)	117 (2.3)	0.75 (0.59, 0.96)
<b>SECONDARY ENDPOINTS</b>			
First CHD with hospitalization	164 (3.3)	122 (2.4)	0.74 (0.59, 0.94)

Endpoint	Atorvastatin 10 mg (N=5,168)	Atorvastatin 80 mg (N=5,137)	HR <sup>a</sup> (95%CI)
First PVD endpoint	282 (5.5)	275 (5.4)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure <sup>b</sup>	904 (18.1)	667 (13.4)	0.72 (0.65, 0.80)
First documented angina endpoint <sup>c</sup>	615 (12.3)	545 (10.9)	0.88 (0.79, 0.99)
All-cause mortality	282 (5.6)	284 (5.7)	1.01 (0.85, 1.19)
<b>Components of All-Cause Mortality</b>			
Cardiovascular death	155 (3.1)	126 (2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127 (2.5)	158 (3.2)	1.25 (0.99, 1.57)
Cancer death	75 (1.5)	85 (1.7)	1.13 (0.83, 1.55)
Other non-CV death	43 (0.9)	58 (1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9 (0.2)	15 (0.3)	1.67 (0.73, 3.82)

<sup>a</sup> Atorvastatin 80 mg, atorvastatin 10 mg  
<sup>b</sup> Component of other secondary endpoints  
<sup>c</sup> Secondary endpoints not included in primary endpoint  
HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CVD=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft  
Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 7). Of the predefined secondary endpoints, treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 7). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the atorvastatin calcium 80 mg group than in the atorvastatin calcium 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin calcium 80 mg group than in the atorvastatin calcium 10 mg treatment group.

##### Primary Hyperlipidemia in Adults

Atorvastatin Calcium reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

In two multicenter, placebo-controlled, dose-response trials in patients with hyperlipidemia, atorvastatin calcium was given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, Apo B, and TG. (Pooled results are provided in Table 8).

Table 8: Dose Response in Patients with Primary Hyperlipidemia (Adjusted Mean % Change From Baseline<sup>a</sup>)

Dose	N	TC	LDL-C	Apo B	TG	HDL-C
Placebo	21	4	4	3	10	-3
10	22	-29	-39	-32	-19	6
20	20	-33	-43	-35	-26	9
40	21	-37	-50	-42	-29	6
80	23	-45	-60	-50	-37	5

<sup>a</sup> Results are pooled from 2 dose-response trials. In three multicenter, double-blind trials in patients with hyperlipidemia, atorvastatin calcium was compared to other statins. After randomization, patients were treated for 16 weeks with either atorvastatin calcium 10 mg per day or a fixed dose of the comparative agent (Table 9).

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

Treatment (Daily Dosage)	N	Total-C	LDL-C	Apo B	TG	HDL-C
<b>Trial 1</b>						
Atorvastatin calcium 10 mg	707	-27 <sup>a</sup>	-36 <sup>a</sup>	-28 <sup>a</sup>	-17 <sup>a</sup>	+7
Rosuvastatin 20 mg	191	-19	-27	-20	-6	+7
95% CI for Diff <sup>b</sup>		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0
<b>Trial 2</b>						
Atorvastatin calcium 10 mg	222	-29 <sup>a</sup>	-39 <sup>a</sup>	-27 <sup>a</sup>	-17 <sup>a</sup>	+6
Pravastatin 20 mg	77	-17	-23	-17	-9	+8
95% CI for Diff <sup>b</sup>		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -9.7	-4.9, 1.6
<b>Trial 3</b>						
Atorvastatin calcium 10 mg	132	-29 <sup>a</sup>	-37 <sup>a</sup>	-34 <sup>a</sup>	-23 <sup>a</sup>	+7
Simvastatin 10 mg	45	-24	-30	-30	-15	+7
95% CI for Diff <sup>b</sup>		-8.7, -2.7	-10.1, -2.6	-8.0, -11.1	-15.1, -9.7	-4.3, 3.9

<sup>a</sup> A negative value for the 95% CI for the difference between treatments favors atorvastatin calcium for all except HDL-C, for which a positive value favors atorvastatin calcium. If the range does not include 0, this indicates a statistically significant difference.  
<sup>b</sup> Significantly different from lovastatin, ANCOVA, p < 0.05  
<sup>c</sup> Significantly different from pravastatin, ANCOVA, p < 0.05  
<sup>d</sup> Significantly different from simvastatin, ANCOVA, p < 0.05  
Table 9 does not contain data comparing the effects of atorvastatin calcium 10 mg and higher dosages of lovastatin, pravastatin, and simvastatin. The drugs compared in the trials summarized in the table are not necessarily interchangeable.