DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

sNDA 021540/S-023
sNDA 021540/S-026

SUPPLEMENT APPROVAL

Pfizer, Inc.
Attention: Denise Andrews
Associate Director WW Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Andrews:

Please refer to your Supplemental New Drug Applications (sNDA) received January 31 and August 9, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Caduet (amlodipine/atorvastatin) 5 / 10 mg, 10 / 10 mg, 5 / 20 mg, 10 / 20 mg, 5 / 40 mg, 10 / 40 mg, 5 / 80 mg and 10 / 80 mg Tablets.

These "Prior Approval" supplemental new drug applications provide for revisions of the label to comply with the PLR formatting requirements, as well as changes made to align the CADUET label with the labels of each of its monotherapy components. In addition to numerous editorial changes, the following content changes were made;

Under **INDICATIONS AND USAGE** the following were added or ~~deleted~~;

1.2 Coronary Artery Disease

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 ~~due to~~ 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 ~~due to~~ 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.

AND

The formatting of **1.4 Hyperlipidemia** was revised.

Under **DOSAGE AND ADMINISTRATION** the following were added or ~~deleted~~;

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. ~~As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of CADUET should be selected based on the continuation of the component being used and the recommended starting dose for the added monotherapy.~~

CADUET may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. ~~The recommended starting dose of CADUET should be based on the appropriate combination of recommendations for the monotherapies. The maximum dose of the amlodipine component of CADUET is 10 mg once daily. The maximum dose of the atorvastatin component of CADUET is 80 mg once daily.~~

~~See above for detailed information related to the dosing and administration of amlodipine and atorvastatin.~~

Amlodipine

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

Pediatric (age > 6 years), ~~S~~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 ~~each patient's need~~blood pressure goals. In general, ~~titration should proceed over~~wait 7 to 14 days ~~so that the physician can fully assess the patient's response to each dose level~~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. ~~*[see Adverse Reactions (6)].*~~

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.
~~Note: A 2.5/80 mg CADUET tablet is not available. Management of patients needing a 2.5/80 mg combination requires individual assessments of dyslipidemia and therapy with the individual components.~~

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)]*.

~~**Dosage in Patients Taking** *Use with Cyclosporine, Clarithromycin, Itraconazole, or a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir*~~*Certain Protease Inhibitors:* In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), avoid therapy ~~should be limited to~~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 ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or lopinavir plus ritonavir~~darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, ~~for doses of~~limit therapy with atorvastatin to~~exceeding~~ 20 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed. In patients with HIV taking nelfinavir, 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)]*.

~~o **Children**~~

~~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)**.~~

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.

Under **DOSAGE FORMS AND STRENGTHS** the following were added or ~~deleted~~;

CADUET ~~non-scored~~ 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

~~Table 1. CADUET Tablet Strengths~~

	~~2.5 mg/ 10mg~~	~~2.5 mg/ 20mg~~	~~2.5 mg/ 40mg~~	~~5 mg/ 10 mg~~	~~5 mg/ 20 mg~~	~~5 mg/ 40 mg~~	~~5 mg/ 80 mg~~	~~10 mg/ 10 mg~~	~~10 mg/ 20 mg~~	~~10 mg/ 40 mg~~	~~10 mg/ 80 mg~~
~~amlodipine equivalent (mg)~~	~~2.5~~	~~2.5~~	~~2.5~~	~~5~~	~~5~~	~~5~~	~~5~~	~~10~~	~~10~~	~~10~~	~~10~~
~~atorvastatin equivalent (mg)~~	~~10~~	~~20~~	~~40~~	~~10~~	~~20~~	~~40~~	~~80~~	~~10~~	~~20~~	~~40~~	~~80~~

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.

Under **CONTRAINDICATIONS** the following were added or ~~deleted~~;

4.2 Pregnancy

~~CADUET contains a~~Atorvastatin ~~and~~ is ~~therefore~~ contraindicated in women who are pregnant or may become pregnant. ~~The a~~Atorvastatin ~~component of CADUET~~ 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~~, WHICH INCLUDES ATORVASTATIN, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS~~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)]*.

~~**4.4 Hypersensitivity**~~

~~CADUET is contraindicated in patients with known hypersensitivity to any component of this medication.~~

Under **CONTRAINDICATIONS** the following were added or ~~deleted~~;

5.1 ~~Skeletal Muscle~~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.

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. 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 ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or~~ 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, ~~plus saquinavir or~~ lopinavir plus ritonavir, darunavir plus ritonavir, ~~immunosuppressive drugs,~~ 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.~~7~~), Drug Interactions (7.13), Clinical Pharmacology (12.3)]*.

Table 2. Atorvastatin Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

~~Interacting Agents~~	~~Prescribing Recommendations~~
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	~~Do not exceed 10 mg atorvastatin daily.~~Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (~~ritonavir plus~~ saquinavir plus ritonavir*, ~~or lopinavir plus ritonavir)~~ darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	~~Caution when exceeding doses > 20 mg atorvastatin daily. The lowest dose necessary should be used.~~ Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

***** Use 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)].*

~~In patients taking CADUET, therapy should be temporarily w~~Withhe~~o~~ld or discontinue~~d~~ 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 ~~the~~ atorvastatin ~~component of CADUET~~, 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 function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CADUET is recommended.~~
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 alternat~~e~~ive 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)]*.

~~**5.5 Beta-Blocker Withdrawal**~~
~~Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.~~

~~5.6~~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. ~~Use caution when administering~~Avoid a statin with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

~~5.8~~5.7 ~~Use in Patients with Recent Stroke or TIA~~Hemorrhagic Stroke

Under **ADVERSE REACTIONS** the following were added or ~~deleted~~;

6.1 Clinical Trials ~~Adverse~~ Experiences

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.

CADUET

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 ~~experiences~~reactions have been mild or moderate in severity. -In clinical trials with CADUET, no adverse ~~experiences~~reactions peculiar to this combination have been observed. Adverse ~~experiences~~reactions are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.

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

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1,730) at doses up to 10 mg to placebo (N=1,250), discontinuation of amlodipine ~~due to~~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 ~~headache~~dizziness and edema. The incidence (%) of side effects that occurred in a dose-related manner are as follows:

~~Adverse Event~~	Amlodipine			
	2.5 mg N=275	5 mg N=296	10 mg N=268	Placebo 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 ~~experiences~~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:

~~*Placebo-Controlled Studies*~~

~~Adverse Event~~	Amlodipine (%) (N=1730)	Placebo (%) (N=1250)
~~Headache~~	~~7.3~~	~~7.8~~
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

~~For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:~~Edema, flushing, palpitations, and somnolence appear to be more common in women than in men.

~~Adverse Event~~	~~Amlodipine~~		~~Placebo~~	
	~~Male=%~~ (N=1218)	~~Female=%~~ (N=512)	~~Male=%~~ (N=914)	~~Female=%~~ (N=336)
~~Edema~~	~~5.6~~	~~14.6~~	~~1.4~~	~~5.1~~
~~Flushing~~	~~1.5~~	~~4.5~~	~~0.3~~	~~0.9~~
~~Palpitations~~	~~1.4~~	~~3.3~~	~~0.9~~	~~0.9~~
~~Somnolence~~	~~1.3~~	~~1.6~~	~~0.8~~	~~0.3~~

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, ~~hypotension,~~peripheral ischemia, syncope, tachycardia, ~~postural dizziness, postural hypotension,~~ vasculitis.

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

Gastrointestinal: anorexia, constipation, ~~dyspepsia,~~[2] 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.

~~The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.~~

~~Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.~~

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.

~~In the CAMELOT and PREVENT studies *[see Clinical Studies (14.4)]*, the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema.~~

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 ~~due to~~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.

~~*Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)*~~
~~In ASCOT *[see Clinical Studies (14.6)]* involving 10,305 participants (age range 40–80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.~~

~~*Collaborative Atorvastatin Diabetes Study (CARDS)*~~
~~In CARDS *[see Clinical Studies (14.6)]* involving 2,838 subjects (age range 39–77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.~~

Treating to New Targets Study (TNT)
In TNT *[see Clinical Studies (14.6)]* 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), ~~there were more~~ serious adverse reactions and discontinuations ~~due to~~because of adverse reactions ~~in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years~~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%).

~~*Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)*~~
~~In IDEAL *[see Clinical Studies (14.6)]* involving 8,888 subjects (age range 26–80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin 80 mg/day (n=4,439) or simvastatin 20–40 mg daily (n=4,449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.~~

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4,731 subjects (age range 21–92 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, ~~memory impairment,~~ depression, ~~and~~ peripheral neuropathy, and pancreatitis.

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).

Under **DRUG INTERACTIONS** the following were added or ~~deleted~~;

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 ~~was~~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:

~~**Studies with**~~ 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 (~~A~~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
1.6-fold 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. Patients should be monitored for adequate clinical effect when amlodipine is co-administered

with CYP3A4 inducers. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A4 inducers.

~~In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.~~

7.12 Drug/Laboratory Test Interactions:
None known.

~~Studies with~~ 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)]*.

7.13 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, ~~use caution when administering~~ avoid atorvastatin doses ≥≥20 mg *[see Warnings and Precautions, Skeletal Muscle (5.1) and Dosage and Administration (2.~~7~~)]*.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin ~~40 mg~~ with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, ~~ritonavir plus saquinavir (400 mg twice daily) or atorvastatin 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily)~~ compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking the HIV protease inhibitor~~s~~ 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.~~7~~)]*.

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, ~~use caution when administering~~ avoid atorvastatin doses ~~≥~~>20 mg *[see Warnings and Precautions (5.1) and Dosage and Administration (2.~~7~~)]*.

7.14 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).

7.15 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)]*. ~~In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg~~ The co-administration of atorvastatin with cyclosporine should be avoided *[see Warnings and Precautions (5.1)]*.

7.16 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)].*

7.17 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)].*

7.18 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.~~16~~19 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. ~~Due to~~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.~~17~~20 Digoxin: When multiple doses of atorvastatin and digoxin were co-administered, steady-state plasma digoxin concentrations increased by approximately 20%. ~~Patients taking digoxin should be monitored appropriately.~~Monitor digoxin levels.

7.~~18~~21 Oral Contraceptives: Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol) *[see Clinical Pharmacology*

(12.3)]. Consider ~~T~~these increases should be ~~considered~~ when selecting an oral contraceptive for a woman taking CADUET.

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

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

Under **USE IN SPECIAL POPULATIONS** the following were added or ~~deleted~~;

8.4 Pediatric Use

~~THERE HAVE BEEN NO STUDIES CONDUCTED TO DETERMINE T~~THE SAFETY ~~OR~~ AND EFFECTIVENESS OF CADUET HAVE NOT BEEN ESTABLISHED IN PEDIATRIC POPULATIONS.

~~*Studies with*~~ aAmlodipine~~:~~
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.

~~*Studies with*~~ aAtorvastatin~~:~~
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.~~3~~1), and Dosage and Administration (2~~.8~~))]*. 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

~~There have been no studies conducted to determine the s~~Safety ~~or~~and effectiveness of CADUET have not been established in geriatric populations.

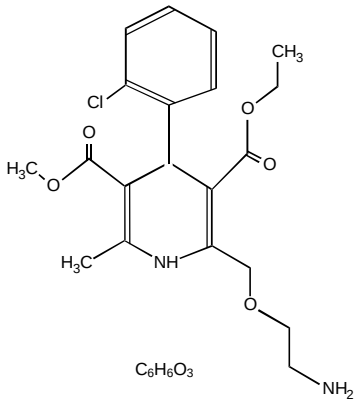
Under **DESCRIPTION** the following were added or ~~deleted~~;

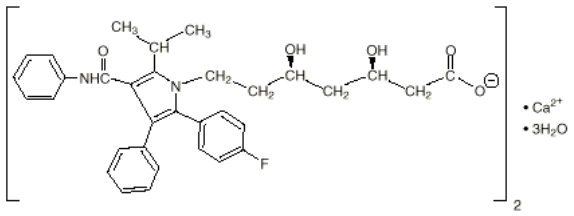
CADUET (amlodipine besylate and atorvastatin calcium) tablets combine the calcium channel blocker amlodipine besylate with the ~~lipid-lowering agent~~HMG CoA-reductase inhibitor atorvastatin calcium.

~~The a~~Amlodipine besylate ~~component of CADUET~~ 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 $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

~~The a~~Atorvastatin calcium ~~component of CADUET~~ 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 $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$.

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

~~Table 4. CADUET Tablet Strengths~~

	~~2.5 mg/ 10~~	~~2.5 mg/ 20~~	~~2.5 mg/ 40~~	~~5 mg/ 10 mg~~	~~5 mg/ 20 mg~~	~~5 mg/ 40 mg~~	~~5 mg/ 80 mg~~	~~10 mg/ 10 mg~~	~~10 mg/ 20 mg~~	~~10 mg/ 40 mg~~	~~10 mg/ 80 mg~~

	~~mg~~	~~mg~~	~~mg~~								
~~amlodipine equivalent (mg)~~	~~2.5~~	~~2.5~~	~~2.5~~	~~5~~	~~5~~	~~5~~	~~5~~	~~10~~	~~10~~	~~10~~	~~10~~
~~atorvastatin equivalent (mg)~~	~~10~~	~~20~~	~~40~~	~~10~~	~~20~~	~~40~~	~~80~~	~~10~~	~~20~~	~~40~~	~~80~~

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).

Under **CLINICAL PHARMACOLOGY** the following were added or ~~deleted~~;

12.1 Mechanism of Action

~~**CADUET**~~

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 ~~(statin)~~, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

Amlodipine

~~Experimental data suggest that a~~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.

12.3 PHARMACOKINETICS

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.

~~***Pharmacokinetic Studies of Atorvastatin and Co-Administered Drugs***~~

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%
~~[#]Lopinavir 400 mg BID/ritonavir 100 mg BID, 14 days~~	~~20 mg QD for 4 days~~	~~↑ 5.9-fold~~	~~↑ 4.7-fold~~
[#,‡]~~Ritonavir~~Saquinavir 400 mg BID/~~saquinavir~~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 QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[#]Rifampin 600 mg QD, 7 days (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%

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.

† ~~Due to~~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, ~~caution should be applied and~~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

[#] ~~See *Drug Interactions (7)* for clinical significance.~~

Under **CLINICAL TRIALS** the following were added or ~~deleted~~;

14.12 ~~Clinical Study of Combined Amlodipine and Atorvastatin in Patients with~~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. ~~EFFICACY IN TERMS OF REDUCTION IN~~ 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**

Table 11. Efficacy in Terms of Reduction in Blood Pressure and LDL-C

Efficacy of the Combined Treatments in Reducing Systolic BP

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean change (mmHg)	-3.0	-4.5	-6.2	-6.2	-6.4
	Difference versus placebo (mmHg)			-3.2	-3.2	-3.4
AML 5 mg	Mean change (mmHg)		-13.	-15.3	-12.7	-12.2
	Difference versus placebo (mmHg)	-9.8	-10.7	-12.3	-9.7	-9.2
AML 10 mg	Mean change (mmHg)	-16.2	-15.9	-16.1	-16.3	-17.6
	Difference versus placebo (mmHg)	-13.2	-12.9	-13.1	-13.3	-14.6

DELETE

Efficacy of the Combined Treatments in Reducing Diastolic BP

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean change (mmHg)	-3.3	-4.1	-3.9	-5.1	-4.1
	Difference versus placebo (mmHg)	-	-0.8	-0.6	-1.8	-0.8
AML 5 mg	Mean change (mmHg)	-7.6	-8.2	-9.4	-7.3	-8.4
	Difference versus placebo (mmHg)	4.3	-4.	-6.1	-4.0	-5.1
AML 10 mg	Mean change (mmHg)	-10.4	-9.1	-10.6	-9.8	-11.1
	Difference versus placebo (mmHg)	-7.1	-5.8	-7.3	-6.5	-7.8

DELETE

Efficacy of the Combined Treatments in Reducing LDL-C (% change)

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean % change	-1.1	-33.4	-39.5	-43.1	-47.2
AML 5 mg	Mean % change	-0	8.7	-42.3	-44.9	-48.4
AML 10 mg	Mean % change	-2.5	-36.6	-38.6	-43.2	-49.1

DELETE

Under **HOW SUPPLIED/STORAGE AND HANDLING** the following were added or ~~deleted~~;

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 ~~"Pfizer" on one side and~~ a unique number on ~~the other~~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 ~~besylate~~/ atorvastatin ~~calcium~~) ~~mg~~	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].

Under **PATIENT COUNSELING INFORMATION** the following were added or ~~deleted~~;

~~**17.2**~~ **Liver Enzymes:**
Advise patients treated with CADUET should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Under **PATIENT INFORMATION** the following were added or ~~deleted~~;

What is CADUET?

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 ~~HDL C~~levels of "good" cholesterol, heart disease in the family.

How should I take CADUET?

~~1.CADUET comes in many different strengths. Your doctor will test your cholesterol and blood pressure to find the right dose for you.~~

What are possible side effects of CADUET?

- **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.** ~~CADUET can cause liver problems.~~ Your doctor ~~may~~should do blood tests to check your liver before you start taking CADUET and ~~while you take it~~ ~~it~~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**

Common side effects of CADUET include:

~~headache~~ ~~• dizziness~~
~~tiredness~~ ~~• extreme sleepiness~~
~~stomach pain~~ ~~• nausea~~
~~upset stomach~~

- ~~d~~Diarrhea
- ~~s~~Swelling of your legs or ankles ~~(edema)~~
- Nausea
- Upset stomach
- ~~hot or warm feeling in your face (flushing)~~
- ~~irregular heartbeat (arrhythmia)~~
- ~~very fast heartbeat (heart palpitations)~~
- ~~m~~Muscle and joint pain
- ~~a~~Alterations in some laboratory blood tests

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

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert),with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Michael Monteleone, MS, RAC, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
07/26/2012