HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CADUET safely and effectively. See full prescribing information for CADUET.

CADUET® (amlodipine besylate and atorvastatin calcium) tablets, for oral use
Initial U.S. Approval: 2004

---------- RECENT MAJOR CHANGES----------
Indications and Usage, Hypertension (1.1) 11/2013

----------INDICATIONS AND USAGE----------
CADUET is 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	10-20[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 2.5, 5, or 10 mg and atorvastatin calcium equivalent to atorvastatin 10, 20, 40, or 80 mg (3).

----------CONTRAINDICATIONS----------
- Active liver disease (4.1)
- Women who are pregnant or may become pregnant (4.2)
- Nursing mothers (4.3)

----------WARNINGS AND PRECAUTIONS----------
- Myopathy and rhabdomyolysis: Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. CADUET therapy should be discontinued if myopathy is diagnoses or suspected (5.1, 8.5).
- Hepatic transaminitis: Monitor liver enzymes before and during treatment (5.2).
- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, acute hypotension is unlikely (5.4).
- Angina or myocardial infarction may occur with initiation or dose increase (5.3).

----------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 Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

Increased Risk of Myopathy/Rhabdomyolysis (2, 5.1, 7, 12.3)	
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
Lopinavir plus ritonavir	Use lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

- Other Lipid-Lowering Medications: Increased risk of myopathy (7).
- Digoxin: Monitor digoxin levels (7.21).
- Oral Contraceptives: Norethindrone and ethinyl estradiol may be increased (7.22).
- Rifampin: Take at same time as CADUET (7.20).

----------USE IN SPECIFIC POPULATIONS----------
- Hepatic Impairment: Plasma concentrations of atorvastatin markedly increased in patients with active liver disease (12.3).

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

Revised: 01/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Hypertension
1.2 Coronary Artery Disease (CAD)
1.3 Prevention of Cardiovascular Disease
1.4 Hyperlipidemia
1.5 Limitations of Use
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Active Liver Disease
4.2 Pregnancy
4.3 Nursing Mothers
5 WARNINGS AND PRECAUTIONS
5.1 Myopathy and Rhabdomyolysis
5.2 Liver Dysfunction
5.3 Increased Angina and Myocardial Infarction
5.4 Hypotension
5.5 Endocrine Function
5.6 CNS Toxicity
5.7 Hemorrhagic Stroke
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
Amlodipine
7.1 *In Vitro* Data
7.2 Cimetidine
7.3 Grapefruit Juice
7.4 Magnesium and Aluminum Hydroxide Antacid
7.5 Sildenafil
7.6 Atorvastatin
7.7 Digoxin
7.8 Ethanol (alcohol)
7.9 Warfarin
7.10 CYP3A4 Inhibitors
7.11 CYP3A4 Inducers
7.12 Cyclosporine
7.13 Drug/Laboratory Test Interactions

Atorvastatin
7.14 Strong Inhibitors of CYP3A4
7.15 Grapefruit Juice
7.16 Cyclosporine
7.17 Gemfibrozil
7.18 Other Fibrates
7.19 Niacin
7.20 Rifampin or other Inducers of CYP3A4
7.21 Digoxin
7.22 Oral Contraceptives
7.23 Warfarin
7.24 Colchicine
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
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 (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)
14.8 Atorvastatin for Hypertriglyceridemia (*Fredrickson* Type IV)
14.9 Atorvastatin for Dysbetalipoproteinemia (*Fredrickson* Type III)
14.10 Atorvastatin for Homozygous Familial Hypercholesterolemia
14.11 Atorvastatin for Heterozygous Familial Hypercholesterolemia in Pediatric Patients
14.12 CADUET for Hypertension and Dyslipidemia
15 REFERENCES
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

CADUET (amlodipine and atorvastatin) is 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 CHD or multiple risk factors for CHD, atorvastatin can be started simultaneously with diet restriction.

1.3 Prevention of Cardiovascular Disease

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

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

- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin is indicated to:
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In 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 CHF
- Reduce the risk of angina

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

CADUET
Dosage of CADUET 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.

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

CADUET may be used to provide additional therapy for patients already on one of its components. CADUET 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 5–10 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 coronary artery disease is 5–10 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 6–17 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 (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb): The recommended starting dose of atorvastatin is 10 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 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 (see current *NCEP Guidelines*). 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 homozygous FH is 10 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, or Certain Protease Inhibitors: In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), avoid therapy with atorvastatin. In patients with HIV taking lopinavir plus ritonavir, use the lowest necessary dose of atorvastatin. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, limit therapy with atorvastatin to 20 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, limit therapy with atorvastatin to 40 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed *[see Warnings and Precautions (5.1), Drug Interactions (7.13)]*.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age): The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy *[see current NCEP Pediatric Panel Guidelines [1], (References (15), Clinical Pharmacology (12), and Indications and Usage (1.4)]*. Adjustments should be made at intervals of 4 weeks or more.

3 DOSAGE FORMS AND STRENGTHS

CADUET tablets are formulated for oral administration in the following strength combinations:

		Atorvastatin (mg)			
		10	20	40	80
Amlodipine (mg)	2.5	X	X	X	--
	5	X	X	X	X
	10	X	X	X	X

Combinations of atorvastatin with 2.5 mg and 5 mg amlodipine are film-coated white, and combinations of atorvastatin with 10 mg amlodipine are film-coated blue.

4 CONTRAINDICATIONS

4.1 Active Liver Disease

Atorvastatin is contraindicated in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels *[see Warnings and Precautions 5.2 and Clinical Pharmacology 12.3]*.

4.2 Pregnancy

Atorvastatin is contraindicated in women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy; however, in rare reports congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. CADUET should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazard. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus *[see Specific Populations (8.1)]*.

4.3 Nursing Mothers

It is not known whether atorvastatin or amlodipine are excreted into human milk; however, a small amount of another statin does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women taking CADUET should not breastfeed their infants *[see Specific Populations (8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

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

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

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; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing CADUET. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with CADUET and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs *[see Drug Interactions (7.13)]*. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 2 *[see also Dosage and Administration (2), Drug Interactions (7.13), Clinical Pharmacology (12.3)]*.

Table 2. Atorvastatin Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

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

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see *Drug Interactions (7.23)*].

Withhold or discontinue in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection; hypotension; major surgery; trauma; severe metabolic, endocrine, and electrolyte disorders; and uncontrolled seizures).

5.2 Liver Dysfunction
Statins, like 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 CADUET, promptly interrupt therapy. If an alternate etiology is not found, do not restart CADUET.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of CADUET *[see Contraindications (4.1)]*.

5.3 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.

5.4 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.

5.5 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.

5.6 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, 0-24 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 (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other 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.

5.7 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:
Rhabdomyolysis and myopathy *[see Warnings and Precautions (5.1)]*
Liver enzyme abnormalities *[see Warnings and Precautions (5.2)]*

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.

<u>CADUET</u>
CADUET (amlodipine besylate/atorvastatin calcium) 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 CADUET was well tolerated. For the most part, adverse reactions have been mild or moderate in severity. In clinical trials with CADUET, 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.

<u>Amlodipine</u>
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 (male[2] 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 triglycerides, total cholesterol, HDL cholesterol, 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 10–93 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 ≥ 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 3 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin (n=8,755), from seventeen placebo-controlled trials.

Table 3. Clinical Adverse Reactions Occurring in ≥ 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 ≥ 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 29–78 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 (≥3 x ULN twice within 4–10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x 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 21–92 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 (≥ 3 x ULN twice within 4–10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x 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 (5.8)]*.

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%).

Pediatrics: In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo *[see Clinical Studies (14.11) and Use in Specific Populations (8.4)]*.

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.

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

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see *Warnings and Precautions (5.1)*].

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 Cmax: 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 CADUET and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Amlodipine

7.1 *In Vitro* Data: *In vitro* data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

7.2 Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

7.3 Grapefruit Juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

7.4 Magnesium and Aluminum Hydroxide Antacid: Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

7.5 Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

7.6 Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

7.7 Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

7.8 Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

7.9 Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

7.10 CYP3A4 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 CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

7.11 CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A4 inducers.

7.12 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.

7.13 Drug/Laboratory Test Interactions: None known.

Atorvastatin

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.14 Strong Inhibitors of CYP3A4: Atorvastatin is metabolized by CYP3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking clarithromycin, avoid atorvastatin doses >20 mg *[see Warnings and Precautions, Skeletal Muscle (5.1) and Dosage and Administration (2)]*.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg *[see Warnings and Precautions (5.1) and Dosage and Administration (2)]*. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of atorvastatin should not exceed 40 mg and close clinical monitoring is recommended.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking itraconazole, avoid atorvastatin doses >20 mg *[see Warnings and Precautions (5.1) and Dosage and Administration (2)]*.

7.15 Grapefruit Juice: Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

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

7.17 Gemfibrozil: Because of an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, avoid concomitant administration of atorvastatin with gemfibrozil [see *Warnings and Precautions (5.1)*].

7.18 Other Fibrates: The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates. [see *Warnings and Precautions (5.1)*].

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

7.20 Rifampin or other Inducers of CYP3A4: Concomitant administration of atorvastatin with inducers of CYP3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Because of 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.

7.21 Digoxin: When multiple doses of atorvastatin and digoxin were co-administered, steady-state plasma digoxin concentrations increased by approximately 20%. Monitor digoxin levels.

7.22 Oral Contraceptives: Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol) *[see Clinical Pharmacology (12.3)]*. Consider these increases when selecting an oral contraceptive for a woman taking CADUET.

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

7.24 Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.2)]*

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

Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

Amlodipine

There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

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 (respectively, 8 times [3] and 23 times [3] the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, 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.

[3] Based on patient weight of 50 kg.

Atorvastatin

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

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2) *[see Contraindications (4.2)]*.

In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

8.2 Labor and Delivery

No studies have been conducted in pregnant women on the effect of CADUET, amlodipine, or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats.

8.3 Nursing Mothers

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while CADUET is administered.

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women taking CADUET should be advised not to nurse their infants *[see Contraindications (4.3)]*.

8.4 Pediatric Use

The safety and effectiveness of CADUET 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
Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. Doses greater than 20 mg have not been studied in this patient population. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls *[see Clinical Studies (14.11), Adverse Reactions (6.1), and Dosage and Administration (2)]*. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy *[see Contraindications (4.2) and Use in Specific Populations (8.1)]*. Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.

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

8.5 Geriatric Use
Safety and effectiveness of CADUET 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 40–60%, 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
CADUET is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels *[see Contraindications (4.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no information on overdosage with CADUET 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 maximum recommended human dose on a mg/m^2 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.

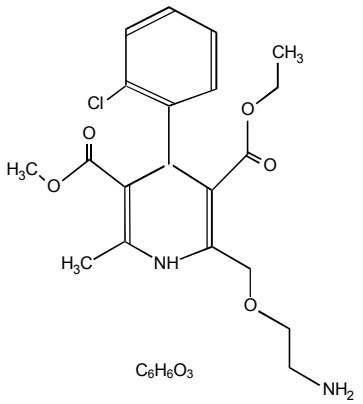
11 DESCRIPTION

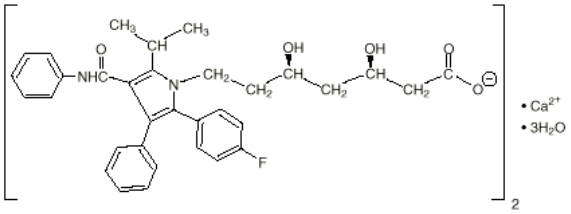
CADUET (amlodipine besylate and atorvastatin calcium) tablets combine the calcium channel blocker amlodipine besylate with the HMG CoA-reductase inhibitor atorvastatin calcium.

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

Atorvastatin calcium is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$.

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





Amlodipine besylate Atorvastatin calcium

CADUET contains amlodipine besylate, a white to off-white crystalline powder, and atorvastatin calcium, also a white to off-white crystalline powder. Amlodipine besylate has a molecular weight of 567.1 and atorvastatin calcium has a molecular weight of 1209.42. 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 very 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 carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate, Opadry® II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000, and talc) or Opadry® II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc, and FD&C blue #2).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

<u>Amlodipine</u>

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

Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

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

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

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

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

12.2 Pharmacodynamics

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 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 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)]*.

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 Cmax 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)]*.

CADUET: Following oral administration of CADUET, 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 CADUET are not significantly different from the bioavailability of amlodipine and atorvastatin administered separately (see above).

The bioavailability of amlodipine from CADUET was not affected by food. Food decreases the rate and extent of absorption of atorvastatin from CADUET 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 ≥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 (4.3) 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 (7.13)]*. 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 30-50 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 40-60%, and a lower initial dose of amlodipine may be required.

Atorvastatin: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax 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: Pharmacokinetic data in the pediatric population are not available.

Gender

Atorvastatin: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax 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 40-60%.

Atorvastatin: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC of atorvastatin are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease *[see Contraindications (4.1)]*.

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 CADUET

Amlodipine: No significant interactions are known.

Atorvastatin: Table 5 shows effects of other drugs on the pharmacokinetics of atorvastatin.

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

Co-administered drug and dosing regimen	**Atorvastatin**		
	Dose (mg)	**Change in AUC**	**Change in Cmax**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 870%	↑1070%
[#]Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 940%	↑ 860%
[#]Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 790%	↑ 1060%
[#, ‡]Saquinavir 400 mg BID/ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 390%	↑ 430%
[#]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 440%	↑ 540%
[#]Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 340%	↑ 230%
[#]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 330%	↑ 20%
[#]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 250%	↑ 280%
[#]Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 230%	↑ 400%
[#]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 220%
[#]Grapefruit Juice, 240 mL QD*	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QID, 2 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[#]Rifampin 600 mg QD, 7 days (co-administered) [†]	40 mg SD	↑ 30%	↑ 2.7-fold
[#]Rifampin 600 mg QD, 5 days (doses separated) [†]	40 mg SD	↓ 80%	↓ 40%
[#]Gemfibrozil 600 mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
[#]Fenofibrate 160 mg QD, 7 days	40mg SD	↑ 3%	↑ 2%
Boceprevir 800 mg TID, 7 days	40 mg SD	↑2.30 fold	↑2.66 fold

[#] See *Warnings and Precautions (5.1)* and *Drug Interactions (7)* for clinical significance.

* Greater increases in AUC (up to 2.5-fold) and/or Cmax (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL – 1.2 liters per day).

** Single sample taken 8-16 h post dose.

† Because of 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, use the lowest dose necessary.

Effects of CADUET on Other Drugs

Amlodipine: No significant interactions are known.

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

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

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	**Change in AUC**	**Change in Cmax**
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 months – norethindrone 1mg – ethinyl estradiol 35 µg	 ↑ 28% ↑ 19%	 ↑ 23% ↑ 30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

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/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day.[4] For the rat, the highest dose level was, on a mg/m^2 basis, about twice the maximum recommended human dose. [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 maximum recommended human dose [4] of 10 mg/day on a mg/m^2 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 (0-24) 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 (0–24) 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.

There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). 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 5–10 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 coronary artery disease were randomized to amlodipine (5–10 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 (5–10 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: 0.540–0.884, 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 7). 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

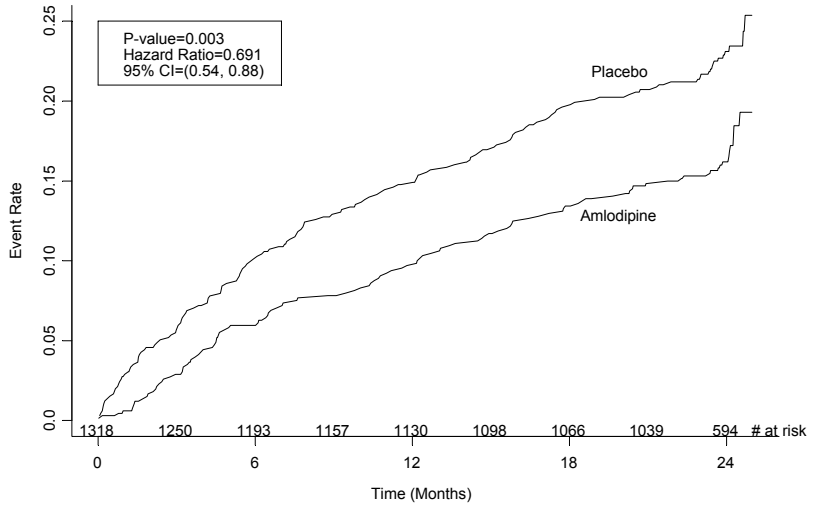
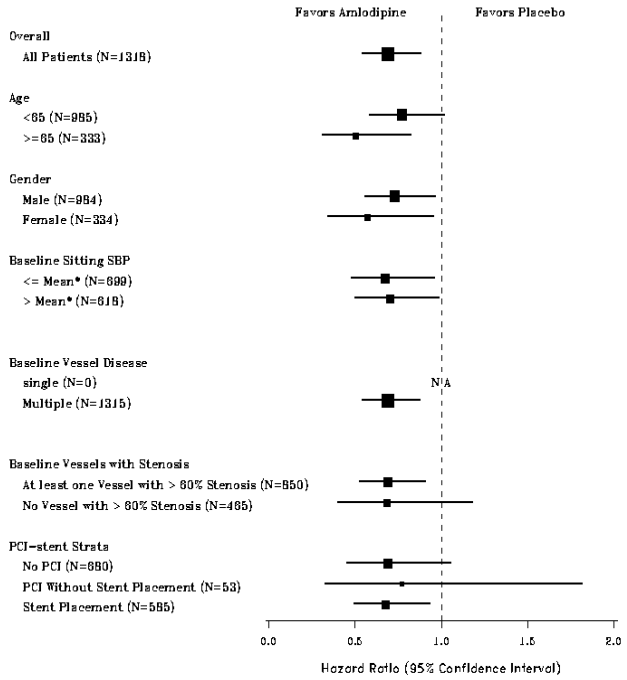


Figure 2. Effects on Primary Endpoint of Amlodipine versus Placebo across Sub-Groups



* The mean sitting baseline SBP is 129 mmHg

Table 7 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.

Table 7. Incidence of Significant Clinical Outcomes for CAMELOT

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 8–12 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 5–10 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.

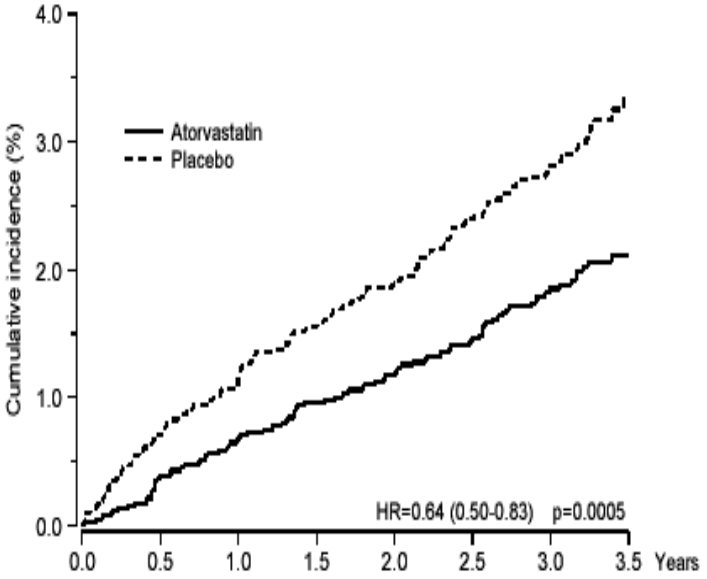
14.6 Atorvastatin for Prevention of Cardiovascular Disease

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 40–80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 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%. 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 (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40–75 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 TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

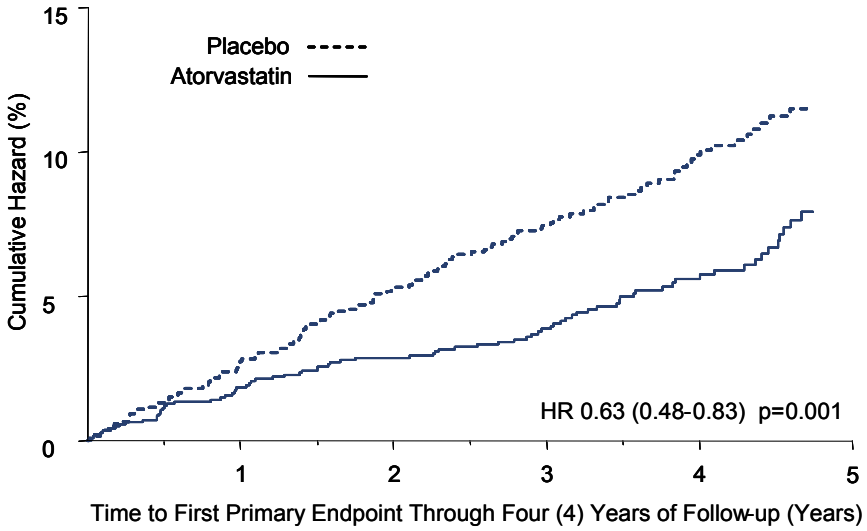
The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 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 cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002 (see Figure 5 and Table 8). 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)

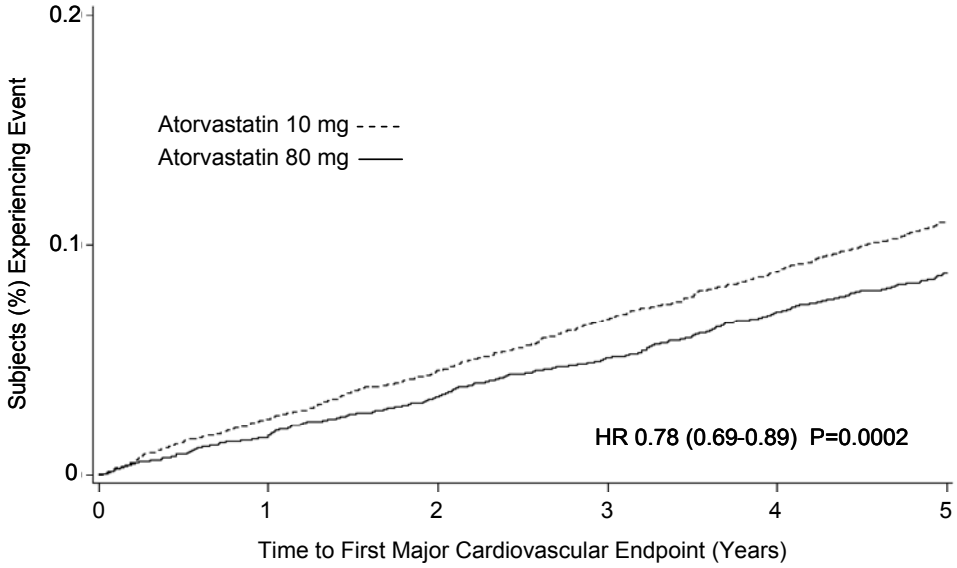


Table 8. Overview of Efficacy Results in TNT

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

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

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

14.7 Atorvastatin for Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

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

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

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, atorvastatin given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 9.)

Table 9. 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 10).

Table 10. 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 10 is not known. Table 10 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 *(Fredrickson* Type IV)

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 11). For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267–1502).

Table 11. Combined Patients with Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 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 *(Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below (Table 12).

Table 12. Open-Label Crossover Study of 16 Patients with Dysbetalipoproteinemia (*Fredrickson* Type III)

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

14.10 Atorvastatin for Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 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 postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 78 (55.7 %).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 13).

Table 13. Lipid-Altering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	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: 70.0–242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

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

14.12 CADUET 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 14).

Table 14. Effects of Amlodipine and Atorvastatin on Blood Pressure and LDL-C

BP (mmHg)	**Atorvastatin**				
Amlodipine	**0 mg**	**10 mg**	**20 mg**	**40 mg**	**80 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**	**80 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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

CADUET® tablets contain amlodipine besylate and atorvastatin calcium equivalent to amlodipine and atorvastatin in the dose strengths described below.

CADUET tablets are differentiated by tablet color/size and are engraved with a unique number on one side. Combinations of atorvastatin with 2.5 mg amlodipine are round and film-coated white, combinations of atorvastatin with 5 mg amlodipine are oval and film-coated white, and combinations of atorvastatin with 10 mg amlodipine are oval and are film-coated blue. CADUET tablets are supplied for oral administration in the following strengths and package configurations:

Table 15. CADUET Packaging Configurations

CADUET					
Package Configuration	Tablet Strength mg (amlodipine / atorvastatin)	NDC #	Engraving Side 1 / Side 2	Tablet Color	Tablet Shape
Bottle of 30	2.5/10	0069-2960-30	CDT 251 / Blank	White	Round
Bottle of 30	2.5/20	0069-2970-30	CDT 252 / Blank	White	Round
Bottle of 30	2.5/40	0069-2980-30	CDT 254 / Blank	White	Round
Bottle of 30	5/10	0069-2150-30	CDT 051 / Pfizer	White	Oval
Bottle of 30	5/20	0069-2170-30	CDT 052 / Pfizer	White	Oval
Bottle of 30	5/40	0069-2190-30	CDT 054 / Pfizer	White	Oval
Bottle of 30	5/80	0069-2260-30	CDT 058 / Pfizer	White	Oval
Bottle of 30	10/10	0069-2160-30	CDT 101 / Pfizer	Blue	Oval
Bottle of 30	10/20	0069-2180-30	CDT 102 / Pfizer	Blue	Oval
Bottle of 30	10/40	0069-2250-30	CDT 104 / Pfizer	Blue	Oval
Bottle of 30	10/80	0069-2270-30	CDT 108 / Pfizer	Blue	Oval

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

17 PATIENT COUNSELING INFORMATION

See 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 CADUET.

Muscle Pain: Advise patients starting therapy with CADUET 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 CADUET. 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 CADUET to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

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

Breast-feeding: Women who are breast-feeding should be advised to not use CADUET. Patients who have a lipid disorder and are breast-feeding should be advised to discuss the options with their healthcare professional.

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LAB-0276-26.0

PATIENT INFORMATION

(**CAD**-oo-et)

Read the patient information that comes with CADUET 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 CADUET, ask your doctor or pharmacist.

What is CADUET?

CADUET is a prescription drug that combines Norvasc® (amlodipine besylate) and Lipitor® (atorvastatin calcium) in one pill.

CADUET is used in adults who need both Norvasc and Lipitor.

Norvasc is used to treat:

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

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

Lipitor 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.

Lipitor 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.

CADUET has not been studied in children.

Who should not use CADUET?

Do not use CADUET if you:

- Are pregnant or think you may be pregnant, or are planning to become pregnant. CADUET may harm your unborn baby. If you get pregnant, stop taking CADUET and call your doctor right away.
- Are breastfeeding. CADUET can pass into your breast milk and may harm your baby. Do not breastfeed if you take CADUET.
- Have liver problems.

- Are allergic to anything in CADUET. 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 CADUET?

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. CADUET and some other medicines can interact, causing serious side effects. Especially tell your doctor if you take medicines for:

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

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

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

How should I take CADUET?

- Take CADUET once a day, exactly as your doctor tells you. Do not change your dose or stop CADUET without talking to your doctor.

- Take CADUET each day at any time of day, at about the same time each day. CADUET 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 CADUET. Stay on this low-fat diet when you take CADUET.

- If you miss a dose, take it as soon as you remember. Do not take CADUET 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 CADUET at the same time.

- If too much CADUET is taken by accident, call your doctor or poison control center, or go to the nearest emergency room.

What should I avoid while taking CADUET?

- Avoid getting pregnant. If you get pregnant, stop taking CADUET right away and call your doctor.

- Do not breastfeed. CADUET can pass into your breast milk and may harm your baby.

What are possible side effects of CADUET?

CADUET 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 CADUET is stopped. These serious side effects include:

- **Muscle problems.** CADUET 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 CADUET.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking CADUET and if you have symptoms of liver problems while you take CADUET. 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**

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 CADUET. 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 CADUET 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 CADUET 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 CADUET. Ask your doctor or pharmacist for a complete list.

How do I store CADUET?

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

General information about CADUET

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use CADUET for a condition for which it was not prescribed. Do not give CADUET to other people, even if they have the same problem you have. It may harm them. This leaflet summarizes the most important information about CADUET. If you want more information, talk with your doctor. Ask your doctor or pharmacist for information about CADUET written for health professionals. You can also go to the CADUET website at www.CADUET.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 CADUET?

Active ingredients: amlodipine besylate, atorvastatin calcium

Inactive ingredients: calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate
Film coating: Opadry® II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000, and talc) or Opadry® II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc, and FD&C blue #2)

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