

ATORVASTATIN CALCIUM- atorvastatin calcium tablet, film coated

AvPAK

HIGHLIGHTS OF PRESCRIBING INFORMATION

Atorvastatin Calcium Tablets

Rx Only

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, for oral use

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Atorvastatin calcium tablets are a HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in adult patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy (1.2).

Limitations of Use:

Atorvastatin calcium has not been studied in *Fredrickson* Types I and V dyslipidemias (1.3).

DOSAGE AND ADMINISTRATION

- Dose range: 10 to 80 mg once daily (2.1).
- Recommended start dose: 10 or 20 mg once daily (2.1).
- Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
- Pediatric patients with HeFH: starting dose: 10 mg once daily; dose range: 10 to 20 mg/day for patients 10 years to 17 years of age (2.2).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

(4)

- Acute liver failure or decompensated cirrhosis (4).
- Hypersensitivity to atorvastatin or any excipient in atorvastatin calcium tablets (4).

WARNINGS AND PRECAUTIONS

(5)

- *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 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 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).

(5)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq$ 5%) are nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1). (6)

(6)

To report SUSPECTED ADVERSE REACTIONS, contact AvKARE at 1-855-361-3993 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

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

- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses ($\geq$ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with atorvastatin (7).
- Digoxin: Patients should be monitored appropriately (7.8).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.9).
- Rifampin should be simultaneously co-administered with atorvastatin (7.7).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (8.6, 12.3).
- Females of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with atorvastatin (8.3)

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Atorvastatin Calcium Tablets are indicated:

- To reduce the risk of:
 1. Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD
 2. MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD
 3. 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 cholesterol (LDL-C) in:
 1. Adults with primary hyperlipidemia.
 2. Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
 - As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).
 - As an adjunct to diet for the treatment of adults with:
 1. Primary dysbetalipoproteinemia
 2. Hypertriglyceridemia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Take Atorvastatin calcium tablet orally once daily at any time of the day, with or without food.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating atorvastatin calcium tablets, and adjust the dosage if necessary.

2.2 Recommended Dosage in Adult Patients

The recommended starting dosage of atorvastatin calcium is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily. Patients who require reduction in LDL-C greater than 45% may be started at 40 mg once daily.

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

The recommended starting dosage of atorvastatin calcium is 10 mg once daily. The dosage range is 10 mg to 20 mg once daily.

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

The recommended starting dosage of atorvastatin calcium is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily.

2.5 Dosage Modifications Due to Drug Interactions

Concomitant use of atorvastatin with the following drugs requires dosage modification of atorvastatin [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].

Anti-Viral Medications

- In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed atorvastatin calcium 20 mg once daily.
- In patients taking nelfinavir, do not exceed atorvastatin calcium 40 mg once daily.

Select Azole Antifungals or Macrolide Antibiotics

- In patients taking clarithromycin or itraconazole, do not exceed atorvastatin calcium 20 mg once daily.

For additional recommendations regarding concomitant use of atorvastatin calcium with other anti-viral medications, azole antifungals or macrolide antibiotics, see Drug Interactions (7.1).

3 DOSAGE FORMS AND STRENGTHS

Atorvastatin calcium tablets, USP:

- 10 mg of atorvastatin calcium tablets, USP: white to off-white, oval, biconvex film-coated tablets, engraved "APO" on one side, "A10" on the other side.
- 20 mg of atorvastatin calcium tablets, USP: white to off-white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV20" on the other side.
- 40 mg of atorvastatin calcium tablets, USP: white to off-white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV40" on the other side.
- 80 mg of atorvastatin calcium tablets, USP: white to off-white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV80" on the other side.

4 CONTRAINDICATIONS

Acute liver failure or decompensated cirrhosis [see Warnings and Precautions (5.3)]

Hypersensitivity to atorvastatin or any excipients in atorvastatin calcium tablets. Hypersensitivity reactions, including anaphylaxis, angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

Atorvastatin calcium may cause myopathy (muscle pain, tenderness, or weakness associated with elevated creatine kinase [CK]) and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of

rhabdomyolysis in patients treated with statins, including atorvastatin.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid-lowering therapies), and higher atorvastatin calcium dosage [see Drug Interactions (7.1) and Use in Specific Populations (8.5, 8.6)].

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

Atorvastatin calcium exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with atorvastatin is not recommended. Atorvastatin calcium dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications [see Dosage and Administration (2.5)]. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin co-administered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis [see Drug Interactions (7.1)]. Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking atorvastatin calcium [see Drug Interactions (7.1)].

Discontinue atorvastatin calcium tablets if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if atorvastatin calcium tablets are discontinued. Temporarily discontinue atorvastatin calcium tablets in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the atorvastatin dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persists despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue atorvastatin calcium tablets if IMNM is suspected.

5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of atorvastatin calcium tablets [see Adverse Reactions (6.1)]. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or

improved on continued therapy or after a brief interruption in therapy. Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 0.7% of patients receiving atorvastatin calcium tablets in clinical trials. There have been rare postmarketing reports of fatal and nonfatal hepatic failure in patients taking statins, including atorvastatin.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury [see Use in Specific Populations (8.7)].

Consider liver enzyme testing before atorvastatin calcium tablets initiation and when clinically indicated thereafter. Atorvastatin calcium tablets are contraindicated in patients with acute liver failure or decompensated cirrhosis [see Contraindications (4)]. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue atorvastatin calcium tablets.

5.4 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including atorvastatin. 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 2365 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)]

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 (8,755 atorvastatin calcium vs. 7,311 placebo; age range 10 to 93 years, 39% women, 91% White, 3% Black, 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 tablets-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=4055	% Any dose N=8,755
Nasopharyngitis	8.2	12.9	5.3	7	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
Urinary tract infection	5.6	6.9	6.4	8	4.1	5.7
Dyspepsia	4.3	5.9	3.2	6	3.3	4.7
Nausea	3.5	3.7	3.7	7.1	3.8	4
Musculoskeletal pain	3.6	5.2	3.2	5.1	2.3	3.8
Muscle spasms	3	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
Adverse Reaction	% Placebo N=7,311	% 10 mg N=3,908	% 20 mg N=188	% 40 mg N=604	% 80 mg N=4055	% Any dose N=8,755
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, cholestasis

Musculoskeletal system: musculoskeletal pain, muscle fatigue, neck pain, joint swelling

Metabolic and nutritional system: transaminases increase, liver function test abnormal, blood alkaline phosphatase

increase, creatine phosphokinase increase, hyperglycemia

Nervous system: nightmare

Respiratory system: epistaxis

Skin and appendages: urticaria

Special senses: vision blurred, tinnitus

Urogenital system: white blood cells urine positive

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 10, 20, 40, 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)

In TNT, [see Clinical Studies (14.1)] 10,001 patients (age range 29 to 78 years, 19% women; 94% White, 3% Black, 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 ($\geq 3 \times$ ULN twice within 4 to 10 days) occurred in 1.3% of individuals with atorvastatin calcium 80 mg and in 0.2% of individuals with atorvastatin calcium 10 mg. Elevations of CK ($\geq 10 \times$ 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, 4731 patients (age range 21 to 92 years, 40% women; 93% White, 3% Black, 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 ($\geq 3 \times$ ULN twice within 4 to 10 days) in the atorvastatin calcium group (0.9%) compared to placebo (0.1%). Elevations of CK ($>10 \times$ ULN) were rare, but were higher in the atorvastatin calcium group (0.1%) compared to placebo (0%). Diabetes was reported as an adverse reaction in 6.1% of subjects in the atorvastatin calcium group and 3.8% of subjects in the placebo group.

In a post-hoc analysis, atorvastatin calcium 80 mg reduced the incidence of ischemic stroke (9.2% vs. 11.6%) and increased the incidence of hemorrhagic 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; 92% White, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 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).

Psychiatric disorders: depression

Respiratory disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: angioneurotic edema, bullous rashes (including erythema multiforme,

Stevens-Johnson syndrome, and toxic epidermal necrolysis)

To report SUSPECTED ADVERSE REACTIONS, contact AvKARE at 1-855-361-3993 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

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

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

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 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

Cyclosporine or Gemfibrozil

Clinical Impact: Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin calcium and cyclosporine, an inhibitor of CYP3A4 and OATP1B1 [see *Clinical Pharmacology* (12.3)]. Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with atorvastatin calcium.

Intervention: Concomitant use of cyclosporine or gemfibrozil with atorvastatin calcium is not recommended.

Anti-Viral Medications

Clinical Impact: 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.

- Intervention:*
- Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with atorvastatin calcium is not recommended.
 - In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin.
 - In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed atorvastatin calcium 20 mg.

In patients taking nelfinavir, do not exceed atorvastatin calcium 40 mg [see *Dosage and Administration* (2.5)].

Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with atorvastatin calcium.

Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Examples: Tipranavir plus ritonavir, glecaprevir plus pibrentasvir, lopinavir plus ritonavir, simeprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir, nelfinavir, and ledipasvir plus sofosbuvir.

Select Azole Antifungals or Macrolide Antibiotics

<i>Clinical Impact:</i>	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin calcium with select azole antifungals or macrolide antibiotics, due to inhibition of CYP3A4 and/or transporters [see <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention:</i>	In patients taking clarithromycin or itraconazole, do not exceed atorvastatin calcium 20 mg [see <i>Dosage and Administration</i> (2.5)]. Consider the risk/benefit of concomitant use of other azole antifungals or macrolide antibiotics with atorvastatin calcium. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
<i>Examples:</i>	Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole.

Niacin

<i>Clinical Impact:</i>	Cases of myopathy and rhabdomyolysis have been observed with concomitant use of lipid modifying dosages of niacin (≥ 1 gram/day niacin) with atorvastatin calcium.
<i>Intervention:</i>	Consider if the benefit of using lipid modifying dosages of niacin concomitantly with atorvastatin calcium outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Fibrates (other than Gemfibrozil)

<i>Clinical Impact:</i>	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with atorvastatin calcium.
<i>Intervention:</i>	Consider if the benefit of using fibrates concomitantly with atorvastatin calcium outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Colchicine

<i>Clinical Impact:</i>	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with atorvastatin calcium.
<i>Intervention:</i>	Consider the risk/benefit of concomitant use of colchicine with atorvastatin calcium. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.

Grapefruit Juice

<i>Clinical Impact:</i>	Grapefruit juice consumption, especially excessive consumption, more than 1.2 liters/daily, can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis.
<i>Intervention:</i>	Avoid intake of large quantities of grapefruit juice, more than 1.2 liters daily, when taking atorvastatin calcium.

7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium

Table 3 presents drug interactions that may decrease exposure to atorvastatin calcium and instructions for preventing or managing them.

Table 3: Drug Interactions that may Decrease Exposure to Atorvastatin Calcium

Rifampin	
<i>Clinical Impact:</i>	Concomitant administration of atorvastatin calcium with rifampin, an inducer of cytochrome P450 3A4 and inhibitor of OATP1B1, can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, delayed administration of atorvastatin calcium after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.
<i>Intervention:</i>	Administer atorvastatin calcium and rifampin simultaneously.

7.3 Atorvastatin Calcium Effects on Other Drugs

Table 4 presents atorvastatin calcium effect on other drugs and instructions for preventing or managing them.

Table 4: Atorvastatin Calcium Effects on Other Drugs

Oral Contraceptives	
<i>Clinical Impact:</i>	Co-administration of atorvastatin calcium and an oral contraceptive increased plasma concentrations of norethindrone and ethinyl estradiol [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention:</i>	Consider this when selecting an oral contraceptive for patients taking atorvastatin calcium.
Digoxin	
<i>Clinical Impact:</i>	When multiple doses of atorvastatin calcium and digoxin were co-administered, steady state plasma digoxin concentrations increased [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention:</i>	Monitor patients taking digoxin appropriately.

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 based on 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 tablets 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 and 20 times, respectively, the human exposure at the

maximum recommended human dose (MRHD) of 80 mg, based on body surface area (mg/m²). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development delay were observed at doses $\geq$ 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 1152 statin-exposed pregnant women compared to 886,996 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 relative 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 also no statistically significant increases in any of the 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 confounders 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

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/m²). In rats, the maternally toxic dose of 300 mg/kg resulted in increased post-implantation loss and decreased fetal body weight. At the maternally toxic doses of 50 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, 100, 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 (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human 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 pediatric patients 10 years of age and older with HeFH. Use of atorvastatin calcium for this indication is based on a double-blind, placebo-controlled clinical trial in 187 pediatric patients 10 years of age and older with HeFH. In this limited controlled trial, there was no significant effect on growth or sexual maturation in the boys or girls, or on menstrual cycle length in girls.

The safety and effectiveness of atorvastatin calcium as an adjunct to other LDL-C-lowering therapies to reduce LDL-C have been established pediatric patients 10 years of age and older with HoFH. 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 HoFH [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).

8.5 Geriatric Use

Of the total number of atorvastatin calcium tablets-treated patients in clinical trials, 15,813 (40%) were ≥ 65 years old and 2,800 (7%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Advanced age (≥ 65 years) is a risk factor for atorvastatin calcium tablets-associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of myopathy. Monitor

geriatric patients receiving atorvastatin calcium tablets for the increased risk of myopathy [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

8.6 Renal Impairment

Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor all patients with renal impairment for development of myopathy. Renal impairment does not affect the plasma concentrations of atorvastatin, therefore there is no dosage adjustment in patients with renal impairment [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin 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. Atorvastatin calcium tablets are contraindicated in patients with acute liver failure or decompensated cirrhosis [see Contraindications (4)].

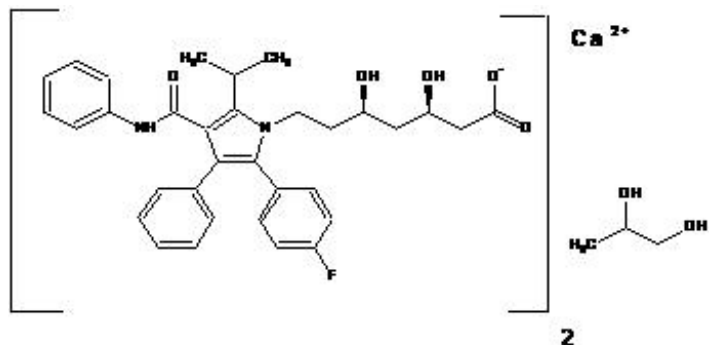
10 OVERDOSAGE

No specific antidotes for atorvastatin 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 clearance.

11 DESCRIPTION

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

The drug substance used in atorvastatin calcium tablets, USP is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis((3R,5R)-7-[3-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is C₆₆H₆₈CaF₂N₄O₁₀ *C₃H₈O₂ and its molecular weight is 1231.46 g/mol. Its structural formula is:



Atorvastatin calcium is a white to off-white solid that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in

methanol.

Atorvastatin calcium tablets, USP for oral administration contain atorvastatin 10, 20, 40, or 80 mg (equivalent to 11, 22, 44 or 88 mg atorvastatin calcium) and the following inactive ingredients: calcium acetate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, magnesium stearate (vegetable source), microcrystalline cellulose, polyethylene glycol, sodium carbonate, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin 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, 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 is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin 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_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin 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 [see *Dosage and Administration* (2)].

Distribution

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is $\geq 98\%$ bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk [see *Contraindications* (4) and *Use in Specific*

Populations (8.2)].

Elimination

Metabolism

Atorvastatin 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. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin 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 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 in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Specific Populations

Geriatric

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

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 in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Impairment

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

Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the

drug is extensively bound to plasma proteins.

Hepatic Impairment

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin 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 *Contraindications (4)*].

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

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC&	Ratio of Cmax&
#Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QDa for 28 days	8.69	10.66
#Tipranavir 500 mg BIDb/ritonavir 200 mg BIDb, 7 days	10 mg, SDc	9.36	8.58
#Glecaprevir 400 mg QDa/pibrentasvir 120 mg QDa, 7 days	10 mg QDa for 7 days	8.28	22
#Telaprevir 750 mg q8hf, 10 days	20 mg, SDc	7.88	10.60
#, ‡Saquinavir 400 mg BIDb/ ritonavir 400 mg BIDb, 15 days	40 mg QDa for 4 days	3.93	4.31
#Elbasvir 50 mg QDa /grazoprevir 200 mg QDa, 13 days	10 mg SDc	1.94	4.34
#Simeprevir 150 mg QDa, 10 days	40 mg SDc	2.12	1.70
#Clarithromycin 500 mg BIDb, 9 days	80 mg QDa for 8 days	4.54	5.38
#Darunavir 300 mg BIDb/ritonavir 100 mg BIDb, 9 days	10 mg QDa for 4 days	3.45	2.25
#Itraconazole 200 mg QDa, 4 days	40 mg SDc	3.32	1.20
#Letermovir 480 mg QDa, 10 days	20 mg SDc	3.29	2.17
#Fosamprenavir 700 mg BIDb/ritonavir 100 mg BIDb, 14 days	10 mg QDa for 4 days	2.53	2.84
#Fosamprenavir 1400 mg BIDb, 14 days	10 mg QDa for 4 days	2.30	4.04
#Nelfinavir 1250 mg BIDb, 14 days	10 mg QDa for 28 days	1.74	2.22
#Grapefruit Juice, 240 mL QDa *	40 mg, SDc	1.37	1.16
Diltiazem 240 mg QDa, 28 days	40 mg, SDc	1.51	1
Erythromycin 500 mg QIDe, 7 days	10 mg, SDc	1.33	1.38
Amlodipine 10 mg, single dose	80 mg, SDc	1.18	0.91
Cimetidine 300 mg QIDe, 2 weeks	10 mg QDa for 2 weeks	1	0.89
Colestipol 10 g BIDb, 24 weeks	40 mg QDa for 8 weeks	NA	0.74**
Maalox TC® 30 mL QIDe, 17 days	10 mg QDa for 15 days	0.66	0.67
Efavirenz 600 mg QDa, 14 days	10 mg for 3 days	0.59	1.01
#Rifampin 600 mg QDa, 7 days (co-administered) †	40 mg SDc	1.12	2.90
#Rifampin 600 mg QDa, 5 days (doses separated) †	40 mg SDc	0.20	0.60
#Gemfibrozil 600 mg BIDb, 7 days	40 mg SDc	1.35	1
#Fenofibrate 160 mg QDa, 7 days	40 mg SDc	1.03	1.02
Boceprevir 800 mg TIDd, 7 days	40 mg SDc	2.32	2.66

& Represents ratio of treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).

See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (ratio of AUC up to 2.5) and/or C_{max} (ratio of C_{max} up to 1.71) have been reported with excessive grapefruit consumption (≥ 750 mL to 1.2 liters per day).

** Ratio based on a single sample taken 8 to 16 h post dose.

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

‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

a Once daily

b Twice daily

c Single dose

d Three times daily

e Four times daily

f Every 8 hours

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

Atorvastatin	Co-administered drug and dosing regimen	Ratio of AUC	Ratio of C _{max}
	Drug/Dose (mg)		
80 mg QDa for 15 days	Antipyrine, 600 mg SDc	1.03	0.89
80 mg QDa for 10 days	# Digoxin 0.25 mg QDa, 20 days	1.15	1.20
40 mg QDa for 22 days	Oral contraceptive QDa, 2 months - norethindrone 1 mg - ethinyl estradiol 35 mcg	1.28 1.19	1.23 1.30
10 mg, SDc	Tipranavir 500 mg BIDb/ritonavir 200 mg BIDb, 7 days	1.08	0.96
10 mg QDa for 4 days	Fosamprenavir 1400 mg BIDb, 14 days	0.73	0.82
10 mg QDa for 4 days	Fosamprenavir 700 mg BIDb/ritonavir 100 mg BIDb, 14 days	0.99	0.94

See Section 7 for clinical significance.

a Once daily

b Twice daily

c Single dose

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

exposure after an 80 mg oral dose.

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

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

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 aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

14.1 Prevention of Cardiovascular Disease

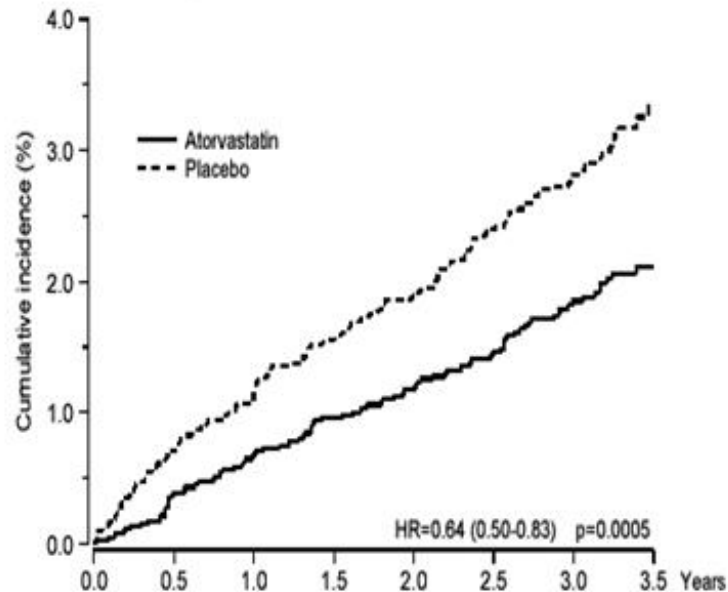
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤ 251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age > 55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL > 6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP $< 140/90$ mm Hg for non-diabetic patients; $< 130/80$ mm Hg for diabetic patients) and allocated to either atorvastatin 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. 60 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. Due to the small number of events, results for women were inconclusive.

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 2838 subjects (94% white, 68% male), ages 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with $\text{LDL} \leq 160$ mg/dL and $\text{TG} \leq 600$ 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 study. 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 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

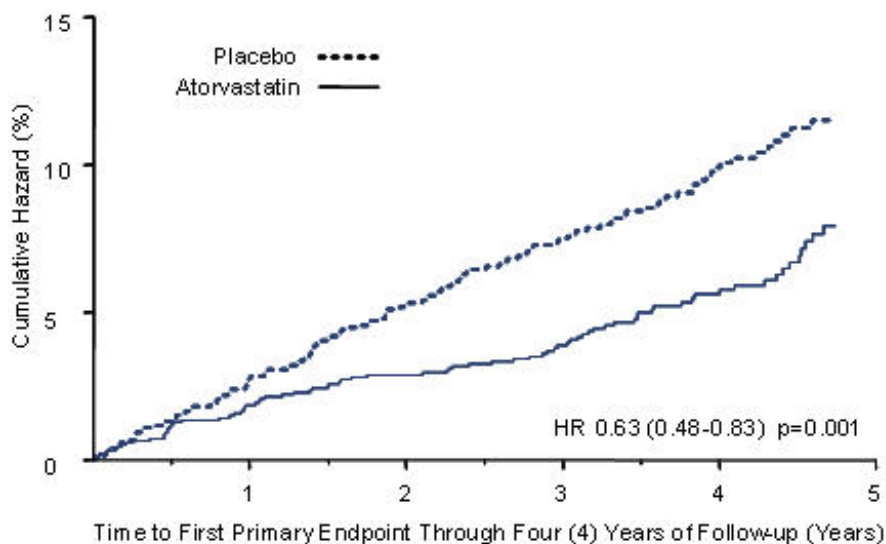
previous clinical trials.

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, 95.1% 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 (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 (MCVE): 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, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin calcium.

Treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of MCVE (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 6). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

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

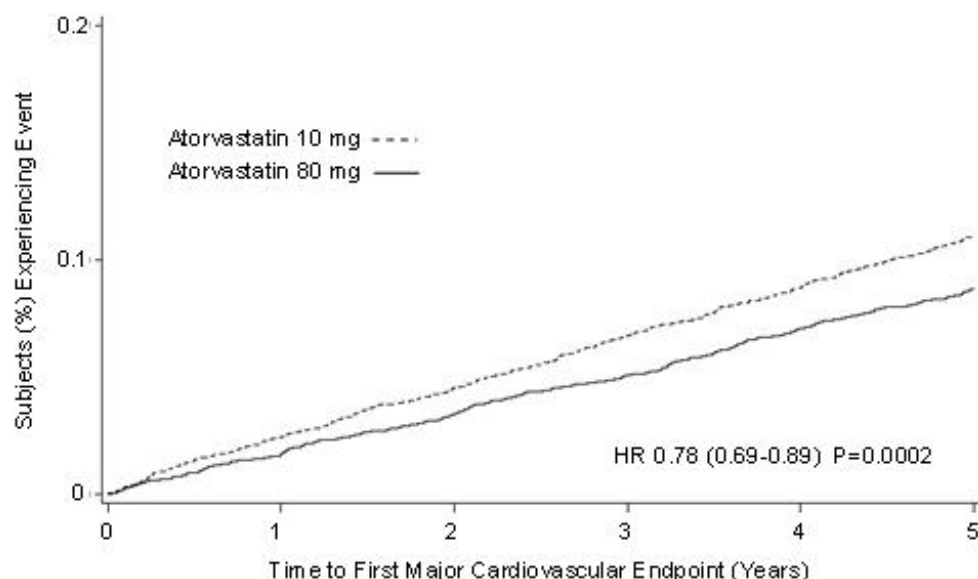


TABLE 6. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR ^a (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
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)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure ^b	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint ^b	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)

Components of All-Cause Mortality

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)

^a Atorvastatin 80 mg: atorvastatin 10 mg

^b Component of other secondary endpoints

* Secondary endpoints not included in primary endpoint

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=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 6). 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 6). 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.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin calcium 80 mg/day was compared to treatment with simvastatin 20 to 40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of atorvastatin calcium and 105, 179, 142, 47, and 132 mg/dL during treatment with 20 to 40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin calcium 80 mg/day group vs. 463 (10.4%) in the simvastatin 20 to 40 mg/day group, HR 0.89, 95% CI (0.78, 1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin calcium 80 mg/day group vs. 374 (8.4%) in the simvastatin 20 to 40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin calcium 80 mg group and the simvastatin 20 to 40 mg group.

14.2 Hyperlipidemia and Mixed Dyslipidemia

Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb). Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin calcium is effective in a wide variety of patient populations with hyperlipidemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, atorvastatin calcium given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 7.)

TABLE 7. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline) *

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

* Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin calcium 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies 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 8).

TABLE 8. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment	Non-
-----------	------

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27 ^a	-36 ^a	-28 ^a	-17 ^a	+7	-37 ^a
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff ¹		-9.2, -6.5	-10.7, - 7.1	-10.0, - 6.5	-15.2, - 7.1	-1.7, 2.0	-11.1, - 7.1
Study 2							
Atorvastatin 10 mg	222	-25 ^b	-35 ^b	-27 ^b	-17 ^b	+6	-36 ^b
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff ¹		-10.8, - 6.1	-14.5, - 8.2	-13.4, - 7.4	-14.1, - 0.7	-4.9, 1.6	-11.5, - 4.1
Study 3							
Atorvastatin 10 mg	132	-29 ^c	-37 ^c	-34 ^c	-23 ^c	+7	-39 ^c
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff ¹		-8.7, -2.7	-10.1, - 2.6	-8.0, -1.1	-15.1, - 0.7	-4.3, 3.9	-9.6, -1.9
¹ A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.							
^a Significantly different from lovastatin, ANCOVA, $p \leq 0.05$							
^b Significantly different from pravastatin, ANCOVA, $p \leq 0.05$							
^c Significantly different from simvastatin, ANCOVA, $p \leq 0.05$							

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 8 is not known. Table 8 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

14.3 Hypertriglyceridemia

The response to atorvastatin calcium in 64 patients with isolated hypertriglyceridemia (*Fredrickson* Type IV) treated across several clinical trials is shown in the table below (Table 9). For the atorvastatin calcium -treated patients, median (min, max) baseline TG level was 565 (267 to 1502).

**TABLE 9. Combined Patients With Isolated Elevated TG:
Median (min, max) Percentage Change From Baseline**

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (- 36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (- 15.5, 10.9)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -25.1)

	24.4)	-0.0)	-13.2)	-3.0)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

14.4 Dysbetalipoproteinemia

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (*Fredrickson* Type III) are shown in the table below (Table 10).

TABLE 10. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (Fredrickson Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 years to 37 years with HoFH received maximum daily doses of 20 to 80 mg of atorvastatin calcium. The mean LDL-C reduction in this study 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%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10 years to 17 years of age (mean age 14.1 years) 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 study required 1) a baseline LDL-C level $\geq$ 190 mg/dL or 2) a baseline LDL-C level $\geq$ 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 218.6 mg/dL (range: 138.5 to 385.0 mg/dL) in the atorvastatin calcium group compared to 230.0 mg/dL (range: 160.0 to 324.5 mg/dL) in the placebo group. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was $>$ 130 mg/dL. The number of atorvastatin calcium-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

Atorvastatin calcium significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 11).

TABLE 11. Lipid-altering Effects of Atorvastatin Calcium in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin Calcium Tablets	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0 to 242.0 mg/dL) in the atorvastatin calcium group compared to 228.5 mg/dL (range: 152.0 to 385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

The long-term efficacy of atorvastatin calcium therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Additional pediatric use information is approved for Pfizer's LIPITOR (atorvastatin calcium) tablets. However, due to Pfizer's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

16 HOW SUPPLIED/STORAGE AND HANDLING

Atorvastatin calcium tablets are supplied as white, oval, biconvex film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets

Atorvastatin calcium tablets, 10 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "A10" on the other side.

NDC 50268-093-15 10 tablets per card, 5 cards per carton.

20 mg tablets

Atorvastatin calcium tablets, 20 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV20" on the other side.

NDC 50268-094-15 10 tablets per card, 5 cards per carton.

40 mg tablets

Atorvastatin calcium tablets, 40 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV40" on the other side.

NDC 50268-095-15 10 tablets per card, 5 cards per carton.

80 mg tablets

Atorvastatin calcium tablets, 80 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV80" on the other side.

NDC 50268-096-12 5 tablets per card, 4 cards per carton.

Dispensed in Unit Dose Package. For Institutional Use Only.

Storage Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight container [see USP].

17 PATIENT COUNSELING INFORMATION

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

Myopathy and Rhabdomyolysis

Advise patients that atorvastatin 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 tablets 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 tablets. 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 can 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 tablets should be discontinued [see Use in Specific Populations (8.1)].

Lactation

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

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Manufactured for:

AvKARE

Pulaski, TN 38478

Mfg. Rev. 06/23

AV Rev. 11/23 (M)

AvPAK

PATIENT INFORMATION

Atorvastatin Calcium Tablets

(a tor" va stat' in kal' see um)

What Are Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets are a prescription medicine that contains cholesterol lowering medicine (statin) called atorvastatin.

Atorvastatin calcium tablets are used:

- to reduce the risk of:
 - heart attack, stroke, certain types of heart surgery and chest pain in adults who do not have heart disease but have other multiple risk factors for heart disease.
 - heart attack and stroke in adults with type 2 diabetes mellitus who do not have heart disease but have other multiple risk factors.
 - heart attack that does not cause death, stroke, certain types of heart surgery, hospitalization for congestive heart failure, and chest pain in adults with heart disease.
 - along with diet to reduce low density lipoprotein cholesterol (LDL-C) or bad cholesterol:
 - in adults with primary hyperlipidemia.
 - in adults and children aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH). This is an inherited condition that causes high levels of bad cholesterol.
 - along with other cholesterol lowering treatments or alone if such treatments are unavailable in adults and children aged 10 years and older with homozygous familial hypercholesterolemia (HoFH). This is an inherited condition that causes high levels of bad cholesterol.
 - along with diet for the treatment of adults with:
 - primary dysbetalipoproteinemia (an inherited condition that causes high levels of cholesterol and fat).
 - hypertriglyceridemia.
- It is not known if atorvastatin calcium tablets are safe and effective in children younger than 10 years of age with HeFH or HoFH or in children with other types of

hyperlipidemias (other than HeFH or HoFH).

Do not take atorvastatin calcium tablets if you:

- have liver problems (acute liver failure or decompensated cirrhosis)
- are allergic to atorvastatin or any of the ingredients in atorvastatin calcium tablets. Stop using atorvastatin calcium tablets and get medical help right away if you have symptoms of a serious allergic reaction including:
 - swelling of your face, lips, tongue or throat
 - problems breathing or swallowing
 - fainting or feeling dizzy
 - very rapid heartbeat
 - severe skin rash or itching
 - flu-like symptoms including fever, sore throat, cough, tiredness, and joint pain

See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

Before you take atorvastatin calcium tablets, tell your doctor about all of your medical conditions, including if you:

- have unexplained muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have thyroid problems
- have kidney problems
- had a stroke
- are pregnant or plan to become pregnant. Atorvastatin may harm your unborn baby. If you become pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breastfeeding or plan to breastfeed. You and your doctor should decide if you will take atorvastatin calcium tablets or breastfeed. You should not do both.

Talk to your doctor about the best way to feed your baby if you take atorvastatin calcium tablets.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can increase the risk of muscle problem or other side effects. Especially tell your doctor if you take medicines for:

- your immune system (cyclosporine)
 - cholesterol (gemfibrozil)
 - infections (erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole)
 - birth control pills
 - heart failure (digoxin)
 - gout (colchicine)
 - niacin
 - fibrates
 - viruses that treat HIV AIDS, or hepatitis C (anti-virals)
- tipranavir plus ritonavir

- ledipasvir plus sofosbuvir
- saquinavir plus ritonavir
- fosamprenavir
- elbasvir plus grazoprevir
- nelfinavir
- glecaprevir plus pibrentasvir
- simeprevir
- darunavir plus ritonavir
- fosamprenavir plus ritonavir
- letermovir

Ask your doctor or pharmacist for a list of medicines if you are not sure. Know all the medicines you take. Keep a list of them to show your doctor and pharmacist.

How Should I Take Atorvastatin Calcium Tablets?

- Take atorvastatin calcium tablets exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium tablets without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium tablets. Your dose of atorvastatin calcium tablets may be changed based on these blood test results.
- Take atorvastatin calcium tablets each day at any time of day at about the same time each day. Atorvastatin calcium tablets can be taken with or without food. Don't break atorvastatin calcium tablets before taking.
- Your doctor should start you on a low-fat diet before giving you atorvastatin calcium tablets. Stay on this low-fat diet when you take atorvastatin calcium tablets.
- If you miss a dose of atorvastatin calcium tablets, take it as soon as you remember. Do not take atorvastatin calcium tablets if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of atorvastatin calcium tablets at the same time.
- If you take too much atorvastatin calcium tablets or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

- Avoid drinking more than 1.2 liters of grapefruit juice each day.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets are stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with atorvastatin calcium tablets.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium tablets and if you have symptoms of liver problems while you take atorvastatin calcium tablets. Call your doctor right away if you have the following symptoms of liver problems:
- feel tired or weak

- loss of appetite
- upper belly pain
- dark amber colored urine
- yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual. This may be an early sign of a rare muscle problem.
- muscle problems that do not go away even after your doctor has advised you to stop taking atorvastatin calcium tablets. Your doctor may do further tests to diagnose the cause of your muscle problems.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: tiredness, tendon problems, memory loss, and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away. These are not all the side effects of atorvastatin calcium tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088..

How do I store Atorvastatin Calcium Tablets

- Store atorvastatin calcium tablets at room temperature, 68°F to 77°F (20°C to 25°C).
- Do not keep medicine that is out of date or that you no longer need.
- **Keep atorvastatin calcium tablets and all medicines out of the reach of children.** Be sure that if you throw medicine away, it is out of the reach of children.

General Information About Atorvastatin Calcium Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium tablets for a condition for which it was not prescribed. Do not give atorvastatin calcium tablets to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about atorvastatin calcium tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium tablets that is written for health professionals. Or for more information contact AvKARE, Inc. at 1-855-361-3993.

What are the Ingredients In Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: calcium acetate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, magnesium stearate (vegetable source), microcrystalline cellulose, polyethylene glycol, sodium carbonate, and titanium dioxide.

Manufactured for:

AvKARE

Pulaski, TN 38478

Mfg. Rev. 06/23

AV Rev. 11/23 (M)

AvPAK

NDC 50268-093-15
Atorvastatin
Calcium Tablets, USP

10 mg*

Rx Only

50 Tablets (5 x 10) Unit Dose



NDC 50268-093-15
Atorvastatin
Calcium Tablets, USP

10 mg*

Rx Only

50 Tablets (5 x 10) Unit Dose



*Each film-coated tablet contains atorvastatin 10 mg (equivalent to 11 mg atorvastatin calcium).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Usual Dosage: See package insert.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured for:
AvKARE
Pulaski, TN 38478
www.avkare.com



Mfg. Rev. 05/24

AV Rev. 02/25 (P)

NDC 50268-094-15

Atorvastatin Calcium Tablets, USP

20 mg*

Rx Only
50 Tablets (5 x 10) Unit Dose



NDC 50268-094-15

Atorvastatin Calcium Tablets, USP

20 mg*

Rx Only
50 Tablets (5 x 10) Unit Dose



PHARMACIST: Dispense the enclosed Patient Information Leaflet to each patient.

*Each film-coated tablet contains atorvastatin 20 mg (equivalent to 22 mg atorvastatin calcium).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Usual Dosage: See package insert.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured for:
AvKARE
Pulaski, TN 38478
www.avkare.com



Mfg. Rev. 01/23

AV Rev. 02/23 (W)

NDC 50268-095-15

Atorvastatin Calcium Tablets

40 mg*

Rx Only
50 Tablets (5 x 10) Unit Dose



5026809515

NDC 50268-095-15

Atorvastatin Calcium Tablets

40 mg*

Rx Only
50 Tablets (5 x 10) Unit Dose



5026809515

PHARMACIST: Dispense the enclosed Patient Information Leaflet to each patient.

*Each film-coated tablet contains atorvastatin 40 mg (equivalent to 44 mg atorvastatin calcium).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Usual Dosage: See package insert.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured for:
AVKARE
Pulaski, TN 38478
www.avkare.com



Mfg. Rev. 06/23

AV Rev. 11/24 (A)

NDC 50268-096-12
Atorvastatin
Calcium Tablets, USP

80 mg*

Rx Only
20 Tablets (4 x 5) Unit Dose



5026809612

NDC 50268-096-12
Atorvastatin
Calcium Tablets, USP

80 mg*

Rx Only
20 Tablets (4 x 5) Unit Dose



5026809612

PHARMACIST: Dispense the Patient Information Leaflet to each patient.

*Each film-coated tablet contains atorvastatin 80 mg (equivalent to 88 mg of atorvastatin calcium.)

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Usual Dosage: See package insert.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured for:
AvKARE
Pulaski, TN 38478
www.avkare.com



Mfg. Rev. 05/24

AV Rev. 07/25(R)

ATORVASTATIN CALCIUM

atorvastatin calcium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50268-093(NDC:60505-2578)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM PROPYLENE GLYCOL SOLVATE (UNII: YRZ 789OWMI) (ATORVASTATIN - UNII:A0JWA85V8F)	ATORVASTATIN	10 mg

Inactive Ingredients	
Ingredient Name	Strength
CALCIUM ACETATE (UNII: Y882YXF34X)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	

Product Characteristics			
Color	white	Score	no score
Shape	OVAL	Size	9mm
Flavor		Imprint Code	APO;A10
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-093-15	50 in 1 BOX, UNIT-DOSE	06/28/2016	
1	NDC:50268-093-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090548	06/28/2016	

ATORVASTATIN CALCIUM

atorvastatin calcium tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50268-094(NDC:60505-2579)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		

Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM PROPYLENE GLYCOL SOLVATE (UNII: YRZ 789OWMI) (ATORVASTATIN - UNII:A0JWA85V8F)	ATORVASTATIN	20 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM ACETATE (UNII: Y882YXF34X)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	

Product Characteristics

Color	white	Score	no score
Shape	OVAL	Size	11mm
Flavor		Imprint Code	APO;ATV20
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-094-15	50 in 1 BOX, UNIT-DOSE	06/28/2016	
1	NDC:50268-094-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090548	06/28/2016	

ATORVASTATIN CALCIUM

atorvastatin calcium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50268-095(NDC:60505-2580)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM PROPYLENE GLYCOL SOLVATE (UNII: YRZ 789OWMI) (ATORVASTATIN - UNII:A0JWA85V8F)	ATORVASTATIN	40 mg

Inactive Ingredients	
Ingredient Name	Strength
CALCIUM ACETATE (UNII: Y882YXF34X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I3O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	

Product Characteristics			
Color	white	Score	no score
Shape	OVAL	Size	14mm
Flavor		Imprint Code	APO;ATV40
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-095-15	50 in 1 BOX, UNIT-DOSE	06/28/2016	
1	NDC:50268-095-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090548	06/28/2016	

ATORVASTATIN CALCIUM

atorvastatin calcium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50268-096(NDC:60505-2671)	
Route of Administration	ORAL			

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM PROPYLENE GLYCOL SOLVATE (UNII: YRZ 789OWMI) (ATORVASTATIN - UNII:A0JWA85V8F)	ATORVASTATIN	80 mg

Inactive Ingredients	
Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	
CALCIUM ACETATE (UNII: Y882YXF34X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	white	Score	no score
Shape	OVAL	Size	19mm
Flavor		Imprint Code	APO;ATV80
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-096-12	20 in 1 BOX, UNIT-DOSE	06/28/2016	
1	NDC:50268-096-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090548	06/28/2016	

