

# ATORVASTATIN CALCIUM- atorvastatin calcium trihydrate tablet, film coated Mylan Pharmaceuticals Inc.

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use atorvastatin calcium tablets safely and effectively. See full prescribing information for atorvastatin calcium tablets.**

### Atorvastatin Calcium Tablets for Oral Administration

**Initial U.S. Approval: 1996**

#### ----- RECENT MAJOR CHANGES -----

Drug Interactions (7) 02/2012

#### ----- INDICATIONS AND USAGE -----

Atorvastatin is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of nonfatal MI, fatal and nonfatal stroke, revascularization procedures, hospitalization for CHF and angina in 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 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 boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

#### Limitations of Use

Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

#### ----- DOSAGE AND ADMINISTRATION -----

Dose range: 10 mg to 80 mg once daily (2.1).

Recommended start dose: 10 mg or 20 mg once daily (2.1).

Patients requiring large LDL-C reduction (> 45%) may start at 40 mg once daily (2.1).

Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

#### ----- DOSAGE FORMS AND STRENGTHS -----

10 mg, 20 mg, 40 mg and 80 mg tablets (3).

#### ----- CONTRAINDICATIONS -----

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).

Women who are pregnant or may become pregnant (4.3).

Nursing mothers (4.4).

Hypersensitivity to any component of this medication (4.2).

#### ----- WARNINGS AND PRECAUTIONS -----

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. In cases of myopathy or rhabdomyolysis, therapy should be temporarily withheld or discontinued (5.1, 8.5).

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the atorvastatin 80 mg group vs. placebo (5.5).

#### ----- ADVERSE REACTIONS -----

The most commonly reported adverse reactions (incidence  $\geq$  2%) in patients treated with atorvastatin in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity and urinary tract infection (6.1).

**To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-4-INFO-RX (1-877-446-3679) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### ----- 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

- 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 coadministered with atorvastatin (7.7).

----- **USE IN SPECIFIC POPULATIONS** -----

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

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

**Revised: 3/2012**

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

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

inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously with diet.

### 1.1 Prevention of Cardiovascular Disease

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

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

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

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

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

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

### 1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  - LDL-C remains  $\geq 190$  mg/dL or
  - LDL-C remains  $\geq 160$  mg/dL and:
    1. there is a positive family history of premature cardiovascular disease or
    2. two or more other CVD risk factors are present in the pediatric patient

### **1.3 Limitations of Use**

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

## **2 DOSAGE AND ADMINISTRATION**

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

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

### **2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 Years of Age)**

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

### **2.3 Homozygous Familial Hypercholesterolemia**

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

### **2.4 Concomitant Lipid-lowering Therapy**

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

### **2.5 Dosage in Patients with Renal Impairment**

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

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

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

recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

### 3 DOSAGE FORMS AND STRENGTHS

White to off-white oval, film-coated tablets containing 10 mg, 20 mg, 40 mg or 80 mg atorvastatin calcium, USP.

### 4 CONTRAINDICATIONS

#### 4.1 Active Liver Disease, which may include Unexplained Persistent Elevations in Hepatic Transaminase Levels

#### 4.2 Hypersensitivity to any Component of this Medication

#### 4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well controlled studies of atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. **ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS.** If the patient becomes pregnant while taking this drug, atorvastatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

#### 4.4 Nursing Mothers

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

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Skeletal Muscle

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

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

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain,

tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

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

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

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

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir <sup>*</sup> , 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

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

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

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

## 5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on two or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6% and 2.3% for 10 mg, 20 mg, 40 mg and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug

interruption or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated. There have been rare post-marketing reports of fatal and nonfatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin.

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

### **5.3 Endocrine Function**

Increases in HbA<sub>1c</sub> and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

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

### **5.4 CNS Toxicity**

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

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

### **5.5 Use in Patients with Recent Stroke or TIA**

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p = 0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the



atorvastatin group [see *Adverse Reactions (6.1)*].

## 6 ADVERSE REACTIONS

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

- Rhabdomyolysis and myopathy [see *Warnings and Precautions (5.1)*].
- Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*].

### 6.1 Clinical Trial Adverse Experiences

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

In the atorvastatin placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin vs. 7,311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%) and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence  $\geq 2\%$  and greater than placebo) regardless of causality, in patients treated with atorvastatin in placebo controlled trials (n = 8,755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6%) and urinary tract infection (5.7%).

Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in  $\geq 2\%$  and at a rate greater than placebo in patients treated with atorvastatin (n = 8,755), from 17 placebo-controlled trials.

**Table 2. Clinical Adverse Reactions Occurring in  $\geq 2\%$  in Patients Treated with Any Dose of Atorvastatin and at an Incidence Greater Than Placebo Regardless of Causality (% of Patients).**

Adverse Reaction*	Any Dose N = 8,755	10 mg N = 3,908	20 mg N = 188	40 mg N = 604	80 mg N = 4,055	Placebo N = 7,311
Nasopharyngitis	8.3	12.9	5.3	7	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6	3.3	4.3
Nausea	4	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

\* Adverse Reaction  $\geq 2\%$  in any dose greater than placebo.

Other adverse reactions reported in placebo-controlled studies include: *Body as a whole*: malaise, pyrexia; *Digestive system*: abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system*: epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system*: white blood cells urine positive.

### **Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT):**

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

### **Collaborative Atorvastatin Diabetes Study (CARDS):**

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

### **Treating to New Targets Study (TNT):**

In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29 to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1% Asians, 2% other) with clinically evident CHD treated with atorvastatin 10 mg daily (n = 5,006) or atorvastatin 80 mg daily (n = 4,995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations ( $\geq 3 \times \text{ULN}$  twice within 4 to 10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK ( $\geq 10 \times \text{ULN}$ ) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

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

In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26 to 80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin 80 mg/day (n = 4,439) or simvastatin 20 mg to 40 mg daily (n = 4,449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

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

In SPARCL involving 4,731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin 80 mg (n = 2,365) or placebo (n = 2,366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations ( $\geq 3 \times \text{ULN}$  twice within 4 to 10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK ( $> 10 \times \text{ULN}$ ) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). The incidence of nonfatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 nonfatal hemorrhagic strokes) as compared to the placebo group (16 nonfatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin vs. 2 (4%) placebo].

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

## 6.2 Post-marketing Experience

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

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

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

## 6.3 Pediatric Patients (Ages 10 to 17 Years)

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

## 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, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

### 7.1 Strong Inhibitors of Cytochrome P450 3A4

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

#### Clarithromycin

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

Administration (2.6)].

### **Combination of Protease Inhibitors**

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

### **Itraconazole**

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

### **7.2 Grapefruit Juice**

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

### **7.3 Cyclosporine**

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

### **7.4 Gemfibrozil**

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

### **7.5 Other Fibrates**

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

### **7.6 Niacin**

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

### **7.7 Rifampin or other Inducers of Cytochrome P450 3A4**

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous coadministration 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.

### 7.8 Digoxin

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

### 7.9 Oral Contraceptives

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

### 7.10 Warfarin

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

### 7.11 Colchicine

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Teratogenic Effects*

#### **Pregnancy Category X**

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

There are no adequate and well controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m<sup>2</sup>) [see *Contraindications, Pregnancy (4.3)*].

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

and 22 times (225 mg/kg) the human AUC at 80 mg/day.

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

Safety and effectiveness in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6)*; *Adverse Reactions, Pediatric Patients (Ages 10 to 17 Years) (6.3)*; and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 Years of Age) (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

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

### 8.5 Geriatric Use

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

### 8.6 Hepatic Impairment

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

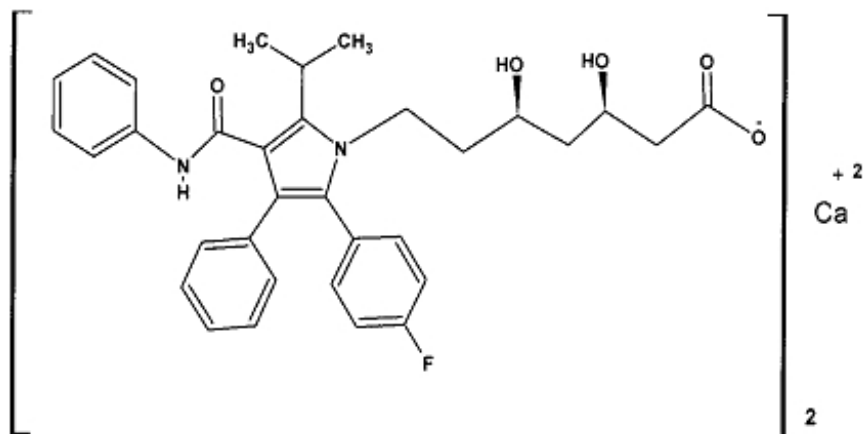
## 10 OVERDOSAGE

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

## 11 DESCRIPTION

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

Atorvastatin calcium is [R-(R\*, R\*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt. The molecular formula of atorvastatin calcium is C<sub>66</sub>H<sub>68</sub>CaF<sub>2</sub>N<sub>4</sub>O<sub>10</sub> and its molecular weight is 1155.36. Its structural formula is:



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

Atorvastatin calcium tablets for oral administration contain 10 mg, 20 mg, 40 mg or 80 mg atorvastatin and the following inactive ingredients: anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-Arginine, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum.

## 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. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein) and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C) and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin 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 also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering

medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis.

Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

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

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

## 12.2 Pharmacodynamics

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

## 12.3 Pharmacokinetics

### Absorption

Atorvastatin calcium is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin 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, Nursing Mothers (4.4)* and *Use in Specific Populations, Nursing Mothers (8.3)*].

### 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 coadministration 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  $\geq 65$  years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

#### Pediatric

Pharmacokinetic data in the pediatric population are not available.

#### Gender

Plasma concentrations of atorvastatin 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, Dosage in Patients with Renal Impairment (2.5), Warnings and Precautions, Skeletal Muscle (5.1)*].

#### Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin 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 (4.1)*].

**Table 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin**

Coadministered Drug and Dosing Regimen	Atorvastatin		
	Dose (mg)	Change in AUC*	Change in $C_{max}$ *
†Cyclosporine 5.2	10 mg QD for 30 days	+87%	+107%

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

\* Data given as x-fold change represent a simple ratio between coadministration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

- † See Sections 5.1 and 7 for clinical significance.
- ‡ 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.
- § Greater increases in AUC (up to 2.5-fold) and/or  $C_{max}$  (up to 71%) have been reported with excessive grapefruit consumption ( $\geq 750$  mL to 1.2 liters per day).
- ¶ Single sample taken 8 to 16 h post-dose.
- # Due to the dual interaction mechanism of rifampin, simultaneous coadministration 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.

**Table 4. Effect of Atorvastatin on the Pharmacokinetics of Coadministered Drugs**

Atorvastatin	Coadministered Drug and Dosing Regimen		
	Drug/Dose (mg)	Change in AUC	Change in $C_{max}$
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	*Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20%
40 mg QD for 22 days	Oral contraceptive QD, 2 months -norethindrone 1 mg -ethinyl estradiol 35 mcg	↑ 28% ↑ 19%	↑ 23% ↑ 30%
10 mg SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

\* See Section 7 for clinical significance.

## 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, two 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 (0-24) 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 (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

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

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

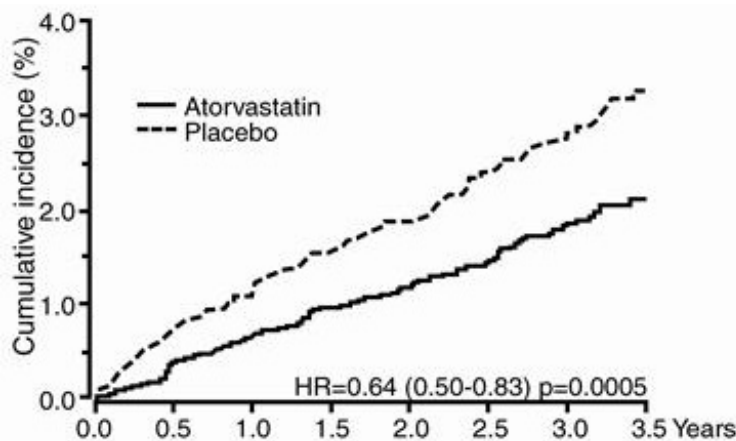
## 14 CLINICAL STUDIES

### 14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and nonfatal 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  $\leq 251$  mg/dL (6.5 mmol/L). Additionally, all patients had at least three of the following cardiovascular risk factors: male gender (81.1%), age  $> 55$  years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL  $> 6$  (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP  $< 140/90$  mm Hg for non-diabetic patients;  $< 130/80$  mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily ( $n = 5,168$ ) or placebo ( $n = 5,137$ ), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

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

Atorvastatin significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin group) or nonfatal MI (108 events in the placebo group vs. 60 events in the atorvastatin group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin vs. 3% 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 was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.



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

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

Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42%.

Although the reduction of fatal and nonfatal 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 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 on cardiovascular disease (CVD) endpoints was assessed in 2,838 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 LDL  $\leq 160$  mg/dL and TG  $\leq 600$  mg/dL. In addition to diabetes, subjects had one 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 10 mg daily (1,429) or placebo (1,411) 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.

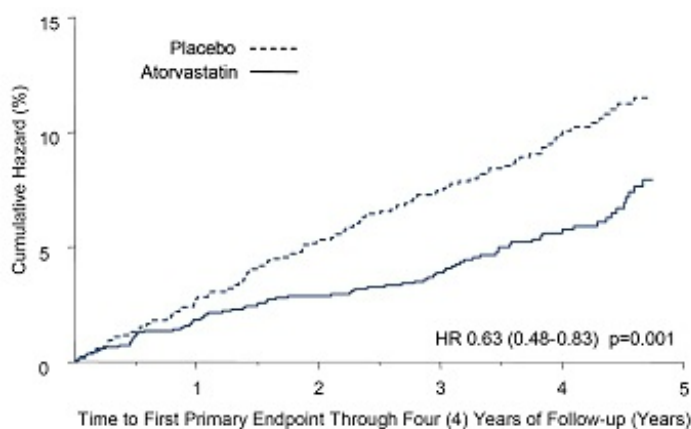
Baseline characteristics of subjects were: mean age of 62 years, mean HbA<sub>1c</sub> 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

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

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin 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 was seen regardless of age, sex or baseline lipid levels.

Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin 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 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,  $p = 0.059$ ).

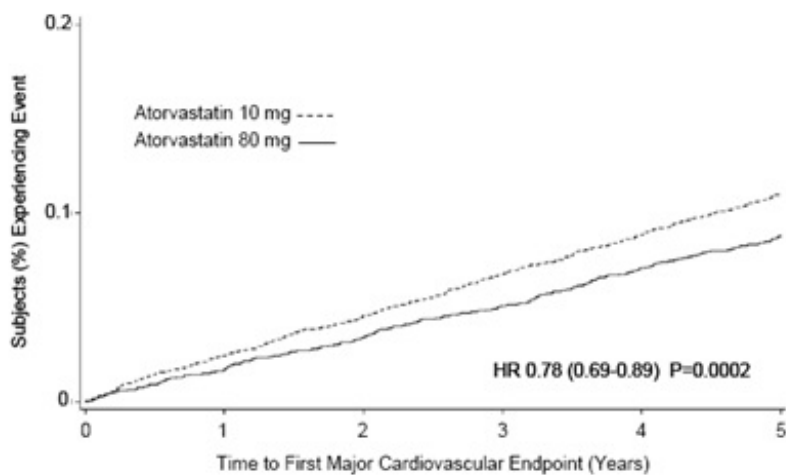


**Figure 2. Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Event (Myocardial Infarction, Acute CHD Death, Unstable Angina, Coronary Revascularization or Stroke) in CARDS**

Figure 2. Effect of Atorvastatin 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 80 mg/day vs. atorvastatin 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38%  $\geq 65$  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 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin 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, nonfatal myocardial infarction, resuscitated cardiac arrest and fatal and nonfatal 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 and 99, 177, 152, 129 and 48 mg/dL during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 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 5). The overall risk reduction was consistent regardless of age ( $< 65$ ,  $\geq 65$ ) or gender.



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

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

**Table 5. Overview of Efficacy Results in TNT**

Endpoint	Atorvastatin 10 mg (N = 5,006)		Atorvastatin 80 mg (N = 4,995)		HR* (95% CI)
	n	(%)	n	(%)	
<b>PRIMARY ENDPOINT</b>					
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
<b>Components of the Primary Endpoint</b>					
CHD death	127	(2.5)	101	(2)	0.8 (0.61, 1.03)
Nonfatal, 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	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)

nonfatal)	155	(3.1)	117	(2.5)	0.75 (0.59, 0.96)
<b>SECONDARY ENDPOINTS<sup>†</sup></b>					
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 <sup>‡</sup>	904	(18.1)	667	(13.4)	0.72 (0.65, 0.8)
First documented angina endpoint <sup>‡</sup>	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
<b>Components of All-Cause Mortality</b>					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2)
Suicide, homicide and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)
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					

\* Atorvastatin 80 mg; atorvastatin 10 mg

† Secondary endpoints not included in primary endpoint

‡ Component of other secondary endpoints

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 80 mg/day significantly reduced the rate of nonfatal, non-procedure related MI and fatal and nonfatal stroke, but not CHD death or resuscitated cardiac arrest (Table 5). Of the predefined secondary endpoints, treatment with atorvastatin 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 5). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 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 and 105, 179,

142, 47 and 132 mg/dL during treatment with 20 mg 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, nonfatal MI and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin 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 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 80 mg group and the simvastatin 20 mg to 40 mg group.

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

Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B and TG and increases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin 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 given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B and TG. (Pooled results are provided in Table 6.)

**Table 6. 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 two dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25<sup>th</sup> and 75<sup>th</sup> percentile) percent changes from baseline in HDL-C for atorvastatin 10 mg, 20 mg, 40 mg 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 was compared to other statins. After randomization, patients were treated for 16 weeks with either atorvastatin 10 mg per day or a fixed dose of the comparative agent (Table 7).

**Table 7. Mean Percentage Change From Baseline at Endpoint (Double-blind, Randomized, Active-controlled Trials)**

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/HDL-C
<i>Study 1</i>							
Atorvastatin 10 mg	707	-27*	-36*	-28*	-17*	+7	-37*



Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff <sup>†</sup>		-9.2, -6.5	-10.7, -7.1	-10, -6.5	-15.2, -7.1	-1.7, 2	-11.1, -7.1
<i>Study 2</i>							
Atorvastatin 10 mg	222	-25 <sup>‡</sup>	-35 <sup>‡</sup>	-27 <sup>‡</sup>	-17 <sup>‡</sup>	+6	-36 <sup>‡</sup>
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff <sup>†</sup>		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
<i>Study 3</i>							
Atorvastatin 10 mg	132	-29 <sup>§</sup>	-37 <sup>§</sup>	-34 <sup>§</sup>	-23 <sup>§</sup>	+7	-39 <sup>§</sup>
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff <sup>†</sup>		-8.7, -2.7	-10.1, -2.6	-8, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

\* Significantly different from lovastatin, ANCOVA,  $p \leq 0.05$

<sup>†</sup> 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.

<sup>‡</sup> Significantly different from pravastatin, ANCOVA,  $p \leq 0.05$

<sup>§</sup> 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 7 is not known. Table 7 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 (*Fredrickson Type IV*)

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 8). For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267 to 1502).

**Table 8. 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 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
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 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30)	-33 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

#### 14.4 Dysbetalipoproteinemia (*Fredrickson Type III*)

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 9).

**Table 9. Open-label Crossover Study of 16 Patients with Dysbetalipoproteinemia (*Fredrickson Type III*)**

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		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 to 37 years with homozygous FH received maximum daily doses of 20 mg to 80 mg of atorvastatin. 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 four patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, two patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining three 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 to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to atorvastatin (n = 140) or placebo (n = 47) for 26 weeks and then all received atorvastatin 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 mg/dL) in the atorvastatin group compared to 230 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin (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-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides and apolipoprotein B during the 26-week double-blind phase (see Table 10).

**Table 10. Lipid-altering Effects of Atorvastatin 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	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12	-34

The mean achieved LDL-C value was 130.7 mg/dL (range: 70 to 242 mg/dL) in the atorvastatin group

compared to 228.5 mg/dL (range: 152 to 385 mg/dL) in the placebo group during the 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

## 15 REFERENCES

<sup>1</sup> National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, *Pediatrics*. 89(3):495-501. 1992.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Atorvastatin Calcium Tablets are available containing atorvastatin calcium, USP equivalent to 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin.

The 10 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **A15** on the other side. They are available as follows:

NDC 0378-2015-77  
bottles of 90 tablets

NDC 0378-2015-05  
bottles of 500 tablets

The 20 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **A17** on the other side. They are available as follows:

NDC 0378-2017-77  
bottles of 90 tablets

NDC 0378-2017-05  
bottles of 500 tablets

The 40 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **121** on the other side. They are available as follows:

NDC 0378-2121-77  
bottles of 90 tablets

NDC 0378-2121-05  
bottles of 500 tablets

The 80 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **122** on the other side. They are available as follows:

NDC 0378-2122-77  
bottles of 90 tablets

NDC 0378-2122-05  
bottles of 500 tablets

**Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

**PHARMACIST:** Dispense a Patient Information Leaflet with each prescription.

## 17 PATIENT COUNSELING INFORMATION

Patients taking atorvastatin calcium tablets should be advised that cholesterol is a chronic condition and

they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program as appropriate and periodic testing of a fasting lipid panel to determine goal attainment.

**Patients should be advised about substances they should not take concomitantly with atorvastatin [see Warnings and Precautions (5.1)]. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking atorvastatin calcium tablets.**

### **17.1 Muscle Pain**

All patients starting therapy with atorvastatin calcium tablets should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (> 1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional.

### **17.2 Liver Enzymes**

It is recommended that liver enzyme tests be performed before the initiation of atorvastatin calcium tablets and if signs or symptoms of liver injury occur. All patients treated with atorvastatin calcium tablets should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

### **17.3 Pregnancy**

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using atorvastatin calcium tablets. Discuss future pregnancy plans with your patients and discuss when to stop atorvastatin calcium tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking atorvastatin calcium tablets and call their healthcare professional.

### **17.4 Breast-feeding**

Women who are breast-feeding should be advised to not use atorvastatin calcium tablets. Patients who have a lipid disorder and are breast-feeding, should be advised to discuss the options with their healthcare professional.

## **PATIENT INFORMATION LEAFLET ATORVASTATIN CALCIUM TABLETS**

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

**10 mg, 20 mg, 40 mg and 80 mg**

Read the Patient Information that comes with atorvastatin before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

If you have any questions about atorvastatin calcium tablets, ask your doctor or pharmacist.

### **What is atorvastatin?**

Atorvastatin is a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. Atorvastatin calcium tablets are for adults and children over 10 whose cholesterol does not come down enough with exercise and a low fat diet alone.

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery and chest pain in patients who have heart disease or risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

Atorvastatin calcium tablets can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking or high blood pressure.

Atorvastatin calcium tablets start to work in about 2 weeks.

### **What is cholesterol?**

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower your cholesterol if you have heart disease, smoke, have diabetes or high blood pressure, are older, or if heart disease starts early in your family.

### **Who should not take atorvastatin calcium tablets?**

Do not take atorvastatin calcium tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast-feeding. Atorvastatin can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

Atorvastatin calcium tablets have not been studied in children under 10 years of age.

### **Before you start atorvastatin calcium tablets:**

Tell your doctor if you:

- have muscle aches or weakness
- drink more than two glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with atorvastatin calcium tablets. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS

Know all the medicines you take. Keep a list of them with you 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 two doses of atorvastatin calcium tablets at the same time.
- If you take too much atorvastatin 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?**

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium tablets right away and call your doctor.

### **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.
- 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. Ask your doctor or pharmacist for a complete list.

**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 at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**
- 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.

#### **What are the ingredients in atorvastatin calcium tablets?**

**Active Ingredient:** atorvastatin calcium, USP

**Inactive Ingredients:** anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-Arginine, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum.

Manufactured in India by:

**Mylan Laboratories Limited**

Hyderabad — 500 034, India

Code No.: MH/DRUGS/25/NKD/89

Manufactured for:

**Mylan Pharmaceuticals Inc.**  
Morgantown, WV 26505 U.S.A.

REVISED MARCH 2012  
75005297  
MX:ATOR:R5ppt

**PRINCIPAL DISPLAY PANEL - 10 mg**

**NDC 0378-2015-77**

**Atorvastatin Calcium  
Tablets  
10 mg\***

**PHARMACIST: Dispense the accompanying Patient  
Information Leaflet to each patient.**

**Rx only 90 TABLETS**

\*Each film-coated tablet contains  
atorvastatin calcium, USP  
equivalent to 10 mg of atorvastatin.

**Usual Dosage:** See accompanying  
prescribing information.

**Keep this and all medication out  
of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).  
[See USP Controlled Room  
Temperature.]**

Manufactured for:  
**Mylan Pharmaceuticals Inc.**  
Morgantown, WV 26505 U.S.A.

Made in India

www.mylan.com

**RMX2015MM3**

Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

**Mylan®**  
NDC 0378-2015-77  
**Atorvastatin Calcium  
Tablets**  
**10 mg\***  
PHARMACIST: Dispense the accompanying Patient  
Information Leaflet to each patient.  
**Rx only 90 TABLETS**

\*Each film-coated tablet contains  
atorvastatin calcium, USP  
equivalent to 10 mg of atorvastatin.  
Usual Dosage: See accompanying  
prescribing information.  
Keep this and all medication out  
of the reach of children.  
Store at 20° to 25° C (68° to 77° F).  
[See USP Controlled Room  
Temperature.]

Manufactured by:  
Mylan Pharmaceuticals Inc.  
Morgantown, WV 26505 U.S.A.  
Made in India

www.mylan.com

RMX2015MM3

Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.  
Keep container tightly closed.  
Code No.: MH/DRUGS/25/NKD/89

**NO VARNISH  
ZONE**

Lot  
Exp.

5 0378-2015-77 5  
75005288



**PRINCIPAL DISPLAY PANEL - 20 mg**

**NDC 0378-2017-77**

**Atorvastatin Calcium  
Tablets  
20 mg\***

**PHARMACIST: Dispense the accompanying Patient  
Information Leaflet to each patient.**

**Rx only 90 TABLETS**

\*Each film-coated tablet contains  
atorvastatin calcium, USP  
equivalent to 20 mg of atorvastatin.

**Usual Dosage:** See accompanying  
prescribing information.

**Keep this and all medication out  
of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).  
[See USP Controlled Room  
Temperature.]**

Manufactured for:  
**Mylan Pharmaceuticals Inc.**  
Morgantown, WV 26505 U.S.A.

Made in India

www.mylan.com

**RMX2017MM3**

Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

**Mylan®**  
NDC 0378-2017-77  
**Atorvastatin Calcium  
Tablets**  
**20 mg\***  
PHARMACIST: Dispense the accompanying Patient  
Information Leaflet to each patient.  
**Rx only 90 TABLETS**

\*Each film-coated tablet contains  
atorvastatin calcium, USP  
equivalent to 20 mg of atorvastatin.  
Usual Dosage: See accompanying  
prescribing information.  
Keep this and all medication out  
of the reach of children.  
Store at 20° to 25°C (68° to 77°F).  
[See USP Controlled Room  
Temperature.]

Manufactured for:  
Mylan Pharmaceuticals Inc.  
Morgantown, WV 26505 U.S.A.  
Made in India  
www.mylan.com  
RMX2017MM3

Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.  
Keep container tightly closed.  
Code No.: MH/DRUGS/25/NKD/89  
Lot  
Exp.

**NO VARNISH  
ZONE**

3 0378-2017-77 9  
75005290

**PRINCIPAL DISPLAY PANEL - 40 mg**

**NDC 0378-2121-77**

**Atorvastatin**

**Calcium  
Tablets  
40 mg\***

**PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.**

**Rx only 90 TABLETS**

\*Each film-coated tablet contains atorvastatin calcium, USP equivalent to 40 mg of atorvastatin.

**Usual Dosage:** See accompanying prescribing information.

**Keep this and all medication out of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).  
[See USP Controlled Room Temperature.]**

Manufactured for:

**Mylan Pharmaceuticals Inc.**  
Morgantown, WV 26505 U.S.A.

Made in India

www.mylan.com

**RMX2121MM3**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

**PRINCIPAL DISPLAY PANEL - 80 mg  
NDC 0378-2122-77**

**Atorvastatin  
Calcium  
Tablets  
80 mg\***

**PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.**

**Rx only 90 TABLETS**

\*Each film-coated tablet contains atorvastatin calcium, USP equivalent to 80 mg of atorvastatin.

**Usual Dosage:** See accompanying prescribing information.

**Keep this and all medication out of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).  
[See USP Controlled Room Temperature.]**

Manufactured for:  
**Mylan Pharmaceuticals Inc.**  
Morgantown, WV 26505 U.S.A.

Made in India

www.mylan.com

**RMX2122MM3**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

<p>*Each film-coated tablet contains atorvastatin calcium, USP equivalent to 80 mg of atorvastatin. <b>Usual Dosage:</b> See accompanying prescribing information. <b>Keep this and all medication out of the reach of children.</b> <b>Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]</b> Manufactured for: <b>Mylan Pharmaceuticals Inc.</b> Morgantown, WV 26505 U.S.A. Made in India</p> <p><b>Mylan®</b>   www.mylan.com</p>	<p><b>Mylan®</b> <b>NDC 0378-2122-77</b> <b>Atorvastatin Calcium Tablets</b> <b>80 mg*</b></p>  <p><b>PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.</b></p> <p><b>Rx only 90 TABLETS</b></p>	 <p>N 3 0378-2122-77 0</p> <p>Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Code No.: MH/DRUGS/25/NKD/89</p> <p>Lot Exp.</p> <p><b>NO VARNISH ZONE</b></p>  <p>75005294</p>
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**ATORVASTATIN CALCIUM**

atorvastatin calcium tablet, film coated

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG LABEL	<b>Item Code (Source)</b>	NDC:0378-2015
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM TRIHYDRATE (ATORVASTATIN)	ATORVASTATIN	10 mg

### Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
SODIUM CARBONATE	
SILICON DIOXIDE	
CROSCARMELLOSE SODIUM	
HYDROXYPROPYL CELLULOSE (TYPE H)	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYVINYL ALCOHOL	
TALC	
TITANIUM DIOXIDE	
XANTHAN GUM	
ARGININE	
LECITHIN, SOYBEAN	

### Product Characteristics

<b>Color</b>	WHITE (white to off-white)	<b>Score</b>	no score
<b>Shape</b>	OVAL	<b>Size</b>	9mm
<b>Flavor</b>		<b>Imprint Code</b>	MX;A15
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-2015-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091226	05/30/2012	10/31/2014

# ATORVASTATIN CALCIUM

atorvastatin calcium tablet, film coated

## Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-2017
Route of Administration	ORAL	DEA Schedule	

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM TRIHYDRATE (ATORVASTATIN)	ATORVASTATIN	20 mg

## Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
SODIUM CARBONATE	
SILICON DIOXIDE	
CROSCARMELOSE SODIUM	
HYDROXYPROPYL CELLULOSE (TYPE H)	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYVINYL ALCOHOL	
TALC	
TITANIUM DIOXIDE	
XANTHAN GUM	
ARGININE	
LECITHIN, SOYBEAN	

## Product Characteristics

Color	WHITE (white to off-white)	Score	no score
Shape	OVAL	Size	11mm
Flavor		Imprint Code	MX;A17
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-2017-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160	05/30/2012	11/30/2014
2	NDC:0378-2017-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160	05/30/2012	08/31/2014

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091226	05/30/2012	

## ATORVASTATIN CALCIUM

atorvastatin calcium tablet, film coated

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-2121
Route of Administration	ORAL	DEA Schedule	

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM TRIHYDRATE (ATORVASTATIN)	ATORVASTATIN	40 mg

### Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
SODIUM CARBONATE	
SILICON DIOXIDE	
CROSCARMELLOSE SODIUM	
HYDROXYPROPYL CELLULOSE (TYPE H)	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYVINYL ALCOHOL	
TALC	
TITANIUM DIOXIDE	
XANTHAN GUM	
ARGININE	
LECITHIN, SOYBEAN	

### Product Characteristics

Color	WHITE (white to off-white)	Score	no score
Shape	OVAL	Size	14mm
Flavor		Imprint Code	MX;121
Contains			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-2121-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160	05/30/2012	12/31/2014

2	NDC:0378-2121-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160	05/30/2012	10/31/2014
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## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091226	05/30/2012	

## ATORVASTATIN CALCIUM

atorvastatin calcium tablet, film coated

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-2122
Route of Administration	ORAL	DEA Schedule	

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATORVASTATIN CALCIUM TRIHYDRATE (ATORVASTATIN)	ATORVASTATIN	80 mg

### Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
SODIUM CARBONATE	
SILICON DIOXIDE	
CROSCARMELLOSE SODIUM	
HYDROXYPROPYL CELLULOSE (TYPE H)	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYVINYL ALCOHOL	
TALC	
TITANIUM DIOXIDE	
XANTHAN GUM	
ARGININE	
LECITHIN, SOYBEAN	

### Product Characteristics

Color	WHITE (white to off-white)	Score	no score
Shape	OVAL	Size	18mm
Flavor		Imprint Code	MX;122
Contains			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-2122-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160	05/30/2012	11/30/2014
2	NDC:0378-2122-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160	05/30/2012	10/31/2014

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091226	05/30/2012	

**Labeler** - Mylan Pharmaceuticals Inc. (059295980)

Revised: 3/2012

Mylan Pharmaceuticals Inc.