

AMLODIPINE AND ATORVASTATIN - amlodipine and atorvastatin tablet, film coated
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMLODIPINE and ATORVASTATIN TABLETS safely and effectively. See full prescribing information for AMLODIPINE and ATORVASTATIN TABLETS.

AMLODIPINE and ATORVASTATIN tablets, for oral use

Initial U.S. Approval: 2004

INDICATIONS AND USAGE

Amlodipine and atorvastatin tablets are a combination of amlodipine besylate, a calcium channel blocker, and atorvastatin calcium, a HMG CoA-reductase inhibitor, indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine is indicated for the treatment of hypertension, to lower blood pressure (1.1). Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Amlodipine is indicated for the treatment of Coronary Artery Disease (1.2).

Atorvastatin is indicated as an adjunct therapy to diet for prevention of cardiovascular disease (1.3) and hyperlipidemia (1.4).

DOSAGE AND ADMINISTRATION

	Usual starting dose (mg daily)	Maximum dose (mg daily)
Amlodipine	5 ^a	10
Atorvastatin	10 to 20 ^b	80

^a Start small adults or children, fragile, or elderly patients, or patients with hepatic insufficiency on 2.5 mg once daily (2)
^b Start patients requiring large LDL-C reduction (>45%) at 40 mg once daily (2)

DOSAGE FORMS AND STRENGTHS

Tablets contain amlodipine besylate equivalent to amlodipine 5 or 10 mg and atorvastatin calcium equivalent to atorvastatin 10, 20, 40, or 80 mg (3).

CONTRAINDICATIONS

- Active liver disease (4)
- Pregnancy (4)
- Lactation (4)

WARNINGS AND PRECAUTIONS

- Myopathy and Rhabdomyolysis: Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. Amlodipine and atorvastatin therapy should be discontinued if myopathy is diagnosed or suspected (2, 5.1, 8.5).
- Immune-Mediated Necrotizing Myopathy (IMNM): Monitor for myalgia and treat (5.2).
- Hepatic Transaminitis: Monitor liver enzymes before and during treatment (5.3).
- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, acute hypotension is unlikely (5.5).
- Angina or myocardial infarction may occur with initiation or dose increase (5.4).

ADVERSE REACTIONS

Most common adverse reaction (3% greater than placebo) to amlodipine is edema (6.1). Most common adverse reactions leading to atorvastatin discontinuation were myalgia and diarrhea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Increased Risk of Myopathy and Rhabdomyolysis (2, 5.1, 7.3, 12.3)

Cyclosporine, tipranavir plus ritonavir, glecaprevir plus pibrentasvir	Avoid atorvastatin
Clarithromycin, itraconazole, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir	Do not exceed 20 mg atorvastatin daily
Nelfinavir	Do not exceed 40 mg atorvastatin daily
Lopinavir plus ritonavir, simeprevir, fibrin acid derivatives, erythromycin, azole antifungals, lipid-modifying doses of niacin, colchicine	Consider the risk/benefit of concomitant use with atorvastatin

- Other Lipid-Lowering Medications: Increased risk of myopathy (7).
- Rifampin should be simultaneously co-administered with atorvastatin (7.4).
- Oral Contraceptives: Norethindrone and ethinyl estradiol may be increased (7.5).
- Digoxin: Patients should be monitored appropriately (7.5).

USE IN SPECIFIC POPULATIONS

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

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

Revised: 9/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Hypertension
- 1.2 Coronary Artery Disease (CAD)
- 1.3 Prevention of Cardiovascular Disease (CVD) in Adults
- 1.4 Hyperlipidemia
- 1.5 Limitations of Use

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Myopathy and Rhabdomyolysis
- 5.2 Immune-Mediated Necrotizing Myopathy
- 5.3 Liver Dysfunction
- 5.4 Increased Angina and Myocardial Infarction
- 5.5 Hypotension
- 5.6 Endocrine Function
- 5.7 CNS Toxicity
- 5.8 Hemorrhagic Stroke

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Impact of Other Drugs on Amlodipine
- 7.2 Impact of Amlodipine on Other Drugs
- 7.3 Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin
- 7.4 Drug Interactions that may Decrease Exposure to Atorvastatin
- 7.5 Atorvastatin Effects on Other Drugs

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Amlodipine for Hypertension
- 14.2 Amlodipine for Chronic Stable Angina
- 14.3 Amlodipine for Vasospastic Angina
- 14.4 Amlodipine for Coronary Artery Disease
- 14.5 Amlodipine for Heart Failure
- 14.6 Atorvastatin for Prevention of Cardiovascular Disease
- 14.7 Atorvastatin for Hyperlipidemia and Mixed Dyslipidemia
- 14.8 Atorvastatin for Hypertriglyceridemia
- 14.9 Atorvastatin for Dysbetalipoproteinemia
- 14.10 Atorvastatin for Homozygous Familial Hypercholesterolemia
- 14.11 Atorvastatin for Heterozygous Familial Hypercholesterolemia in Pediatric Patients
- 14.12 Amlodipine and Atorvastatin for Hypertension and Dyslipidemia

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Amlodipine and atorvastatin tablets are indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine

1.1 Hypertension

Amlodipine is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including amlodipine.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Amlodipine may be used alone or in combination with other antihypertensive agents.

1.2 Coronary Artery Disease (CAD)

Chronic Stable Angina

Amlodipine is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina)

Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal agents.

Angiographically Documented CAD

In patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%, amlodipine is indicated to reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure.

Atorvastatin

Therapy with HMG CoA-reductase inhibitors (lipid-altering agents) should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease from 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 coronary heart disease (CHD) or multiple risk factors for CHD, atorvastatin can be started simultaneously with diet restriction.

1.3 Prevention of Cardiovascular Disease (CVD) in Adults

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C), or a family history of early coronary heart disease, atorvastatin is indicated to:

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

In adult 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 is indicated to:

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

In adult patients with clinically evident coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for congestive heart failure (CHF)
- Reduce the risk of angina

1.4 Hyperlipidemia

Atorvastatin is indicated:

- As an adjunct to diet to reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) levels and to increase HDL-C in adult 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 adult patients with elevated serum TG levels (*Fredrickson* Type IV);
- For the treatment of adult 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 (HoFH) 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 pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present:
 - a. LDL-C remains ≥ 190 mg/dL or
 - b. LDL-C remains ≥ 160 mg/dL and:
 - there is a positive family history of premature CVD or
 - two or more other CVD risk factors are present in the pediatric patient

1.5 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

Amlodipine and Atorvastatin Tablets

Dosage of amlodipine and atorvastatin tablets must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently.

Amlodipine and atorvastatin tablets may be substituted for its individually titrated components. Patients may be given the equivalent dose of amlodipine and atorvastatin or a dose of amlodipine and atorvastatin with increased amounts of amlodipine, atorvastatin, or both for additional antianginal effects, blood pressure lowering, or lipid-lowering effect.

Amlodipine and atorvastatin tablets may be used to provide additional therapy for patients already on one of its components. Amlodipine and atorvastatin tablets may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina.

Amlodipine

The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily, and the maximum dose is 10 mg once daily.

Pediatric (age > 6 years), small adult, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy.

Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: The recommended dose of amlodipine for chronic stable or vasospastic angina is 5 to 10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Coronary Artery Disease: The recommended dose range of amlodipine for patients with CAD is 5 to 10 mg once daily. In clinical studies, the majority of patients required 10 mg [see *Clinical Studies* (14.4)].

Pediatrics: The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6 years to 17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients [see *Clinical Pharmacology* (12.3), *Clinical Studies* (14.1)].

Atorvastatin (Hyperlipidemia)

Hyperlipidemia and Mixed Dyslipidemia: The recommended starting dose of atorvastatin 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 is 10 mg to 80 mg once daily. Atorvastatin 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 should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Homozygous Familial Hypercholesterolemia: The dosage range of atorvastatin in patients with HoFH is 10 mg to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Lipid-Lowering Therapy: Atorvastatin may be used with bile acid resins. Monitor for signs of myopathy in patients receiving the combination of HMG-CoA reductase inhibitors (statins) and fibrates [see *Warnings and Precautions (5.1), Drug Interactions (7)*].

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

Use with Cyclosporine, Clarithromycin, Itraconazole, Letemovir, or Certain Protease Inhibitors: In patients taking cyclosporine or the human immunodeficiency virus (HIV) protease inhibitor tipranavir plus ritonavir or the hepatitis C virus (HCV) protease inhibitor glecaprevir plus pibrentasvir, or letemovir when co-administered with cyclosporine, therapy with atorvastatin should be avoided. In patients with HIV taking lopinavir plus ritonavir, use the lowest dose necessary of atorvastatin. In patients taking clarithromycin, itraconazole, elbasvir plus grazoprevir, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, or letemovir therapy with atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is used. In patients taking the HIV protease inhibitor nelfinavir therapy with atorvastatin should be limited to 40 mg. [see *Warnings and Precautions (5.1), Drug Interactions (7.3)*].

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 Years to 17 Years of Age): The recommended starting dose of atorvastatin is 10 mg/day; the usual dose range is 10 to 20 mg orally once daily [see *Clinical Studies (14.11)*]. Doses should be individualized according to the recommended goal of therapy [see *Indications and Usage (1.4) and Clinical Pharmacology (12)*]. Adjustments should be made at intervals of 4 weeks or more.

3 DOSAGE FORMS AND STRENGTHS

Amlodipine and atorvastatin tablets, USP are formulated for oral administration in the following strength combinations:

Table 1

	Atorvastatin (mg)			
	10	20	40	80
Amlodipine (mg) 5	X	X	X	X
Amlodipine (mg) 10	X	X	X	X

Combinations of atorvastatin with 5 mg amlodipine are film-coated white to off-white, and combinations of atorvastatin with 10 mg amlodipine are film-coated light blue.

4 CONTRAINDICATIONS

- **Active Liver Disease, Which May Include Unexplained Persistent Elevations in Hepatic Transaminase Levels**
- **Pregnancy**[see *Use in Specific Populations (8.1)*]
- **Lactation**[see *Use in Specific Populations (8.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

Amlodipine and atorvastatin tablets may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase (CK) above ten times the upper limit of normal) and rhabdomyolysis (with or without acute renal failure secondary to myoglobinuria). Rare fatalities have occurred as a result of rhabdomyolysis with statin use, including amlodipine and atorvastatin tablets.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher amlodipine and atorvastatin dosage [see *Drug Interactions (7.3)*].

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

Amlodipine and atorvastatin exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir or glecaprevir plus pibrentasvir with amlodipine and atorvastatin is not recommended. Amlodipine and atorvastatin dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications [see *Dosage and Administration (2)*]. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin co-administered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis [See *Drug Interaction (7.3)*]

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking amlodipine and atorvastatin tablets [see *Drug Interactions (7.3)*].

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

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

5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.

5.3 Liver Dysfunction

Statins, like atorvastatin, and some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials with atorvastatin 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 postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with amlodipine and atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart amlodipine and atorvastatin.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of amlodipine and atorvastatin [see *Contraindications (4)*].

5.4 Increased Angina and Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

5.5 Hypotension

Symptomatic hypotension is possible with use of amlodipine, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

5.6 Endocrine Function

Increases in HbA1c 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. Avoid a statin with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

5.7 CNS Toxicity

Brain hemorrhage was seen in a female dog treated with atorvastatin 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 to 24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0 to 24) based on the maximum recommended human dose (MRHD) 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 statins. 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.

5.8 Hemorrhagic Stroke

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 non-fatal 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:

- Myopathy and Rhabdomyolysis [see *Warnings and Precautions (5.1)*]
- Liver enzyme abnormalities [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

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

Amlodipine and Atorvastatin

Amlodipine and atorvastatin has been evaluated for safety in 1,092 patients in double-blind placebo-controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with amlodipine and atorvastatin was well tolerated. For the most part, adverse reactions have been mild or moderate in severity. In clinical trials with amlodipine and atorvastatin, no adverse reactions peculiar to this combination have been observed. Adverse reactions are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.

The following information is based on the clinical experience with amlodipine and atorvastatin.

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and

foreign clinical trials. In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1,730) at doses up to 10 mg to placebo (N=1,250), discontinuation of amlodipine because of adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most commonly reported side effects more frequent than placebo are dizziness and edema. The incidence (%) of side effects that occurred in a dose-related manner are as follows:

Amlodipine				
	2.5 mg	5 mg	10 mg	Placebo
	N=275	N=296	N=268	N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse reactions that were not clearly dose related but were reported at an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

	Amlodipine (%)	Placebo (%)
	(N=1730)	(N=1250)
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

Edema, flushing, palpitations, and somnolence appear to be more common in women than in men.

The following events occurred in < 1% but > 0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia,² back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps,² myalgia.

Psychiatric: sexual dysfunction (male² and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea,² epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus,² rash,² rash erythematous, rash maculopapular.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

² These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total TG, TC, HDL-C, uric acid, blood urea nitrogen, or creatinine.

Atorvastatin

In the atorvastatin placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin vs. 7,311 placebo; age range 10 years 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 because of 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 (6.0%), 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 seventeen 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=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	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	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	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	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	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.

Treating to New Targets Study (TNT)

In TNT [see *Clinical Studies (14.6)*] involving 10,001 subjects (age range 29 years to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin 10 mg daily (n=5,006) or atorvastatin 80 mg daily (n=4,995), serious adverse reactions and discontinuations because of adverse reactions increased with dose. Persistent transaminase elevations ($\geq 3 \times$ 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 ($\geq 10 \times$ 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%).

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4,731 subjects (age range 21 years to 92 years, 40% women; 93.3% Caucasians, 3.0% 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 ($\geq 3 \times$ ULN twice within 4 to 10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK ($>10 \times$ ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). 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 (5.6)*].

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin 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 (5.0%) than in the placebo group (4.0%).

Adverse Reactions from Clinical Studies of Atorvastatin in Pediatric Patients

In a 26-week controlled study in boys and postmenarchal girls with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% Other), the safety and tolerability profile of atorvastatin 10 to 20 mg daily, as an adjunct to diet to reduce TC, LDL-C, and apo B levels, was generally similar to that of placebo [see Use in Special Populations (8.4) and Clinical Studies (14.11)].

6.2 Postmarketing Experience

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

Amlodipine

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Atorvastatin

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, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, pancreatitis and interstitial lung disease.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see Warnings and Precautions (5.2)].

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

7 DRUG INTERACTIONS

Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are co-administered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the C_{max} : 91% (90% confidence interval: 80 to 103%), but the AUC of atorvastatin increased by 18% (90% confidence interval: 109 to 127%) in the presence of amlodipine, which is not clinically meaningful.

No drug interaction studies have been conducted with amlodipine and atorvastatin and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Amlodipine

7.1 Impact of Other Drugs on Amlodipine

CYP3A Inhibitors

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment [see Clinical Pharmacology (12.3)].

CYP3A Inducers

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with

CYP3A inducers.

Sildenafil

Monitor for hypotension when sildenafil is co-administered with amlodipine [see *Clinical Pharmacology (12.2)*].

7.2 Impact of Amlodipine on Other Drugs

Immunosuppressants

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate [see *Clinical Pharmacology (12.3)*].

Atorvastatin

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

Atorvastatin is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp, or BCRP). Atorvastatin plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters. Table 3 includes a list of drugs that may increase exposure to atorvastatin and may increase the risk of myopathy and rhabdomyolysis when used concomitantly and instructions for preventing or managing them [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

Table 3. Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin

Cyclosporine or Gemfibrozil	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin and cyclosporine, an inhibitor of CYP3A4 and OATP1B1 [see <i>Clinical Pharmacology (12.3)</i>]. Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with atorvastatin
Intervention:	Concomitant use of cyclosporine or gemfibrozil with atorvastatin is not recommended.
Anti-Viral Medications	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin with many anti-viral medications, which are inhibitors of CYP3A4 and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2) [see <i>Clinical Pharmacology (12.3)</i>]. Cases of myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir plus sofosbuvir with atorvastatin.
Intervention:	Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with atorvastatin is not recommended. In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin. In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letemovir do not exceed atorvastatin 20 mg. In patients taking nelfinavir, do not exceed atorvastatin 40 mg [see <i>Dosage and Administration (2)</i>]. Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with atorvastatin. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Tipranavir plus ritonavir, glecaprevir plus pibrentasvir, lopinavir plus ritonavir, simeprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letemovir, nelfinavir, and ledipasvir plus sofosbuvir
Select Azole Antifungals or Macrolide Antibiotics	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin with select azole antifungals or macrolide antibiotics, due to inhibition of CYP3A4 and/or transporters [see <i>Clinical Pharmacology (12.3)</i>].
Intervention:	In patients taking clarithromycin or itraconazole, do not exceed atorvastatin 20 mg [see <i>Dosage and Administration (2)</i>]. Consider the risk/benefit of concomitant use of other azole antifungals or macrolide antibiotics with atorvastatin. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been observed with concomitant use of lipid modifying dosages of niacin (>1 gram/day niacin)

Impact:	with atorvastatin.
Intervention:	Consider if the benefit of using lipid modifying dosages of niacin concomitantly with atorvastatin outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Fibrates (other than Gemfibrozil)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with atorvastatin.
Intervention:	Consider if the benefit of using fibrates concomitantly with atorvastatin outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with atorvastatin.
Intervention:	Consider the risk/benefit of concomitant use of colchicine with atorvastatin. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Grapefruit Juice	
Clinical Impact:	Grapefruit juice consumption, especially excessive consumption, more than 1.2 liters/daily can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis.
Intervention:	Avoid intake of large quantities of grapefruit juice, more than 1.2 liters daily, when taking atorvastatin.

7.4 Drug Interactions that may Decrease Exposure to Atorvastatin

Table 4 presents drug interactions that may decrease exposure to atorvastatin and instructions for preventing or managing them.

Table 4. Drug Interactions that may Decrease Exposure to Atorvastatin

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

7.5 Atorvastatin Effects on Other Drugs

Table 5 presents atorvastatin's effect on other drugs and instructions for preventing or managing them.

Table 5. Atorvastatin Effects on Other Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Amlodipine and atorvastatin tablets are contraindicated in women who are pregnant.

Atorvastatin

Atorvastatin is contraindicated for use in pregnant women since safety in pregnant

women has not been established and there is no apparent benefit of lipid lowering drugs during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, atorvastatin may cause fetal harm when administered to a pregnant woman. Amlodipine and atorvastatin tablets should be discontinued as soon as pregnancy is recognized [see *Contraindications (4)*]. Limited published data on the use of atorvastatin are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies in rats and rabbits there was no evidence of embryo-fetal toxicity or congenital malformations at doses up to 30 and 20 times, respectively, the human exposure at the MRHD of 80 mg, based on body surface area (mg/m^2). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development was observed at doses ≥ 6 times the MRHD (see Data).

Amlodipine

The limited available data based on post-marketing reports with amlodipine use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy (see Clinical Considerations). In animal reproduction studies, there was no evidence of adverse developmental effects when pregnant rats and rabbits were treated orally with amlodipine maleate during organogenesis at doses approximately 10 and 20-times MRHD, respectively. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Data

Human Data

Atorvastatin

Limited published data on atorvastatin calcium from observational studies, meta-analyses and case reports have not shown an increased risk of major congenital malformations or miscarriage. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate to exclude a ≥ 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Animal Data

Atorvastatin

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. When administered to pregnant rats and rabbits during organogenesis at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively, atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure at the MRHD based on surface area (mg/m^2). In rats, the maternally toxic dose of 300 mg/kg resulted in increased post-implantation loss and decreased fetal body weight. At the maternally toxic doses of 50 and 100 mg/kg/day in rabbits, there was increased post-implantation loss, and at 100 mg/kg/day fetal body weights were decreased.

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

Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the MRHD based on body surface area, respectively) during their respective periods of major organogenesis. However, for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

8.2 Lactation

Risk Summary

Amlodipine and atorvastatin tablets are contraindicated during breastfeeding.

Atorvastatin

Atorvastatin use is contraindicated during breastfeeding [see *Contraindications (4)*]. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. It is not known whether atorvastatin is present in human milk, but it has been shown that another drug in this class passes into human milk and atorvastatin is present in rat milk. Because of the potential for serious adverse reactions in a breastfed infant, advise women that breastfeeding is not recommended during treatment with amlodipine and atorvastatin.

Amlodipine

Limited available data from a published clinical lactation study reports that amlodipine is present in human milk at an estimated median relative infant dose of 4.2%. No adverse effects of amlodipine on the breastfed infant have been observed. There is no available information on the effects of amlodipine on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Atorvastatin may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with amlodipine and atorvastatin [see *Use in Specific Populations (8.1)*].

8.4 Pediatric Use

The safety and effectiveness of amlodipine and atorvastatin tablets have not been established in pediatric populations.

Amlodipine

Amlodipine (2.5 to 5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years [see *Clinical Studies (14.1)*]. The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Atorvastatin

Heterozygous Familial Hypercholesterolemia (HeFH)

Safety and effectiveness of atorvastatin have been established in patients 10 years to 17 years of age with HeFH as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels when, after an adequate trial of diet therapy, the following are present:

- LDL-C \geq 190 mg/dL, or
- LDL-C \geq 160 mg/dL and
 - a positive family history of FH, or premature CVD in a first, or second-degree relative, or
 - two or more other CVD risk factors are present.

Use of atorvastatin for this indication is supported by evidence from [see *Dosage and Administration (2)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.11)*]:

- A placebo-controlled clinical trial of 6 months duration in 187 boys and postmenarchal girls, 10 years to 17 years of age. Patients treated with 10 mg or 20 mg daily atorvastatin had an adverse reaction profile generally similar to that of patients treated with placebo. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls
- A three year open-label uncontrolled trial that included 163 pediatric patients 10 years to 15 years of age with HeFH who were titrated to achieve a target LDL-C $<$ 130 mg/dL. The safety and efficacy of atorvastatin in lowering LDL-C appeared generally consistent with that observed for adult patients, despite limitations of the

uncontrolled study design

Advise postmenarchal girls of contraception recommendations, if appropriate for the patient [see *Use in Specific Populations (8.1)*].

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

The safety and efficacy of atorvastatin have not been established in pediatric patients younger than 10 years of age with HeFH.

Homozygous Familial Hypercholesterolemia (HoFH)

Clinical efficacy of atorvastatin with dosages up to 80 mg/day for 1 year was evaluated in an uncontrolled study of patients with HoFH including 8 pediatric patients [see *Clinical Studies (14.10)*].

8.5 Geriatric Use

Safety and effectiveness of amlodipine and atorvastatin have not been established in geriatric populations.

Amlodipine

Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40 to 60%, and a lower initial dose may be required [see *Dosage and Administration (2)*].

Atorvastatin

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

8.6 Hepatic Impairment

Amlodipine and atorvastatin are contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no information on overdosage with amlodipine and atorvastatin in humans.

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the MRHD on a mg/m² basis) caused a marked peripheral vasodilation and hypotension.

If overdose should occur with amlodipine, initiate active cardiac and respiratory monitoring. Perform frequent blood pressure measurements. Should hypotension occur, provide cardiovascular support including elevation of the extremities and administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with specific attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Atorvastatin

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. Because of extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

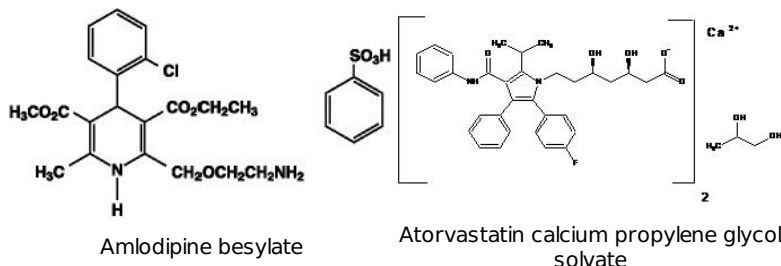
11 DESCRIPTION

Amlodipine and atorvastatin tablets, USP combine the calcium channel blocker amlodipine besylate with the HMG CoA-reductase inhibitor atorvastatin calcium.

Amlodipine besylate, USP is chemically described as 3-ethyl-5-methyl (\pm)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

Atorvastatin calcium, USP in the form of propylene glycol solvate, is chemically described as calcium bis((3R,5R)-7-[3-(anilinoacetyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. Its molecular formula is $C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$.

The structural formulae for amlodipine besylate and atorvastatin calcium propylene glycol solvate are shown below.



Amlodipine and atorvastatin tablets, USP for oral administration contains amlodipine besylate, a white or almost white powder, and atorvastatin calcium a white to off-white solid. Amlodipine besylate, USP has a molecular weight of 567.1 g/mol and atorvastatin calcium propylene glycol solvate, USP has a molecular weight of 1231.46 g/mol. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Each film-coated tablet also contains calcium acetate, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide. In addition, the 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg strengths also contain FD&C Blue #2.

USP Dissolution Test Pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amlodipine and atorvastatin tablets are a combination of two drugs, a dihydropyridine calcium channel blocker (amlodipine) and an HMG-CoA reductase inhibitor (atorvastatin). The amlodipine component of amlodipine and atorvastatin tablets inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of amlodipine and atorvastatin tablets 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.

Amlodipine

Amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for

the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

Atorvastatin

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In animal models, atorvastatin 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.

12.2 Pharmacodynamics

Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Atorvastatin

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)*].

Drug interactions

Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect [see *Drug Interactions (7.1)*].

12.3 Pharmacokinetics

Absorption

Amlodipine: After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%.

Atorvastatin: After oral administration alone, atorvastatin is rapidly absorbed; 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. 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)*].

Amlodipine and atorvastatin tablets: Following oral administration of amlodipine and atorvastatin tablets, peak plasma concentrations of amlodipine and atorvastatin are seen at 6 to 12 hours and 1 to 2 hours post dosing, respectively. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from amlodipine and atorvastatin tablets are not significantly different from the bioavailability of amlodipine and atorvastatin administered separately (see above).

The bioavailability of amlodipine from amlodipine and atorvastatin tablets was not affected by food. Food decreases the rate and extent of absorption of atorvastatin from amlodipine and atorvastatin tablets by approximately 32% and 11%, respectively, as it does with atorvastatin when given alone. LDL-C reduction is similar whether atorvastatin is given with or without food.

Distribution

Amlodipine: *Ex vivo* studies have shown that approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Atorvastatin: 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 calcium is likely to be secreted in human milk [see *Contraindications (4)* and *Use in Specific Populations (8.3)*].

Metabolism

Amlodipine: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Atorvastatin: 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 P4503A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Amlodipine: Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Ten percent of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.

Atorvastatin: 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 because of the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Specific Populations

Geriatric

Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40 to 60%, and a lower initial dose of amlodipine may be required.

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

Pediatric

Amlodipine: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

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

Gender

Atorvastatin: 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

Amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial amlodipine dose.

Atorvastatin: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary [see *Dosage and Administration (2) and Warnings and Precautions (5.1)*].

Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to clear atorvastatin or amlodipine since both drugs are extensively bound to plasma proteins.

Hepatic Impairment

Amlodipine: Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40 to 60%.

Atorvastatin: 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 of atorvastatin are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4)*].

Atorvastatin is contraindicated in patients with active liver disease.

Heart Failure

Amlodipine: In patients with moderate to severe heart failure, the increase in AUC for amlodipine was similar to that seen in the elderly and in patients with hepatic insufficiency.

Effects of Other Drugs on Amlodipine and Atorvastatin

Amlodipine:

Co-administered cimetidine, magnesium- and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent [see *Drug Interactions (7.1)*].

Atorvastatin:

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

Table 6 shows effects of other drugs on the pharmacokinetics of atorvastatin.

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

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC ^{&}	Ratio of C _{max} ^{&}
#Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD ^a for 28 days	8.69	10.66
#Tipranavir 500 mg BID ^b /ritonavir 200 mg BID ^b , 7 days	10 mg SD ^c	9.36	8.58
#Glecaprevir 400 mg QD ^a /pibrentasvir 120 mg QD ^a , 7 days	10 mg QD ^a for 7 days	8.28	22.00
#Telaprevir 750 mg q8h ^f , 10 days	20 mg SD ^c	7.88	10.60
#,‡Saquinavir 400 mg BID ^b /ritonavir 400 mg BID ^b , 15 days	40 mg QD ^a for 4 days	3.93	4.31
#Elbasvir 50 mg QD ^a /grazoprevir 200 mg QD ^a , 13 days	10 mg SD ^c	1.95	4.34
#Simeprevir 150 mg QD ^a , 10 days	40 mg SD ^c	2.12	1.70
#Clarithromycin 500 mg BID ^b , 9 days	80 mg QD ^a for 8 days	4.54	5.38

#Darunavir 300 mg BID ^b /ritonavir 100 mg BID ^b , 9 days	10 mg QD ^a for 4 days	3.45	2.25
#Itraconazole 200 mg QD ^a , 4 days	40 mg SD ^c	3.32	1.20
#Letermovir 480 mg QD ^a , 10 days	20 mg SD ^c	3.29	2.17
#Fosamprenavir 700 mg BID ^b /ritonavir 100 mg BID ^b , 14 days	10 mg QD ^a for 4 days	2.53	2.84
#Fosamprenavir 1400 mg BID ^b , 14 days	10 mg QD ^a for 4 days	2.30	4.04
#Nelfinavir 1250 mg BID ^b , 14 days	10 mg QD ^a for 28 days	1.74	2.22
#Grapefruit Juice, 240 mL QD ^{a,*}	40 mg SD ^c	1.37	1.16
Diltiazem 240 mg QD ^a , 28 days	40 mg SD ^c	1.51	1.00
Erythromycin 500 mg QID ^e , 7 days	10 mg SD ^c	1.33	1.38
Amlodipine 10 mg, single dose	80 mg SD ^c	1.18	0.91
Cimetidine 300 mg QID ^e , 2 weeks	10 mg QD ^a for 2 weeks	1.00	0.89
Colestipol 10 g BID ^b , 24 weeks	40 mg QD ^a for 8 weeks	NA	0.74**
Maalox TC [®] 30 mL QID ^e , 17 days	10 mg QD ^a for 15 days	0.66	0.67
Efavirenz 600 mg QD ^a , 14 days	10 mg for 3 days	0.59	1.01
#Rifampin 600 mg QD ^a , 7 days (co-administered) [†]	40 mg SD ^c	1.12	2.90
#Rifampin 600 mg QD ^a , 5 days (doses separated) [†]	40 mg SD ^c	0.20	0.60
#Gemfibrozil 600 mg BID ^b , 7 days	40 mg SD ^c	1.35	1.00
#Fenofibrate 160 mg QD ^a , 7 days	40 mg SD ^c	1.03	1.02
Boceprevir 800 mg TID ^d , 7 days	40 mg SD ^c	2.32	2.66

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

See Sections 5.1 and 7 for clinical significance.

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

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

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

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

^a Once daily

^b Twice daily

^c Single dose

^d Three times daily

^e Four times daily

^f Every 8 hours

Effects of Amlodipine and Atorvastatin on Other Drugs

Amlodipine:

Amlodipine is a weak inhibitor of CYP3A and may increase exposure to CYP3A substrates.

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Co-administered

amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine [see *Drug Interactions (7.2)*].

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly

administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs [see Drug Interactions (7.2)].

Atorvastatin:

Table 7 shows the effects of atorvastatin on the pharmacokinetics of other drugs.

Table 7. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

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

See Section 7 for clinical significance.

^a Once daily

^b Twice daily

^c Single dose

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m² basis, similar to the MRHD of 10 mg amlodipine/day.⁴ For the rat, the highest dose level was, on a mg/m² basis, about twice the MRHD.⁴

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the MRHD⁴ of 10 mg/day on a mg/m² basis).

⁴ Based on patient weight of 50 kg.

Atorvastatin

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

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

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

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects on fertility. Studies in male rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/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 atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years.

14 CLINICAL STUDIES

14.1 Amlodipine for Hypertension

Adult Patients

The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients

Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults.

14.2 Amlodipine for Chronic Stable Angina

The effectiveness of 5 to 10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies, significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina, there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

14.3 Amlodipine for Vasospastic Angina

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p < 0.01$). Two of 23 amlodipine and 7 of 27 placebo patients discontinued from the study for lack of clinical improvement.

14.4 Amlodipine for Coronary Artery Disease

In PREVENT, 825 patients with angiographically documented CAD were randomized to amlodipine (5 to 10 mg once daily) or placebo and followed for 3 years. Although the study did not show significance on the primary objective of change in coronary luminal diameter as assessed by quantitative coronary angiography, the data suggested a favorable outcome with respect to fewer hospitalizations for angina and revascularization procedures in patients with CAD.

CAMELOT enrolled 1318 patients with CAD recently documented by angiography,

without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at U.S. sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine (5 to 10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anticoagulants (40%), and diuretics (32%), but excluded other calcium channel blockers. The mean duration of follow-up was 19 months. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease. A total of 110 (16.6%) and 151 (23.1%) first events occurred in the amlodipine and placebo groups, respectively, for a hazard ratio of 0.691 (95% CI: 0.540 to 0.884, $p = 0.003$). The primary endpoint is summarized in Figure 1 below. The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures (see Table 8). Effects in various subgroups are shown in Figure 2.

In an angiographic substudy ($n=274$) conducted within CAMELOT, there was no significant difference between amlodipine and placebo on the change of atheroma volume in the coronary artery as assessed by intravascular ultrasound.

Figure 1. Kaplan-Meier Analysis of Composite Clinical Outcomes for Amlodipine versus Placebo

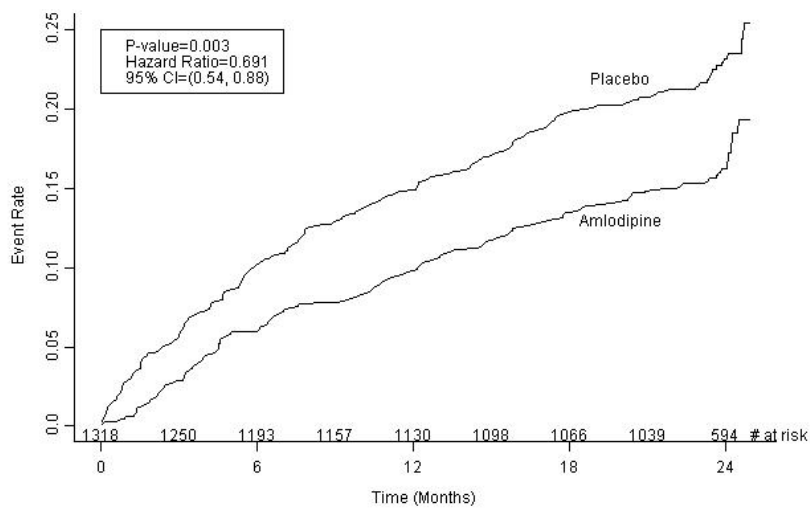
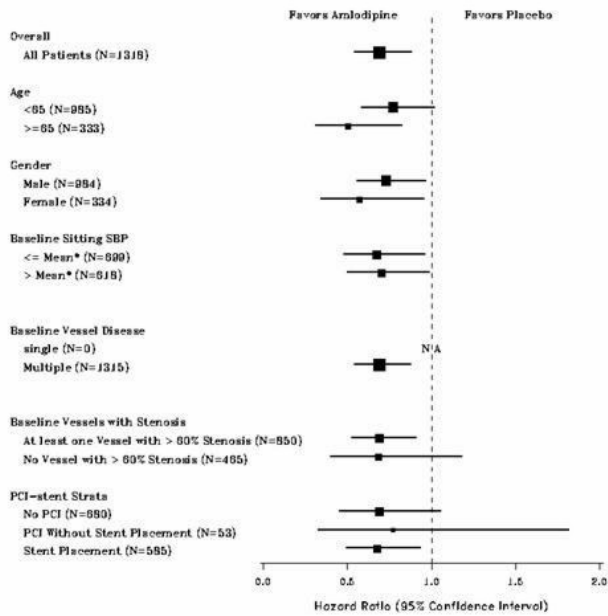


Figure 2. Effects on Primary Endpoint of Amlodipine versus Placebo across Sub-Groups



* The mean sitting baseline SBP is 129 mmHg

Table 8 below summarizes the significant composite endpoint and clinical outcomes from the composites of the primary endpoint. The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, myocardial infarction, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease did not demonstrate a significant difference between amlodipine and placebo.

Clinical Outcomes N (%)	Amlodipine (N=663)	Placebo (N=655)	Risk Reduction (p-value)
Composite CV Endpoint	110 (16.6)	151 (23.1)	31% (0.003)
Hospitalization for Angina*	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization*	78 (11.8)	103 (15.7)	27% (0.033)

* Total patients with these events.

14.5 Amlodipine for Heart Failure

Amlodipine has been compared to placebo in four 8 to 12 week studies of patients with NYHA Class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine 5 mg to 10 mg in 1153 patients with NYHA Classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA Class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitors (99%), digitalis (99%), and diuretics (99%), to placebo (n=827) or amlodipine (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine and placebo in the primary endpoint of all-cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine). With amlodipine there were more reports of pulmonary edema.

14.6 Atorvastatin for Prevention of Cardiovascular Disease

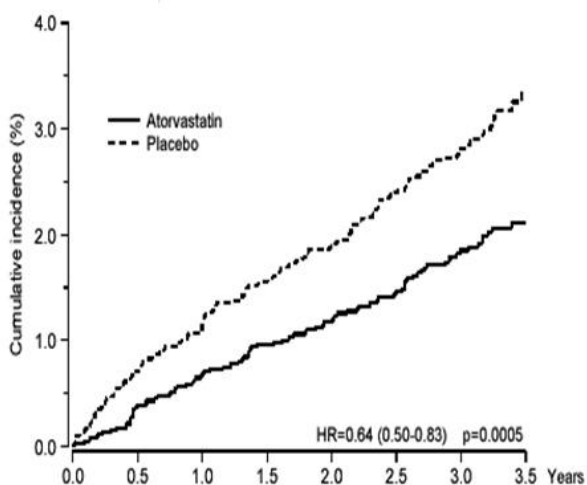
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients

40 years to 80 years of age (mean of 63 years), without a previous myocardial infarction and with total-C levels ≤ 251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age > 55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL > 6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP < 140/90 mmHg for non-diabetic patients; < 130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method that 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 non-fatal 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. 3.0% for placebo), $p=0.0005$ (see Figure 3)]. 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. Because of the small number of events, results for women were inconclusive.

Figure 3. Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42% (incidences of 1.4% for atorvastatin and 2.5% for placebo). Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level ($p=0.01$), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin and 2.3% for placebo). There was no significant difference between the treatment groups for death from 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 endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease, and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the 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_{1c} 7.7%; median LDL-C 120 mg/dL; median total-C 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

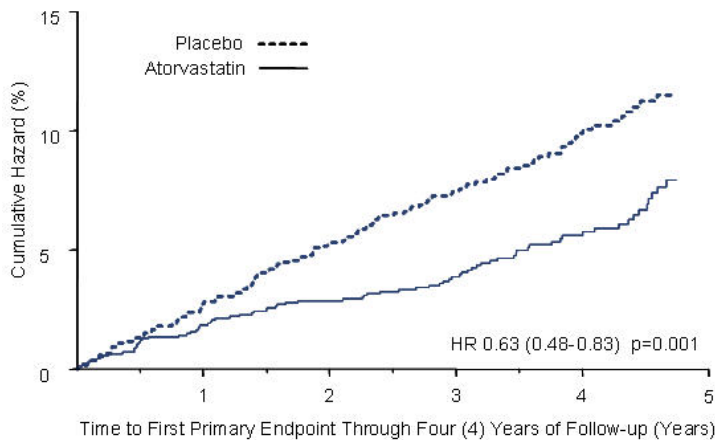
The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

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 4). 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 group vs. 82 deaths in the placebo group (HR 0.73, $p=0.059$).

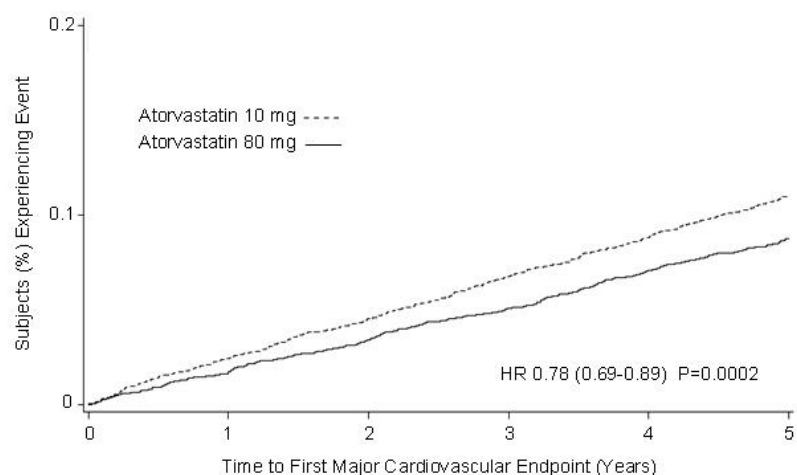
Figure 4. Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Events (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



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% ≥ 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 from CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL-C 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 5 and Table 9). The overall risk reduction was consistent regardless of age (< 65 , ≥ 65) or gender.

Figure 5. Effect of Atorvastatin 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)



Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR ^a (95% CI)
	n	(%)	n	(%)	
PRIMARY ENDPOINT					
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure ^b	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint ^b	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

^aAtorvastatin 80 mg: atorvastatin 10 mg

^bComponent of other secondary endpoints

*Secondary endpoints not included in primary endpoint

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons.

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 9). 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 9). 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-C 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, non-fatal 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 to 40 mg group.

14.7 Atorvastatin for Hyperlipidemia and Mixed Dyslipidemia

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

Atorvastatin 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 10.)

Table 10. Dose Response in Patients with Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)^a

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

^a Results are pooled from 2 dose-response studies.

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

and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hyperlipidemia, atorvastatin 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 11).

Table 11. 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
Study 1							
Atorvastatin 10 mg	707	-27 ^a	-36 ^a	-28 ^a	-17 ^a	+7	-37 ^a
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff ¹		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25 ^b	-35 ^b	-27 ^b	-17 ^b	+6	-36 ^b
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff ¹		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29 ^c	-37 ^c	-34 ^c	-23 ^c	+7	-39 ^c
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff ¹		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

¹ A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.

^a Significantly different from lovastatin, ANCOVA, $p \leq 0.05$

^b Significantly different from pravastatin, ANCOVA, $p \leq 0.05$

^c Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 11 is not known. Table 11 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.

14.8 Atorvastatin for Hypertriglyceridemia

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia (*Fredrickson* Type IV) treated across several clinical trials is shown in the table below (Table 12). For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267 to 1502).

Table 12. 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)
TG	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 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)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

14.9 Atorvastatin for Dysbetalipoproteinemia

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (*Fredrickson* Type III) are shown in the table below (Table 13).

Table 13. 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)
TG	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
Intermediate-density lipoprotein cholesterol (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)

14.10 Atorvastatin for Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 years to 37 years with HoFH received maximum daily doses of 20 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 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.11 Atorvastatin for Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and post-menarchal girls 10 years to 17 years of age (mean age 14.1 years) with HeFH 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 385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0 to 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 78 (55.7 %).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, TG, and apolipoprotein B during the 26-week double-blind phase (see Table 14).

Table 14. 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	CTG	Apo B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

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

Atorvastatin was also studied in a three year open-label, uncontrolled trial that included 163 patients with HeFH who were 10 years to 15 years old (82 boys and 81 girls). All patients had a clinical diagnosis of HeFH confirmed by genetic analysis (if not already confirmed by family history). Approximately 98% were Caucasian, and less than 1% were Black or Asian. Mean LDL-C at baseline was 232 mg/dL. The starting atorvastatin dosage was 10 mg once daily and doses were adjusted to achieve a target of $<$ 130 mg/dL LDL-C. The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous clinical studies in both adult and pediatric placebo-controlled trials.

14.12 Amlodipine and Atorvastatin for Hypertension and Dyslipidemia

In a double-blind, placebo-controlled study, a total of 1660 patients with co-morbid hypertension and dyslipidemia received once daily treatment with eight dose combinations of amlodipine and atorvastatin (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, or 10/80 mg), amlodipine alone (5 mg or 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, or 80 mg), or placebo. In addition to concomitant hypertension and dyslipidemia, 15% of the patients had diabetes mellitus, 22% were smokers, and 14% had a positive family history of cardiovascular disease. At eight weeks, all eight

combination-treatment groups of amlodipine and atorvastatin demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP), and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP, and LDL-C (Table 15).

Table 15. Effects of Amlodipine and Atorvastatin on Blood Pressure and LDL-C

BP (mmHg)	Atorvastatin				
	Amlodipine	0 mg	10 mg	20 mg	40 mg
0 mg	—	-1.5/-0.8	-3.2/-0.6	-3.2/-1.8	-3.4/-0.8
5 mg	-9.8/-4.3	-10.7/-4.9	-12.3/-6.1	-9.7/-4.0	-9.2/-5.1
10 mg	-13.2/-7.1	-12.9/-5.8	-13.1/-7.3	-13.3/-6.5	-14.6/-7.8
LDL-C (% change)	Atorvastatin				
	Amlodipine	0 mg	10 mg	20 mg	40 mg
0 mg	—	-32.3	-38.4	-42.0	-46.1
5 mg	1.0	-37.6	-41.2	-43.8	-47.3
10 mg	-1.4	-35.5	-37.5	-42.1	-48.0

16 HOW SUPPLIED/STORAGE AND HANDLING

Amlodipine and atorvastatin tablets, USP contain amlodipine besylate and atorvastatin calcium, in the form of propylene glycol solvate, equivalent to amlodipine and atorvastatin in the dose strengths described below.

Amlodipine and atorvastatin tablets, USP 10 mg/20 mg are light blue, oval, biconvex, film-coated tablets, engraved "10/20" on one side, "APO" on the other side. They are supplied as follows:

NDC 72162-2090-3 Bottles of 30 with child-resistant closure

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

Repackaged/Relabeled by:
Bryant Ranch Prepack, Inc.
Burbank, CA 91504

17 PATIENT COUNSELING INFORMATION

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

Information for Patients

Because of the risk of myopathy with statins, the drug class to which atorvastatin belongs, advise patients to report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Advise patients taking atorvastatin 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.

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

Muscle Pain: Advise patients starting therapy with amlodipine and atorvastatin tablets of the risk of myopathy and to report promptly any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing amlodipine and atorvastatin tablets. 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.

Liver Enzymes: Advise patients treated with amlodipine and atorvastatin tablets to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Embryofetal Toxicity: Advise females of reproductive potential of the risk to a fetus, to use effective contraception during treatment and to inform their healthcare provider of a known or suspected pregnancy while using amlodipine and atorvastatin tablets [see *Contraindications* (4) and *Use in Specific Populations* (8.1, 8.3)].

Lactation: Advise women not to breastfeed during treatment with amlodipine and atorvastatin tablets [see *Contraindications* (4) and *Use in Specific Populations* (8.2)].

All registered trademarks are the property of their respective owners.

APOTEX INC.

AMLODIPINE AND ATORVASTATIN TABLETS, USP

5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg

Manufactured by: Manufactured for:
Apotex Inc. Apotex Corp.
Toronto, Ontario Weston, Florida
Canada M9L 1T9 USA 33326

Revision: 11

PATIENT INFORMATION

AMLODIPINE AND ATORVASTATIN TABLETS, USP

(am loe' di peen and a tor" va stat' in)

Read the patient information that comes with amlodipine and atorvastatin tablets before you start taking it, and each time you get a refill. There may be new information. This information does not replace talking with your doctor about your condition or treatment. If you have any questions about amlodipine and atorvastatin tablets, ask your doctor or pharmacist.

What are amlodipine and atorvastatin tablets?

Amlodipine and atorvastatin tablets are a prescription drug that combines amlodipine besylate and atorvastatin calcium in one pill.

Amlodipine and atorvastatin tablets are used in adults who need both amlodipine besylate and atorvastatin calcium.

Amlodipine besylate is used to treat:

- High blood pressure (hypertension) and
- Chest pain (angina) and
- Blocked arteries of the heart (coronary artery disease)

Atorvastatin calcium is used to lower the levels of "bad" cholesterol and triglycerides in your blood. It can also raise the levels of "good" cholesterol.

Atorvastatin calcium is also used to 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 levels of "good" cholesterol, heart disease in the family.

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

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

Amlodipine and atorvastatin tablets have not been studied in children.

Who should not use amlodipine and atorvastatin tablets?

Do not use amlodipine and atorvastatin tablets if you:

- Are pregnant or think you may be pregnant, or are planning to become pregnant. Amlodipine and atorvastatin tablets may harm your unborn baby. If you get pregnant, stop taking amlodipine and atorvastatin tablets and call your doctor right away.
- Are breastfeeding. Amlodipine and atorvastatin can pass into your breast milk and may harm your baby. Do not breastfeed if you take amlodipine and atorvastatin tablets.
- Have liver problems.
- Are allergic to anything in amlodipine and atorvastatin tablets. The active ingredients are atorvastatin calcium and amlodipine besylate. See the end of this leaflet for a complete list of ingredients.

What should I tell my doctor before taking amlodipine and atorvastatin tablets?

Tell your doctor about all of your health conditions, including, if you have:

- heart disease
- muscle aches or weakness
- diabetes
- thyroid problems
- kidney problems
- or drink more than 2 glasses of alcohol daily

Tell your doctor about all the medicines you take including prescription and

nonprescription medicines, vitamins, and herbal supplements. Amlodipine and atorvastatin tablets and some other medicines can interact, causing serious side effects. Especially tell your doctor if you take medicines for:

-
- | | |
|----------------------|-----------------|
| • your immune system | • birth control |
| • infections | • heart failure |
| • cholesterol | • HIV (AIDS) |
| • hepatitis C virus | • anti-virals |
-

You can use nitroglycerin and amlodipine and atorvastatin tablets together. If you take nitroglycerin for chest pain (angina), do not stop taking it while taking amlodipine and atorvastatin tablets.

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How should I take amlodipine and atorvastatin tablets?

- Take amlodipine and atorvastatin tablets once a day, exactly as your doctor tells you. Do not change your dose or stop amlodipine and atorvastatin tablets without talking to your doctor.
- Take amlodipine and atorvastatin tablets each day at any time of day, at about the same time each day. Amlodipine and atorvastatin tablets can be taken with or without food.
- Do not break the tablets before taking them. Talk to your doctor if you have a problem swallowing pills.
- Your doctor should start you on a low-fat diet before giving you amlodipine and atorvastatin tablets. Stay on this low-fat diet when you take amlodipine and atorvastatin tablets.
- If you miss a dose, take it as soon as you remember. Do not take amlodipine and atorvastatin tablets if it has been more than 12 hours since your missed dose. Just take the next dose at your regular time. Do not take 2 doses of amlodipine and atorvastatin tablets at the same time.
- If too much amlodipine and atorvastatin tablets are taken by accident, call your doctor or poison control center, or go to the nearest emergency room.

What should I avoid while taking amlodipine and atorvastatin tablets?

- Avoid getting pregnant. If you get pregnant, stop taking amlodipine and atorvastatin tablets right away and call your doctor.
- Do not breastfeed. Amlodipine and atorvastatin can pass into your breast milk and may harm your baby.

What are possible side effects of amlodipine and atorvastatin tablets?

Amlodipine and atorvastatin tablets can cause serious side effects. These side effects happen 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 amlodipine and atorvastatin tablets are stopped. These serious side effects include:

- **Muscle problems.** Amlodipine and atorvastatin 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 amlodipine and atorvastatin tablets.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking amlodipine and atorvastatin tablets and if you have symptoms of liver problems while you take amlodipine and atorvastatin 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
- **Low blood pressure or dizziness**
- **Muscle rigidity, tremor and/or abnormal muscle movement**

Call your doctor right away if:

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

- you have allergic skin reactions
- **Chest pain that does not go away or gets worse.** Sometimes when you start amlodipine and atorvastatin tablets or increase your dose, chest pain can get worse or a heart attack can happen. If this happens, call your doctor or go to the emergency room right away.

Common side effects of amlodipine and atorvastatin tablets include:

- Diarrhea
- Swelling of your legs or ankles
- Nausea
- Upset stomach
- Muscle and joint pain
- Alterations in some laboratory blood tests

Additional side effects have been reported: tiredness, tendon problems, memory loss, and confusion.

Talk to your doctor or pharmacist about side effects that bother you or do not go away.

There are other side effects of amlodipine and atorvastatin tablets. Ask your doctor or pharmacist for a complete list.

How do I store amlodipine and atorvastatin tablets?

- Store amlodipine and atorvastatin tablets at room temperature, 20°C to 25°C (68°F to 77°F). Protect from moisture.
- Do not keep medicine that is out-of-date or that you no longer need.
- **Keep amlodipine and atorvastatin tablets and all medicines out of the reach of children.** Keep medicines in places where children cannot get it.

General information about amlodipine and atorvastatin tablets

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use amlodipine and atorvastatin tablets for a condition for which it was not prescribed. Do not give amlodipine and atorvastatin 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 amlodipine and atorvastatin tablets. If you want more information, talk with your doctor. Ask your doctor or pharmacist for information about amlodipine and atorvastatin tablets written for health professionals.

For more information, call Apotex Corp. at 1-800-706-5575 or go to www.apotex.com.

What is high blood pressure (hypertension)?

You have high blood pressure when the force of blood against the walls of your arteries stays high. This can damage your heart and other parts of your body. Drugs that lower blood pressure lower your risk of having a stroke or heart attack.

What is angina (chest pain)?

Angina is a pain that keeps coming back when part of your heart does not get enough blood. It feels like something is pressing or squeezing your chest under the breastbone. Sometimes you can feel it in your shoulders, arms, neck, jaw, or back.

What is cholesterol?

Cholesterol is a fat-like substance made in your body. It is also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol can clog your blood vessels.

What is a heart attack?

A heart attack occurs when heart muscle does not get enough blood. Symptoms include chest pain, trouble breathing, nausea, and weakness. Heart muscle cells may be damaged or die. The heart cannot pump well or may stop beating.

What is a stroke?

A stroke occurs when nerve cells in the brain do not get enough blood. The cells may be damaged or die. The damaged cells may cause weakness or problems speaking or thinking.

WHAT ARE THE INGREDIENTS IN AMLODIPINE AND ATORVASTATIN TABLETS?

Active ingredients: amlodipine besylate, atorvastatin calcium

Inactive ingredients: calcium acetate, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide. In addition, the 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg strengths also contain FD&C Blue #2.

APOTEX INC.

AMLODIPINE AND ATORVASTATIN TABLETS, USP

5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg

Manufactured by: Manufactured for:
 Apotex Inc. Apotex Corp.
 Toronto, Ontario Weston, Florida
 Canada M9L 1T9 USA 33326

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revision: 11

Date: November 2022

Amlodipine/Atorvastatin 10 mg/20 mg Tablet



Each film-coated tablet contains:
 Amlodipine Besylate equivalent to 10 mg
 Amlodipine and Atorvastatin Calcium
 equivalent to 20 mg Atorvastatin.

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

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

Protect from moisture.

NDC 72162-2090-3

Amlodipine and Atorvastatin Tablets, USP

10 mg/20 mg



Relabeled by:
 Bryant Ranch Prepack, Inc.
 Burbank, CA 91504 USA

Rx only
30 Tablets
 Manufactured by:
 Apotex Inc.



AMLODIPINE AND ATORVASTATIN

amlodipine and atorvastatin tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72162-2090(NDC:60505-3484)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	10 mg
ATORVASTATIN CALCIUM TRIHYDRATE (UNII: 48A5M73Z4Q) (ATORVASTATIN - UNII:A0JWA85V8F)	ATORVASTATIN	20 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CALCIUM ACETATE (UNII: Y882YXF34X)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	BLUE	Score	no score
Shape	OVAL	Size	11mm
Flavor		Imprint Code	APO;10;20
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72162-2090-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	09/15/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205199	07/29/2020	

Labeler - Bryant Ranch Prepack (171714327)**Registrant** - Bryant Ranch Prepack (171714327)**Establishment**

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(72162-2090) , RELABEL(72162-2090)

Revised: 9/2023

Bryant Ranch Prepack