PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCADUET®

amlodipine besylate and atorvastatin calcium tablets

tablets 5/10 mg, 5/20 mg, 5/40 mg, 5/80 mg and 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg amlodipine (as amlodipine besylate) and atorvastatin (as atorvastatin calcium), Oral

Anti-hypertensive/Anti-anginal Agent and Lipid Metabolism Regulator

BGP Pharma ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

Date of Initial Authorization:
AUG 16, 2023

Submission Control No: 277411

RECENT MAJOR LABEL CHANGES

2 Contraindications	12/2020
7 Warnings and Precautions, Musculoskeletal	11/2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CADUET (amlodipine besylate/atorvastatin calcium) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate, specifically, patients at cardiovascular risk.

CADUET is not for initial therapy. The dose of CADUET should be determined by the titration of individual components (see 4 DOSAGE AND ADMINISTRATION).

1.1 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of CADUET in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. However, there have been studies using amlodipine or atorvastatin only in pediatrics (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

CADUET (amlodipine besylate/atorvastatin calcium) is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medical ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- patients with severe hypotension (less than 90 mmHg systolic) and in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- pregnancy and for breastfeeding women (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, 7.1.1 Pregnant Women, 7.1.2 Breast-feeding).
- concomitant treatment with hepatitis C antivirals (see 9.4 Drug-Drug Interactions).
- concomitant treatment with the immunosuppressant cyclosporine (see 9.4 Drug-Drug Interactions).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- CADUET is a combination product containing amlodipine besylate and atorvastatin calcium
- CADUET is not intended for initial therapy.
- The dosage of atorvastatin should be individualized according the baseline LDL-C, total-C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest dose needed to achieve LDL-C desired level. Lipid levels should be monitored periodically and, if necessary, the dose of atorvastatin adjusted based on desired lipid levels recommended by guidelines.

- Patients should be placed on a standard cholesterol-lowering diet before receiving atorvastatin, and should continue on this diet during treatment with atorvastatin. If appropriate, a program of weight control and physical exercise should be implemented.
- Prior to initiating therapy with atorvastatin, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

4.2 Recommended Dose and Dosage Adjustment

The dosage of CADUET in adults must be individualized on the basis of both effectiveness and tolerance for each component which should be determined by titration as described below. CADUET is not indicated for pediatric use.

Amlodipine

- For Adults

  For both hypertension and angina, the recommended initial dose of amlodipine besylate is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.

- For Elderly or in Patients with Impaired Renal Function

  The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see 7 WARNINGS AND PRECAUTIONS, Renal; 7.1.4 Geriatrics).

- Patients with Impaired Hepatic Function

  Dosage requirements have not been established in patients with impaired hepatic function. When amlodipine is used in these patients, the dosage should be carefully and gradually adjusted depending on patients tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Atorvastatin

- Primary Hypercholesterolemia and Combined (Mixed) Dyslipidemia, Including Familial Combined Hyperlipidemia

  The recommended starting dose of atorvastatin is 10 or 20 mg once daily, depending on patient's LDL-C reduction required. 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. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Adjustments of dosage, if necessary, should be made at intervals of 2 to 4 weeks. The maximum dose is 80 mg/day.

- Severe Dyslipidemias

  In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, 7 WARNINGS AND PRECAUTIONS, Muscle Effects; 9 DRUG INTERACTIONS).

- Prevention of Cardiovascular Disease

  The recommended starting dose of atovastatin for the primary prevention of myocardial infarction is 10 mg/day.

For secondary prevention of myocardial infarction, optimal dosing may range from 10 mg to 80 mg atorvastatin once daily, to be given at the discretion of the prescriber, taking into account the expected benefit and safety considerations relevant to the patient to be treated.

- Patients with Renal Insufficiency

  Patients with a history of renal insufficiency of unknown severity and severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)] should be given lowest dose (10 mg/day) of atorvastatin. See 7 WARNINGS AND PRECAUTIONS, Renal.

- Drug discontinuation

  If the patient becomes pregnant while taking CADUET, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus (see 7.1.1 Pregnant Women).

  If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage of the atorvastatin component of CADUET should be reduced or the drug discontinued (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

  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 (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

  CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

  The concurrent use of CADUET and fusidic acid should be avoided, therefore, temporary suspension of atorvastatin during fusidic acid therapy is advised (see 9.4 Drug-Drug Interactions).

CADUET therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as sepsis, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures) (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

Although to date hypersensitivity syndrome has not been described as such with CADUET, CADUET should be discontinued if hypersensitivity is suspected (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued (see 8.5 Post-Market Adverse Reactions).

4.4 Administration

CADUET can be administered once daily, at any time of the day, with or without food.

4.5 Missed dose

If patient misses a dose, it should be taken immediately unless the time is close to the next dose. In such an event, patient should wait for next scheduled dose and continue on the regular schdule. A double dose should not be taken to make up for a missed dose.

5 OVERDOSAGE

There is no information on overdosage with CADUET in humans.

Amlodipine

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of the amlodipine component of CADUET is limited. Gastric lavage may be worthwhile in some cases. In healthy volunteers, the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19-month old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment

Clinically significant hypotension due to overdosage requires active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

Atorvastatin

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets (amlodipine besylate /atorvastatin calcium): 5/10 mg, 5/20 mg, 5/40 mg, 5/80 mg and 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg	Calcium Carbonate, Croscarmellose Sodium, Microcrystalline Cellulose, Pregelatinized Starch, Polysorbate 80, Hydroxypropyl Cellulose, Purified Water, Colloidal Silicon Dioxide (anhydrous), Magnesium Stearate, Opadry® II White 85F28751 or Opadry® II Blue 85F10919. ®Registered trademark of the Colorcon Company

CADUET (amlodipine besylate/atorvastatin calcium) tablets are differentiated by tablet color/size and are engraved with "Pfizer" on one side and a unique number on the other side. CADUET tablets are supplied for oral administration to contain amlodipine besylate and atorvastatin calcium in 5 mg/10 mg (white), 5 mg/20 mg (white), 5 mg/40 mg (white), 5 mg/80 mg (white), 10 mg/10 mg (blue), 10 mg/20 mg (blue), 10 mg/40 mg (blue) and 10 mg/80 mg (blue) tablets.

CADUET Tablets		
Package Configuration	**Tablet Strength (amlodipine besylate/atorvastatin calcium) mg**	**Engraving**
Bottle of 90	5 mg/40 mg	CDT 054
Bottle of 90	5 mg/80 mg	CDT 058
Bottle of 90	10 mg/40 mg	CDT 104
Bottle of 90	10 mg/80 mg	CDT 108
Bottle of 90	5 mg/10 mg	CDT 051
Bottle of 90	5 mg/20 mg	CDT 052
Bottle of 90	10 mg/10 mg	CDT 101
Bottle of 90	10 mg/20 mg	CDT 102

CADUET tablets are available in high-density polyethylene (HDPE) bottles, containing desiccant, in packs of 90 tablets, with child-resistant closure.

7 WARNINGS AND PRECAUTIONS

General

Patients should be advised to inform health professionals of the prior use of atorvastatin or any other lipid-lowering agents.

Cardiovascular

Hemorrhagic Stroke in Patients with Recent Stroke or Transient Ischemic Attack (TIA)

The highest dose of atorvastatin (80mg) was associated with an increased risk of hemorrhagic stroke in a post-hoc analysis of a clinical study in 4,731 patients without coronary heart disease (CHD) who had a stroke or TIA within the preceding six months compared to placebo. Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke. The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1-6 months) stroke or TIA.

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow Obstruction (Aortic Stenosis)

CADUET should be used with caution in the presence of fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Congestive Heart Failure

Although generally calcium channel blockers should be used with caution in patients with heart failure, it has been observed that the amlodipine component of CADUET had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.

Of note, in an amlodipine long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV), the reported incidence of pulmonary edema was higher in the amlodipine treated group than in the placebo group.

Hypotension

The amlodipine component of CADUET may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure. CoQ10 Levels should be measured when clinically indicated.

Beta-blocker Withdrawal

The amlodipine component of CADUET gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

Peripheral Edema

Mild to moderate peripheral edema was the most common adverse event in clinical trials with the amlodipine component of CADUET (see 8.2 Clinical Trial Adverse Reactions). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp (a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp (a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy.

Patients with Severe Hypercholesterolemia

Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of the atorvastatin component of CADUET. Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, 7 WARNINGS AND PRECAUTIONS, Muscle Effects; 9.4 Drug-Drug Interactions; 4 DOSAGE AND ADMINISTRATION).

Endocrine and Metabolism

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and, as such, might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with the atorvastatin component of CADUET and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve, and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors 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.

Patients treated with the atorvastatin component of CADUET who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Increases in fasting glucose and HbA1c levels have been reported with inhibitors of HMG-CoA reductase as a class. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The benefit of treatment continues to outweigh the small increased risk. Periodic monitoring of these patients is recommended.

Hepatic/Biliary/Pancreatic

Hepatic Effects

In clinical trials with the atorvastatin component of CADUET, persistent increases in serum transaminases greater than 3 times the upper limit of normal occurred in <1% of patients who received atorvastatin. When the dosage of atorvastatin was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally

not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of atorvastatin without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin.

CADUET, as well as other products containing HMG-CoA reductase inhibitors, should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of the atorvastatin component of CADUET; if such a condition should develop during therapy, CADUET should be discontinued.

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment in which a single dose of 5 mg of the amlodipine component of CADUET was given, half-life has been prolonged (see 10.3 Pharmacokinetics). CADUET should therefore be administered with caution in these patients and careful monitoring should be performed. A lower starting dose of the amlodipine component of CADUET may be required (see 4.2 Recommended Dose and Dosage Adjustment).

Monitoring and Laboratory Tests

The atorvastatin component of CADUET may elevate serum transaminase and CPK levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with CADUET, cardiac and noncardiac fractions of these enzymes should be determined.

Musculoskeletal

Pharmacokinetic Interactions

The use of HMG CoA reductase inhibitors like some other lipid-lowering therapies has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P450 enzyme system. The atorvastatin component of CADUET is metabolized by cytochrome P450 isoform 3A4 and, as such, may interact with agents that inhibit this enzyme (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects; 9.2 Drug Interactions Overview, Cytochrome P450-mediated Interactions).

Muscle Effects

Effects on skeletal muscle such as myalgia, myositis, myopathy and rarely, rhabdomyolysis have been reported in patients treated with the atorvastatin component of CADUET.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported with the atorvastatin component of CADUET and with other HMG-CoA reductase inhibitors.

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine kinase (CK) values to greater than 10 times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured.

Pre-disposing Factors for Myopathy/Rhabdomyolysis: the atorvastatin component of CADUET, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate, or niacin
- Hypothyroidism
- Alcohol abuse
- Excessive physical exercise
- Age >65 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of active ingredient may occur

The risk of myopathy and rhabdomyolysis is increased with concurrent administration of drugs that increase the systemic concentration of atorvastatin via the inhibition of CYP 3A4 or transporter proteins (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions; 9.4 Drug-Drug Interactions).

Although patients with renal impairment are known to be predisposed to the development of rhabdomyolysis with administration of HMG-CoA reductase inhibitors (also known as statins), those with a history of renal impairment may also be predisposed to the development of rhabdomyolysis. Such patients merit close monitoring for skeletal muscle effects.

There have been rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with statins (see 8.5 Post-Market Adverse Reactions). IMNM is clinically characterized by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment
- positive anti-HMG CoA reductase antibody
- muscle biopsy showing necrotizing myopathy without significant inflammation
- improvement with immunosuppressive agents.

Ophthalmologic

Current long-term data from clinical trials do not indicate an adverse effect of the atorvastatin component of CADUET on the human lens.

Renal

Plasma concentrations and LDL-C lowering efficacy of the atorvastatin component of CADUET were shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of atorvastatin should be used in these patients. Similar precautions apply in patients with severe renal insufficiency (creatinine clearance <30 mL/min [<0.5 mL/sec]); the lowest dosage should be used and implemented cautiously (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects, 9 DRUG INTERACTIONS; 4.2 Recommended Dose and Dosage Adjustment).

Concomitant Use with Strong Inhibitors of CYP 3A4

Use of CADUET with drugs that result in strong inhibition of CYP 3A4, such as ketoconazole, clarithromycin, ritonavir, may lead to increased plasma levels of amlodipine and associated serious

adverse events (see 9.4 Drug-Drug Interactions). Such concomitant use should be avoided.

An observational study demonstrated an increased risk of hospitalization with acute kidney injury when amlodipine was used concomitantly with clarithromycin in elderly patients (>65 years of age) compared to when it was used concomitantly with azithromycin, odds ratio [amlodipine: 1.61 (95% C.I. 1.29-2.02)].

Reproductive Health: Female and Male Potential

Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). CADUET should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women).

Sensitivity/Resistance

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

7.1 Special Populations

7.1.1 Pregnant Women

CADUET is contraindicated during pregnancy (see 2 CONTRAINDICATIONS).

The extent of exposure in pregnancy during clinical trials: No experience. 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 hazards. If the patient becomes pregnant while taking CADUET, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology)

Although amlodipine was not teratogenic in the rat and rabbit, some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There was no effect on the fertility of rats treated with amlodipine (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). There is no clinical experience with amlodipine in pregnant women.

7.1.2 Breast-feeding

In human study, the mean maternal daily dose of amlodipine was 6.0 mg and the medians of the plasma and milk concentrations of amlodipine were 15.5 and 11.5 ng/mL, respectively, with median milk/plasma concentration ratio of 0.85. Since amlodipine safety in newborns has not been established, CADUET should not be given to nursing mothers. A decision should be made whether to discontinue

nursing or discontinue the drug, taking into account the importance of the drug to the mother (see 2 CONTRAINDICATIONS).

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether the atorvastatin component of CADUET is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking CADUET should not breast-feed (see 2 CONTRAINDICATIONS).

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

7.1.3 Pediatrics

Pediatrics (0 to 18 years of age): There have been no studies conducted to determine the safety or efficacy of amlodipine/atorvastatin (combination product) in pediatric patients. Based on the data submitted and reviewed by Health Canada, the safety and efficacy of CADUET in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics). However, there have been studies with pediatrics with amlodipine alone and atorvastatin alone (see below).

Amlodipine

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known. Pediatric safety and efficacy studies beyond 8 weeks of duration have not been conducted.

Please refer to the Product Monograph for NORVASC (amlodipine).

Atorvastatin

Since the safety and tolerability profile of atorvastatin in pediatric patients (10-<18 years) is generally similar to the known safety profile of atorvastatin in adult patients, similar warning apply to this patient population. Patients should be particularly monitored for liver enzymes (AST/ALT) and creatine kinase, and adverse events of interest (e.g.: headache, gastrointestinal, musculoskeletal and connective tissue disorders). Doses greater than 20 mg have not been studied in this patient population. Please refer to the Product Monograph for LIPITOR (atorvastatin).

Safety and effectiveness of atorvastatin in pediatric patients has not been determined in the prevention of myocardial infarction. Please refer to the Product Monograph for LIPITOR (atorvastatin).

7.1.4 Geriatrics

Amlodipine

In elderly patients (>65 years), clearance of amlodipine is decreased with a resulting increase in AUC of approximately 40-60%. In general, dose selection of the amlodipine component of CADUET 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 (see 10.3 Pharmacokinetics). In clinical trials, the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. The amlodipine component of CADUET should be used cautiously in elderly patients. Dosage adjustment is advisable (see 4.2 Recommended Dose and Dosage Adjustment).

Atorvastatin

Treatment experience in adults 70 years or older (N=221) with doses of atorvastatin up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose of the atorvastatin component of CADUET should be administered initially (see 10.3 Pharmacokinetics, Special Populations and Conditions: Geriatrics).

Elderly patients may be more susceptible to myopathy (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects – Pre-disposing Factors for Myopathy/Rhabdomyolysis).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Amlodipine

The most serious adverse reaction associated with the amlodipine component of CADUET is hypotension (including syncope) especially under gross overdose (see 5 OVERDOSAGE). The most commonly reported adverse reactions in placebo controlled trials, that may be associated with amlodipine therapy were oedema (9.4%), headaches (8.0%), fatigue (4.5%), dizziness (3.8%) and nausea (3.4%) (see 8.2 Clinical Trial Adverse Reactions).

Atorvastatin

The most serious adverse reactions associated with the atorvastatin component of CADUET are rhabdomyolysis, with acute renal failure secondary to myoglobinuria, myalgia, myositis, myopathy (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal; 8.5 Post-Market Adverse Reactions). The most commonly reported adverse reactions in placebo controlled trials, that may be associated with atorvastatin therapy were nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and hyperglycemia (5.9%) (see 8.2 Clinical Trial Adverse Reactions).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates of adverse drug reactions in real-world use.

For CADUET, itself

CADUET (amlodipine besylate /atorvastatin calcium) has been evaluated for safety in 1,092 patients in two double-blind, placebo-controlled studies treated for co-morbid hypertension and dyslipidemia. In these studies, no unexpected adverse experiences particular to this combination have been observed. Adverse experiences have been limited to those that were reported previously with amlodipine and/or atorvastatin.

For the most part, adverse experiences with CADUET have been mild or moderate in severity. In these controlled clinical trials, adverse events or laboratory abnormalities leading to discontinuation occurred in 5.1% of patients treated with both amlodipine and atorvastatin compared to 4.0% of patients given placebo. The most common safety-related reasons for discontinuation from these studies in the combination treatment groups were headache and peripheral edema.

In a double-blind, controlled clinical trial of all available CADUET doses (5/10 mg to 10/80 mg amlodipine/atorvastatin respectively), the incidences of treatment-emergent adverse events (all causalities) that occurred in at least 1% of all combination treatment groups, pooled across all the combination doses, are summarized below.

Table 1 Adverse Events (All Causality) > 1% of Patients taking Concurrent Amlodipine and Atorvastatin

Body System COSTART Preferred Term	Placebo N = 111(%)	AML Only N = 221 (%)	ATO Only N = 443 (%)	AML + ATO N = 885 (%)
Body as a whole	**16 (14.4)**	**28 (12.7)**	**69 (15.6)**	**137 (15.5)**
Abdominal pain	0 (0.0)	2 (0.9)	10 (2.3)	20 (2.3)
Asthenia	3 (2.7)	4 (1.8)	8 (1.8)	19 (2.1)
Back pain	1 (0.9)	4 (1.8)	5 (1.1)	15 (1.7)
Flu syndrome	1 (0.9)	0 (0.0)	8 (1.8)	9 (1.0)
Headache	11 (9.9)	11 (5.0)	34 (7.7)	47 (5.3)
Cardiovascular	**8 (7.2)**	**16 (7.2)**	**26 (5.9)**	**67 (7.6)**
Palpitation	2 (1.8)	4 (1.8)	4 (0.9)	17 (1.9)
Vasodilatation	3 (2.7)	2 (0.9)	3 (0.7)	18 (2.0)
Digestive	**10 (9.0)**	**16 (7.2)**	**39 (8.8)**	**77 (8.7)**
Constipation	1 (0.9)	3 (1.4)	2 (0.5)	15 (1.7)
Diarrhea	2 (1.8)	2 (0.9)	5 (1.1)	17 (1.9)
GGT increased	0 (0.0)	1 (0.5)	6 (1.4)	16 (1.8)
Nausea	3 (2.7)	3 (1.4)	7 (1.6)	9 (1.0)
Metabolic and nutritional	**6 (5.4)**	**32 (14.5)**	**21 (4.7)**	**133 (15.0)**
Alkaline phosphatase increased	0 (0.0)	0 (0.0)	2 (0.5)	10 (1.1)
Hyperglycemia	0 (0.0)	1 (0.5)	4 (0.9)	10 (1.1)
Peripheral edema	3 (2.7)	27 (12.2)	5 (1.1)	88 (9.9)
SGOT increased	1 (0.9)	1 (0.5)	3 (0.7)	13 (1.5)
SGPT increased	0 (0.0)	1 (0.5)	5 (1.1)	15 (1.7)
Musculoskeletal	**7 (6.3)**	**12 (5.4)**	**25 (5.6)**	**35 (4.0)**
Arthralgia	4 (3.6)	3 (1.4)	4 (0.9)	10 (1.1)
Myalgia	2 (1.8)	3 (1.4)	8 (1.8)	14 (1.6)
Nervous	**9 (8.1)**	**12 (5.4)**	**25 (5.6)**	**47 (5.3)**
Dizziness	3 (2.7)	7 (3.2)	5 (1.1)	21 (2.4)
Respiratory	**9 (8.1)**	**12 (5.4)**	**28 (6.3)**	**69 (7.8)**
Pharyngitis	1 (0.9)	1 (0.5)	3 (0.7)	9 (1.0)
Respiratory tract infection	5 (4.5)	7 (3.2)	17 (3.8)	43 (4.9)
Skin and appendages	**4 (3.6)**	**4 (1.8)**	**6 (1.4)**	**32 (3.6)**
Rash	1 (0.9)	1 (0.5)	3 (0.7)	15 (1.7)

AML = amlodipine
ATO = atorvastatin

The incidence (%) of dose-related adverse events was consistent with those seen for amlodipine and/or atorvastatin.

In this clinical trial, the most frequently reported adverse events among patients who took concurrent amlodipine and atorvastatin were peripheral edema (9.9%), headache (5.3%), respiratory tract infection (4.9%), dizziness (2.4%), abdominal pain (2.3%), asthenia (2.1%), and vasodilatation (2.0%).

In this controlled clinical trial, similar percentages of patients who took concurrent amlodipine and atorvastatin (5.6%) versus patients who took placebo (4.5%), amlodipine only (5.4%), or atorvastatin only (4.1%) discontinued due to adverse safety experiences. Only 1 subject discontinued due to laboratory abnormalities. The most common safety-related reasons for discontinuation from the study in the combination treatment groups were peripheral edema (1.5%) and headache (1.4%), but these events led to the discontinuation of subjects in the combination treatment groups no more frequently than they did among subjects treated with either amlodipine alone or atorvastatin alone within this study.

The following information is based on the clinical experience with the parent compounds, NORVASC (amlodipine) and LIPITOR (atorvastatin).

Amlodipine

Amlodipine besylate has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials, when compared to placebo alone or active comparators. Most adverse reactions reported during therapy were of mild to moderate severity.

Hypertension

In the 805 hypertensive patients treated with amlodipine in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: oedema (8.9%), and headaches (8.3%).

The following adverse reactions were reported with an incidence of >0.5% in the controlled clinical trials program (n=805):

Autonomic Nervous System: flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%).

Cardiovascular: oedema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%).

Central and Peripheral Nervous System: headaches (8.3%), dizziness (3.0%), paresthesia (0.5%)

Gastrointestinal: nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%).

General: fatigue (4.1%), pain (0.5%).

Musculoskeletal: muscle cramps (0.5%).

Psychiatric: somnolence (1.4%).

Skin and Appendages: pruritus (0.7%).

Angina

In the controlled clinical trials in 909 angina patients treated with amlodipine, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: oedema (9.9%) and headaches (7.8%).

The following adverse reactions occurred at an incidence of >0.5% in the controlled clinical trials program (n=909):

Autonomic Nervous System: flushing (1.9%).

Cardiovascular: oedema (9.9%), palpitations (2.0%), postural dizziness (0.6%).

Central and Peripheral Nervous System: headaches (7.8%), dizziness (4.5%), paraesthesia (1.0%), hypoaesthesia (0.9%)

Gastrointestinal: nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%).

General: fatigue (4.8%), pain (1.0%), asthenia (1.0%).

Musculoskeletal: muscle cramps (1.0%).

Psychiatric: somnolence (1.2%), insomnia (0.9%), nervousness (0.7%).

Respiratory System: dyspnoea (1.1%).

Skin and Appendages: rash (1.0%), pruritus (0.8%).

Special Senses: visual impairment (1.3%), tinnitus (0.6%).

Atorvastatin

Dyslipidemia

Adverse reactions with atorvastatin have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8,755 LIPITOR versus 7,311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of atorvastatin and reported to be possibly, probably or definitely drug related are shown below:

Gastrointestinal disorders: diarrhea (6.8%, placebo 6.3%), dyspepsia (4.6%, placebo 4.3%), nausea (4.0%, placebo 3.5%), constipation (3.9%, placebo 4.3%), flatulence (1.2%, placebo 1.0%)

General disorders and administration site conditions: Asthenia (1.1%, placebo 1.1%)

Infections and Infestation: nasopharyngitis (8.3%, placebo 8.2%)

Metabolism and nutrition disorders: liver function test abnormal* (4.1%, placebo2.0%), blood creatine phosphokinase increased (1.9%, placebo 1.8%), hyperglycemia (5.9%, placebo 5.5%)

Musculoskeletal and connective tissue disorders: arthralgia (6.9%, placebo 6.5%), pain in extremity (6.0%, placebo 5.9%), musculoskeletal pain (3.8%, placebo 3.6%), muscle spasms (3.6%, placebo 3.0), myalgia (3.5%, placebo 3.1%), joint swelling (1.3%, placebo 1.2%)

Nervous system disorders: headache (6.5%, placebo 6.7%)

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain (2.3%, placebo 2.1%), epistaxis (1.2%, placebo 1.1%)

*alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, liver function test abnormal and transaminases increased.

8.3 Less Common Clinical Trial Adverse Reactions

CADUET

In clinical trials, no unexpected adverse events particular to combination therapy with amlodipine and atorvastatin have been observed as compared to either amlodipine alone or atorvastatin alone. Adverse events have been limited to those that have been reported with amlodipine and/or atorvastatin.

Amlodipine

Amlodipine has been evaluated for safety in about 11,000 patients with hypertension and angina. The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.

Autonomic Nervous System: dry mouth, hyperhidrosis.

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

Central and Peripheral Nervous System: hypoaesthesia/paraesthesia, neuropathy peripheral, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dysphagia, vomiting, gingival hyperplasia, change in bowel habits, dyspepsia.

General: allergic reaction, asthenia*, back pain, pain, hot flushes, malaise, rigors, weight increased/weight decreased.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

Metabolic and Nutritional: hyperglycaemia, thirst.

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

Psychiatric: sexual dysfunction (male* and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood altered.

Reproductive system and breast disorders: gynecomastia, erectile dysfunction.

Respiratory System: dyspnoea, epistaxis.

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

Special Senses: conjunctivitis, diplopia, eye pain, visual impairment, tinnitus.

Urinary System: pollakiuria, micturition disorder, nocturia.

*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, skin discoloration*, urticaria*, skin dryness, Stevens-Johnson syndrome, alopecia*, twitching, ataxia, hypertonia*, migraine, apathy, amnesia, gastritis*, pancreatitis*, increased appetite, coughing*, rhinitis*, parosmia, taste perversion*, and xerophthalmia.

* these events were observed in marketing experience as well.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty.

Atorvastatin

The following additional adverse events were reported in placebo-controlled clinical trials during atorvastatin therapy: Muscle cramps, myositis, muscle fatigue, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, cholestasis, anorexia, vomiting, abdominal

discomfort, alopecia, pruritus, rash, urticaria, erectile dysfunction, nightmare, vision blurred, tinnitus, eructation, neck pain, malaise, pyrexia and white blood cells urine positive.

In summary, the adverse events occurring at a frequency <1% are listed below:

Ear and labyrinth disorders: tinnitus

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal discomfort, eructation, pancreatitis, anorexia, vomiting

General disorders and administration site conditions: malaise; pyrexia

Hepatobiliary disorders: hepatitis, cholestasis, cholestatic jaundice

Investigations: white blood cells urine positive

Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain, myopathy, muscle cramps, myositis

Neurological: peripheral neuropathy, paresthesia

Psychiatric disorders: nightmare

Skin and subcutaneous tissue disorders: alopecia, rash, pruritus, urticaria

Urogenital: erectile dysfunction

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Atorvastatin: Laboratory Tests: Increases in serum transaminase levels and serum glucose have been noted in clinical trials (see 7 WARNINGS AND PRECAUTIONS, 8.2 Clinical Trial Adverse Reactions, Atorvastatin).

8.5 Post-Market Adverse Reactions

Amlodipine

In post-marketing 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 the use of amlodipine. Postmarketing reporting has also revealed cases of extrapyramidal disorders induced by amlodipine.

Atorvastatin

The following adverse events have also been reported during post-marketing experience with the atorvastatin component of CADUET, regardless of causality assessment:

Rare reports: severe myopathy with or without rhabdomyolysis (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects, 7 WARNINGS AND PRECAUTIONS, Renal, 9 DRUG INTERACTIONS).

There have been rare reports of immune-mediated necrotizing myopathy with statins (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects).

Isolated reports: Gynecomastia, thrombocytopenia, arthralgia and allergic reactions including urticaria, angioedema (angioneurotic edema), anaphylaxis and bullous rashes (including erytheme multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), fatigue, myositis, back pain, chest pain, malaise, dizziness, amnesia, peripheral edema, weight gain, abdominal pain, insomnia, hypoesthesia, tinnitus, tendon rupture, pancreatitis, dysgeusia and Ewing's sarcoma (pediatric).

Ophthalmologic observations: see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic.

Cases of erectile dysfunction have been reported in association with the use of statins.

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares;
- Mood related disorders, including depression;
- Very rare cases of interstitial lung disease, especially with long term therapy.

Endocrine disorders: Increases in fasting glucose and HbA1c levels have been reported with CADUET.

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant treatment with hepatitis C antivirals (see 9.4 Drug-Drug Interactions)
- Concomitant treatment with cyclosporine (see 9.4 Drug-Drug Interactions)
- Concomitant treatment with HIV protease inhibitors (see 9.4 Drug-Drug Interactions)
- Concomitant treatment with strong inhibitors of CYP 3A4 (see 9.4 Drug-Drug Interactions)
- Concomitant treatment with clarithromycin (see 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also 7 WARNINGS AND PRECAUTIONS, Renal, 7 WARNINGS AND PRECAUTIONS, Patients with Severe Hypercholesterolemia, 7.1.4 Geriatric Use).

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.

No drug interaction studies have been conducted with CADUET (amlodipine besylate /atorvastatin calcium) and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Cytochrome P-450 Mediated Interactions

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin, diltiazem.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin, hypericum perforatum (St John's wort).

Drugs known to be biotransformed via the cytochrome P450 system include: benzodiazepines, flecainide, imipramine, propafenone, and theophylline.

Amlodipine: As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Coadministration of the amlodipine component of CADUET with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers (18 to 43 years of age) increased the systemic exposure of amlodipine by 22%. These pharmacokinetic changes may be more pronounced in the elderly. Close monitoring and dose adjustments may be required. Strong inhibitors of CYP3A4 may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Due to the amlodipine component of CADUET, CADUET should be used with caution together with CYP3A4 inhibitors. Monitoring of therapy is required.

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine which in turn can result in decreased blood pressure lowering effects. Due to the amlodipine component of CADUET, CADUET should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Hence, monitoring of therapy is required.

The amlodipine component of CADUET has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.

In clinical trials, the amlodipine component of CADUET 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.

Atorvastatin: The atorvastatin component of CADUET is metabolized by the cytochrome P450 isoenzyme, CYP 3A4. Interaction may occur when CADUET is administered with inhibitors of cytochrome P450 3A4. Concomitant administration can lead to increased plasma concentrations of atorvastatin (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, 7 WARNINGS AND PRECAUTIONS, Muscle Effects, 7 WARNINGS AND PRECAUTIONS, Renal and 7 WARNINGS AND PRECAUTIONS, Endocrine Function; 9.4 Drug-Drug Interactions, Table 2 – Established or Predicted Drug-Drug Interactions).

Inducers of cytochrome P450 3A4

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin.

Transporter Inhibitors

Atorvastatin is a substrate of the hepatic transporters (see 10.3 Pharmacokinetics). Active liver disease or unexplained transaminase elevations are contraindications to the use of CADUET; if treatment for active liver disease is necessary during therapy with CADUET, the drug should be discontinued (see 2 CONTRAINDICATIONS).

Concomitant Therapy with Other Lipid Metabolism Regulators

Based on post-marketing surveillance, increase in the risk of myopathy may be seen when given concomitantly with HMG-CoA reductase inhibitors (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects; 9.4 Drug-Drug Interactions, Table 2 – Established or Predicted Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

CADUET should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Plasma concentrations of atorvastatin are markedly increased in patients with chronic alcoholic liver disease (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

9.4 Drug-Drug Interactions

Atorvastatin

Pharmacokinetic interaction studies have been conducted in healthy subjects with 3 macrolide antibiotics: erythromycin and clarithromycin (both of which inhibit CYP 3A4), and with azithromycin. Coadministration of atorvastatin with erythromycin or clarithromycin, resulted in moderately increased atorvastatin plasma levels but atorvastatin plasma levels were not altered by azithromycin. Twelve (12) healthy subjects were administered atorvastatin 10 mg on Days 1 and 15; erythromycin 500 mg QID was administered from days 8 to 19. Erythromycin increased atorvastatin C_{max} (ratio of C_{max}: 1.38) and AUC (ratio of AUC: 1.33). In a second study, atorvastatin 10 mg was administered daily for 8 days; clarithromycin (500 mg BID) or azithromycin (500 mg QD) was coadministered from Days 6 - 8 (N=12/treatment). Coadministration with clarithromycin increased atorvastatin AUC (ratio of AUC: 1.82) and C_{max} (ratio of C_{max}: 1.56) but atorvastatin plasma levels were not significantly altered by coadministration with azithromycin.

Steady-state, open-label, pharmacokinetic studies with digoxin have been performed in healthy subjects with both low and high doses of atorvastatin. Atorvastatin (10 mg or 80 mg QD; N=11 and N=12, respectively), was administered from days 1 - 20 and digoxin (0.25 mg QD) from Days 11 - 20. At steady-state, atorvastatin 10 mg daily had no significant effect on steady-state digoxin pharmacokinetics. However, following co-administration with atorvastatin 80 mg QD, the mean steady-state digoxin AUC and C_{max} increased (ratio of atorvastatin AUC: 1.15; ratio of atorvastatin C_{max} :1.20). Patients taking digoxin should be monitored appropriately.

The effect of amlodipine on the pharmacokinetics of atorvastatin was assessed at steady-state in a randomised, open-label, placebo-controlled, crossover study in healthy male subjects (N=16). Atorvastatin (80 mg QD) was administered with amlodipine (10 mg QD) or placebo from Days 1-8. Following a 14 day washout, the alternate combination was administered from Days 22 - 29. At steady-state, the coadministration of maximum doses of atorvastatin and amlodipine did not significantly alter the pharmacokinetics of atorvastatin and there were no apparent changes in blood pressure or heart rate.

The effect of quinapril on the pharmacokinetics of atorvastatin was assessed in a randomized, open-label study in healthy volunteers (N=22). Single doses of atorvastatin (10 mg) were administered on

Days 1 to 14, and single doses of quinapril (80 mg) were administered on days 1 to 7 or Days 8 to 14. The mean T_{max} value for atorvastatin during steady state quinapril administration was shortened by 1.25 hours compared to that of atorvastatin administered alone, but with no change in absorption/AUC or C_{max}. No significant changes in blood pressure or heart rates were observed.

Concomitant administration of atorvastatin 20-40 mg and itraconazole 200 mg daily resulted in an increase in atorvastatin AUC (ratio of atorvastatin AUC:3.3 and ratio of atorvastatin C_{max}: 1.20 for atorvastatin 40 mg only).

Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of atorvastatin AUC: 8.7 and ratio of atorvastatin C_{max}: 10.7).

For more detailed pharmacology information please refer to the individual Product Monographs for NORVASC and LIPITOR.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Predicted Drug-Drug Interactions*

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Amlodipine		↔ In healthy subjects, atorvastatin PK were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state. No apparent changes in BP or HR. In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no clinical significant change in the AUC or C_{max} or T_{max} of atorvastatin (ratio of atorvastatin AUC: 1.18 and ratio of atorvastatin C_{max}: 0.91).	Close monitoring is required.
Antacids (aluminum- and magnesium-based)	↔ on the disposition of amlodipine	↓ in plasma concentrations of atorvastatin (ratio of atorvastatin AUC: 0.66 and ratio of atorvastatin C_{max}: 0.67) ↔in LDL-C reduction - triglyceride-lowering effect may be affected	This decrease in exposure should be considered when prescribing atorvastatin with antacids.

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Antipyrine		↔ in the PK of antipyrine Ratio of antipyrine AUC: 1.03 and ratio of antipyrine C_{max}: 0.89 with atorvastatin 80mg QD and antipyrine 600mg SD.	Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Interactions with other drugs metabolized via the same cytochrome isozymes are not expected.
Beta-blockers	blood pressure lowering effect of beta-blockers may be ↑by amlodipine		Patients should be carefully monitored
Bile Acid Sequestrants		↓ in plasma concentration of atorvastatin (ratio of 0.74)	See 10 CLINICAL PHARMACOLOGY When atorvastatin is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of atorvastatin may be impaired by the resin.
Cimetidine	↔ in the PK of amlodipine	↔ in plasma concentration of atorvastatin (ratio of atorvastatin AUC: 1.00 and ratio of atorvastatin C_{max}: 0.89) ↔ in LDL-C reduction ↓ triglyceride lowering effect from 34% to 26%	This decrease in TG-lowering should be considered when prescribing atorvastatin with cimetidine.
Clarithromycin	In elderly patients (>65 years of age), concomitant use of amlodipine with clarithromycin was associated with increased risk of hospitalization with acute kidney injury.		Avoid concomitant use.

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Colchicine		Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administrated with colchicine.	Caution should be exercised when prescribing atorvastatin with colchicine. (See 7 WARNINGS AND PRECAUTIONS, Muscle Effects).
Cyclosporine	No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients. A prospective study in hypertensive renal transplant patients (N=11) showed on an average increase of 40% in trough cyclosporine levels when concomitantly treated with amlodipine	↑ Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of atorvastatin AUC: 8.7; ratio of atorvastatin C_{max}: 10.7).	Concomitant use is contraindicated (See 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Muscle Effects).
Dantrolene	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene.		Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Digoxin	↔ in serum digoxin levels or digoxin renal clearance	↔ in digoxin PK by coadministration with atorvastatin 10 mg daily ↑ in digoxin concentrations (ratio of atorvastatin AUC:1.15 and ratio of atorvastatin C_{max}: 1.20) following coadministration with atorvastatin 80 mg daily	Patients taking digoxin should be monitored appropriately.
Diltiazem Hydrochloride	In elderly patients, the plasma concentration of amlodipine increased by 50 %	Steady-state diltiazem increases the atorvastatin exposure, based on AUC_{LASTs}, of a single dose of atorvastatin by approximately 50% (ratio of atorvastatin AUC: 1.51 and ratio of atorvastatin C_{max}: 1.00).	
Efavirenz		Ratio of AUC: 0.59 and ratio of C_{max}: 1.01 with atorvastatin 10mg and Efavirenz 600mg daily	This decrease in exposure should be considered when prescribing atorvastatin with efavirenz.
Fibric Acid Derivatives (gemfibrozil, fenofibrate, bezafibrate) and Niacin (nicotinic acid):		↑ in the risk of myopathy during treatment with other drugs in this class, including atorvastatin	The concomitant therapy with CADUET and gemfibrozil should be avoided. The benefits and risks of combined therapy with atorvastatin and fenofibrate, bezafibrate and niacin should be carefully considered; lower starting and maintenance doses of atorvastatin should be considered (See 7 WARNINGS AND PRECAUTIONS, Muscle Effects).

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Fusidic Acid		Although interaction studies with the atorvastatin component of CADUET and fusidic acid have not been conducted, rhabdomyolysis resulting in fatal outcome has been reported in patients receiving a combination of statins, including atorvastatin, and fusidic acid. The mechanism of this interaction is not known.	The concurrent use of CADUET and fusidic acid should be avoided. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. Statin therapy may be re-introduced at least seven days after the last dose of fusidic acid. Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects).
Hepatitis C virus inhibitors: Telaprevir Boceprevir Glecaprevir / Pibrentasvir		Ratio of atorvastatin AUC: 7.9 and ratio of atorvastatin C_{max}: 10.6 with atorvastatin 20mg SD and Telaprevir 750mg q8h, 10 days* Ratio of atorvastatin AUC: 2.3 and ratio of atorvastatin C_{max}: 2.7 with atorvastatin 40mg SD and Boceprevir 800 mg TID, 7 days Ratio of atorvastatin AUC: 8.3 and ratio of atorvastatin C_{max}: 22.0 with atorvastatin 10mg QD for 7 days and Glecaprevir 400mg QD/Pibrentasvir 120mg QD for 7 days*	Concomitant use of atorvastatin and drugs used for the treatment of active liver disease, such as HCV inhibitors, is contraindicated. (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS) Discontinue CADUET if treatment for active liver disease is necessary.

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Elbasvir / Grazoprevir		Ratio of atorvastatin AUC: 1.95 and ratio of atorvastatin C_{max}: 4.3 with atorvastatin 10mg SD and Elbasvir 50mg QD/Grazoprevir 200mg QD for 13 days*	
Simeprevir		Ratio of atorvastatin AUC: 2.12 and ratio of atorvastatin C_{max}: 1.70 with atorvastatin 40mg SD and Simeprevir 150mg QD for 10 days*	
Ledipasvir / Sofosbuvir		Although interaction studies with atorvastatin and ledipasvir/sofosbuvir have not been conducted, cases of myopathy and rhabdomyolysis have been reported with atorvastatin co-administrated with ledipasvir/sofosbuvir.	
Velpatasvir / Sofosbuvir		Co-administration of atorvastatin (40 mg) with velpatasvir (100 mg)/sofosbuvir (400 mg) resulted in increased exposure to atorvastatin by 1.68-fold for C_{max} and 1.54-fold for AUC.	
Itraconazole		Concomitant administration of atorvastatin 20-40mg and itraconazole 200mg daily resulted in an increase in atorvastatin (ratio of atorvastatin AUC: 3.3 and ratio of atorvastatin C_{max}: 1.20 for atorvastatin 40 mg only).	The dose of the atorvastatin component of CADUET used in combination with itraconazole should not exceed 20 mg daily

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Letermovir		Concomitant administration of atorvastatin 20 mg SD and letermovir 480 mg daily resulted in an increase in exposure to atorvastatin (ratio of AUC 3.29 and ratio of atorvastatin C_{max}: 2.17).	The dose of atorvastatin used in combination with letermovir should not exceed 20 mg daily. Patients should be closely monitored for statin-associated adverse events such as myopathy or rhabdomyolysis (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects).
Macrolide antibiotics	In young patients the plasma concentration of amlodipine increased by 22% with concomitant use of erythromycin	↑ in atorvastatin plasma levels with erythromycin (ratio of atorvastatin AUC: 1.33 and ratio of atorvastatin C_{max}: 1.38) and with clarithromycin (ratio of atorvastatin AUC: 1.82 and ratio of atorvastatin C_{max}: 1.56) ↔ in atorvastatin plasma levels with azithromycin	See 7 WARNINGS AND PRECAUTIONS, Muscle Effects.
Mechanistic Target of Rapamycin (mTOR) Inhibitors	mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.		
Oral Contraceptives and Hormone Replacement Therapy		↑ in AUC of norethindrone (ratio of atorvastatin AUC: 1.28 and ratio of atorvastatin C_{max}: 1.23) and ethinyl estradiol (ratio of atorvastatin AUC: 1.19 and ratio of atorvastatin C_{max}: 1.30)	These increases should be considered when selecting an oral contraceptive. In clinical studies, atorvastatin was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Protease Inhibitor (nelfinavir mesylate, lopinavir/ritonavir, tipranavir/ritonavir, saquinavir/ ritonavir, darunavir/ritonavir, fosamprenavir/ ritonavir, fosamprenavir)		Ratio of atorvastatin AUC: 1.74 and ratio of atorvastatin C_{max}: 2.2 by nelfinavir mesylate 1250 mg BID, 14 days	The dose of the atorvastatin component of CADUET used in combination with nelfinavir should not exceed 40 mg daily.
		Ratio of atorvastatin AUC: 5.9 and ratio of atorvastatin C_{max}: 4.7 with atorvastatin 20mg daily and Lopinavir 400mg / Ritonavir 100mg twice daily	The concomitant therapy with CADUET and the combination of lopinavir/ritonavir should be used with caution and lowest atorvastatin dose necessary. (See 7 WARNINGS AND PRECAUTIONS, Muscle Effects)
		Ratio of atorvastatin AUC: 3.9 and ratio of atorvastatin C_{max}: 4.3 with atorvastatin 40mg daily, for 4 days, and Ritonavir 400mg, BID,15 days / Saquinavir 400mg twice daily†	† The dose of saquinavir/ ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used.
		Ratio of atorvastatin AUC: 9.4 and ratio of atorvastatin C_{max}: 8.6 with atorvastatin 10mg SD and Tipranavir 500mg BID / Ritonavir 200mg BID, 7 days. Atorvastatin 10 mg SD had no effect on the PK of Tripanavir 500mg BID / Ritonavir 200 mg BID, 7 days*	The concomitant therapy with CADUET and the combination of tipranavir/ritonavir or CADUET and telaprevir should be avoided.
		Ratio of atorvastatin AUC: 3.4 and ratio of atorvastatin C_{max}: 2.2 with atorvastatin 10mg QD for 4 days and Darunavir 300mg BID/ Ritonavir 100 mg BID, 9 days*	The dose of the atorvastatin component of CADUET should be restricted to 20 mg daily when used in combination with saquinavir/ ritonavir, darunavir/ ritonavir, fosamprenavir alone or fosamprenavir/ ritonavir
		Ratio of atorvastatin AUC: 2.5	

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
		and ratio of atorvastatin C_{max}: 2.8 with atorvastatin 10mg QD for 4 days and Fosamprenavir 700 mg BID/ritonavir 100mg BID,14 days* Ratio of atorvastatin AUC: 2.3 and ratio of atorvastatin C_{max}: 4.0 with atorvastatin 10mg QD for 4 days and Fosamprenavir 1400 mg BID, 14 days*. Atorvastatin 10mg QD for 4 days had the following effect on the PK of Fosamprenavir 1400 mg BID, 14 days: ratio of atorvastatin AUC: 0.73 and ratio of atorvstatin C_{max}: 0.82 Atorvastatin 10mg QD, 4 days had no effect on the PK of Fosamprenavir 700mg BID/ Ritonavir 100 mg BID, 14 days* (ratio of atorvastatin AUC: 0.99 and ratio of atorvastatin C_{max}: 0.94)	
Quinapril		↔ in PK profile of atorvastatin	

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Rifampin		Co-administration: Ratios of AUC and C_{max} are 1.12 and 2.9, respectively, for co-administered atorvastatin 40mg single dose and 7 day Rifampin 600mg daily vs. atorvastatin 40mg single dose alone. Separate administration Ratio of atorvastatin AUC: 0.20 and ratio of atorvastatin C_{max}: 0.60 with atorvastatin 40mg single dose and Rifampin 600mg daily (doses separated)	Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), 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.
Sildenafil	↔ in AUC or C_{max} of amlodipine - mean additional reduction of supine systolic and diastolic blood pressure was 8 mmHg and 7 mmHg, respectively		
Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)	May significantly increase the plasma concentrations of amlodipine to a greater extent than diltiazem.		Amlodipine should be used with caution together with CYP3A4 inhibitors and monitoring of therapy is required. Appropriate dosage adjustment of amlodipine may be necessary when used with CYP3A4 inhibitors. Patients should be advised to seek medical attention if they experience edema or swelling of the lower extremities; sudden, unexplained weight gain; difficulty breathing; chest pain or tightness; or hypotension as indicated by dizziness, fainting, or orthostasis. Avoid concomitant administration of amlodipine with strong CYP3A4 inhibitors.

Effect			Clinical comment
Proper Name	**Amlodipine**	**Atorvastatin**	
Tacrolimus	There is a risk of increased tacrolimus blood levels when co-administered with amlodipine.		In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustments of tacrolimus when appropriate.
Warfarin	↔ in warfarin-induced prothrombin response time	↔ in warfarin-induced prothrombin response time	

* For more detailed drug interaction information please refer to individual Product Monographs for NORVASC and LIPITOR.

** Legend: ↔ = no change; ↑ = increase; ↓ = decrease; ~ approximately; AUC = area under the curve; C_{max} = maximal concentrations; LDL-C = low density lipoprotein cholesterol; PK = pharmacokinetics; T_{max} = time to maximal concentrations

Ratio of AUC and C_{max} represent ratio treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

9.5 Drug-Food Interactions

Grapefruit Juice

Because of the potential effects of grapefruit juice on both the amlodipine and atorvastatin components of CADUET, administration of CADUET with grapefruit is not recommended.

Amlodipine: Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers.

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. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine, therefore administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Atorvastatin: Co-administration of grapefruit juice has the potential to increase plasma concentrations of HMG CoA reductase inhibitors including LIPITOR. The equivalent of 1.2 litres per day resulted in an increase in AUC (ratio of AUC up to 2.5) and C_{max} (ratio of C_{max} up to 1.71) of atorvastatin. For 240 ml of grapefruit juice, the ratio of AUC was 1.37 and the ratio of C_{max} was 1.16 for atorvastatin 40 mg.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

CADUET (amlodipine besylate/atorvastatin calcium), is a combination tablet which combines 2 mechanisms of action: the dihydropyridine calcium antagonist (calcium entry blocker or calcium ion antagonist) action of amlodipine and the HMG-CoA reductase inhibition of 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.

The antihypertensive/antianginal action of CADUET

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac and vascular smooth muscle tissues 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. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound and its kinetic interaction with the calcium channel receptor is characterized by the gradual association and dissociation with the receptor binding site.

- Hypertension: The mechanism by which amlodipine reduces arterial blood pressure involves direct peripheral arterial vasodilation and reduction in peripheral vascular resistance.
- Angina: The precise mechanism by which amlodipine relieves angina has not been fully delineated. Amlodipine is a dilator of peripheral arteries and arterioles which reduces the total peripheral resistance and, therefore, reduces the workload of the heart (afterload). The unloading of the heart is thought to decrease ischemia and relieve effort angina by reducing myocardial energy oxygen consumption and oxygen requirements.

The antidyslipidemic action of CADUET

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 for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL-C and the number of LDL particles. Atorvastatin also reduces VLDL-C, serum TG and IDL, as well as the number of apo B containing particles, but increases HDL-C. Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDL-C and high plasma TG promote human atherosclerosis, and are risk factors for developing cardiovascular disease. Some studies have also shown that the total (TC):HDL-C ratio (TC:HDL-C) is the best predictor of coronary artery disease. In contrast, increased levels of HDL-C are associated with decreased cardiovascular risk. Drug therapies that reduce levels of LDL-C or decrease TG while simultaneously increasing HDL-C have demonstrated reductions in rates of cardiovascular mortality and morbidity.

10.2 Pharmacodynamics

CADUET

Studies have been conducted in which placebo, amlodipine alone, atorvastatin alone, and the 8 dose combinations of amlodipine and atorvastatin have been administered once daily, in patients with co-morbid dyslipidemia and hypertension. Analyses of changes in systolic blood pressure demonstrated that there was no overall modification of amlodipine's effect on systolic blood pressure when the drug was taken in combination with atorvastatin compared to amlodipine alone. Analyses of changes in LDL-C demonstrated that there was no overall modification of atorvastatin's effect on LDL-C when the drug was taken in combination with amlodipine compared with atorvastatin alone (see 14 CLINICAL TRIALS).

Amlodipine

Hemodynamics

Following administration of recommended 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 any significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily oral administration (5 and 10 mg once daily), antihypertensive effectiveness is maintained throughout the 24-hour dose interval with minimal peak to trough differences in plasma concentration. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. In normotensive patients with angina, amlodipine has not been associated with any clinically significant reductions in blood pressure or changes in heart rate.

Negative inotropic effects have not been observed when amlodipine was administered at the recommended doses to man, but has been demonstrated in animal models. Hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in angina patients with normal ventricular function 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 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.

Electrophysiologic 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 of amlodipine and a further 10 mg of amlodipine after a 30-minute interval produced peripheral vasodilation and afterload reduction, but 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, amlodipine as monotherapy did not alter electrocardiographic intervals.

Atorvastatin

Human Pharmacology

The lowering of total cholesterol, LDL-C and apo B have been shown to reduce the risk of cardiovascular events and mortality.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase. In both subjects and in patients with homozygous and heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia, and dysbetalipoproteinemia, atorvastatin has been shown to reduce levels of total-C, LDL-C, apo B and total TG, and raises HDL-C levels.

Epidemiologic and clinical studies have associated the risk of coronary artery disease (CAD) with elevated levels of total-C, LDL-C and decreased levels of HDL-C. These abnormalities of lipoprotein metabolism are considered as major contributors to the development of the disease. Like LDL, cholesterol-enriched lipoproteins, including VLDL, 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 (metabolic syndrome). Clinical studies have also shown that serum triglycerides can be an independent risk factor for CAD. CAD risk is especially increased if the hypertriglyceridemia is due to increased intermediate density lipoproteins (IDL) or associated with decreased HDL or increased LDL-C. In addition, high TG levels are associated with an increased risk of pancreatitis. Although epidemiological and preliminary clinical evidence link low HDL-C levels and high triglyceride levels with coronary artery disease and atherosclerosis, the independent effect of raising HDL or lowering TG on the risk of coronary and cerebrovascular morbidity and mortality has not been demonstrated in prospective, well-controlled outcome studies. Other factors, e.g., interactions between lipids/lipoproteins and endothelium, platelets and macrophages, have also been incriminated in the development of human atherosclerosis and of its complications. Regardless of the intervention used (low-fat/low-cholesterol diet, partial ileal bypass surgery or pharmacologic therapy), effective treatment of hypercholesterolemia/dyslipidemia has consistently been shown to reduce the risk of CAD.

Atorvastatin reduces LDL-C and the number of LDL particles, lowersVLDL-C and serum TG, reduces the number of apo B containing particles, and also increases HDL-C. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolemia, a condition that rarely responds to any other lipid-lowering medication. In addition to the above effects, atorvastatin reduces IDL-C and apolipoprotein E (apo E) in patients with dysbetalipoproteinemia (Type III).

In patients with Type II dyslipidemia, atorvastatin improved endothelial dysfunction. Atorvastatin significantly improved flow-mediated endothelium-dependent dilatation induced by reactive hyperemia, as assessed by brachial ultrasound ($p<0.01$).

10.3 Pharmacokinetics

Absorption

CADUET

Following oral administration of therapeutic doses of CADUET tablets, 2 distinct peak plasma concentrations are observed. The first peak is attributable to atorvastatin and occurs within 1 to 2 hours after dosing. The second peak is attributable to amlodipine and occurs between 6 and 12 hours after dosing. The rate and extent of absorption (bioavailability) of both amlodipine and atorvastatin from CADUET combination tablet are not significantly different from those observed during coadministration of separate amlodipine and atorvastatin tablets, as assessed by C_{max}: 101% (90% CI: 98, 104) and AUC: 100% (90% CI: 97, 103) for the amlodipine component and C_{max}: 94% (90% CI: 85, 104) and AUC: 105% (90% CI: 99, 111) for the atorvastatin component, respectively.

The bioavailability of amlodipine from the CADUET tablet was not affected under the fed state as assessed by C_{max} and AUC. Food decreases the rate and extent of absorption of atorvastatin from the

CADUET tablets by approximately 32% and 11%, respectively. Similar reductions in plasma concentrations were observed with atorvastatin in the fed state without a reduction in LDL-C effect.

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption occurs gradually with peak plasma concentration reached between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Atorvastatin

Atorvastatin is rapidly absorbed after oral administration; maximal plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. The absolute bioavailability (parent drug) of atorvastatin is approximately 12% 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 first-pass metabolism in the liver. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, as assessed by C_{max} and AUC respectively, LDL-C reduction and HDL-C elevation are similar when atorvastatin is given with and without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following drug administration in the evening compared with morning dosing. However, LDL-C reduction and HDL-C elevation are the same regardless of the time of drug administration.

Distribution

Amlodipine

Ex vivo studies have shown that approximately 93% of the circulating 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 is likely to be secreted in human milk (see 2 CONTRAINDICATIONS, 7.1.2 Breast-feeding).

Metabolism

Amlodipine

Amlodipine is metabolized through the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Amlodipine is extensively (about 90%) converted to inactive metabolites (via hepatic metabolism).

Atorvastatin

Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives by cytochrome P450 system via the CYP 3A4 isoenzyme and to various beta-oxidation products. In vitro, inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation. Atorvastatin and its metabolites are eliminated by biliary excretion.

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1.

Atorvastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Elimination

Amlodipine

Elimination from the plasma is biphasic with a terminal elimination half-life of about 35-50 hours. Ten percent (10%) of the parent compound and 60% of the metabolites are excreted in the urine.

Atorvastatin

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life for inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations and Conditions

Geriatrics

Amlodipine

In elderly hypertensive patients (mean age 69 years) there was a decrease in clearance of amlodipine from plasma as compared to young volunteers (mean age 36 years) with a resulting increase in the area under the curve (AUC) of about 60%.

Atorvastatin

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age 65 years or older) compared with younger individuals. LDL-C reduction, however, is comparable to that seen in younger patient populations.

Sex

Atorvastatin

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

Ethnic origin

Amlodipine

No data are available to Health Canada to suggest that ethnic origin is associated with differences in pharmacokinetics, safety or effectiveness of amlodipine.

Atorvastatin

Plasma concentrations of atorvastatin are similar in black and white subjects.

Hepatic Insufficiency

Amlodipine

Following single oral administration of 5 mg of amlodipine, patients with chronic mild-moderate hepatic insufficiency showed about 40% increase in AUC of amlodipine as compared to normal volunteers. This was presumably due to a reduction in clearance of amlodipine as the terminal elimination half-life was

prolonged from 34 hrs in young normal subjects to 56 hrs in the elderly patients with hepatic insufficiency.

Atorvastatin

Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

Renal Insufficiency

Amlodipine

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Plasma concentrations in the patients with moderate to severe renal failure were higher than in the normal subjects. Accumulation and mean elimination half-life in all patients were within the range of those observed in other pharmacokinetic studies with amlodipine in normal subjects.

Atorvastatin

Plasma concentrations and LDL-C lowering efficacy of atorvastatin are similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of atorvastatin should be used in these patients. Similar precautions apply in patients with severe renal insufficiency (creatinine clearance <30 mL/min [<0.5 mL/sec]); the lowest dosage should be used and implemented cautiously (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects, 9 DRUG INTERACTIONS; 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

CADUET

Proper Name

amlodipine besylate/atorvastatin calcium

Physical Form

CADUET is a white to off-white crystalline powder, containing amlodipine besylate with a molecular weight of 567.11 and atorvastatin calcium with a molecular weight of 1209.422.

Drug Substance

Amlodipine component of CADUET

Proper Name

amlodipine besylate

Chemical Name

3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate.

Molecular Formula

$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$

Structural Formula

Molecular Mass

567.1

Physical Form

Amlodipine besylate is a white crystalline substance.

Solubility

Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol, M.P.= 203ºC with decomposition. pKa = 9.02 at 23.5ºC.

Atorvastatin component of CADUET

Proper Name

atorvastatin calcium

Chemical Name

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

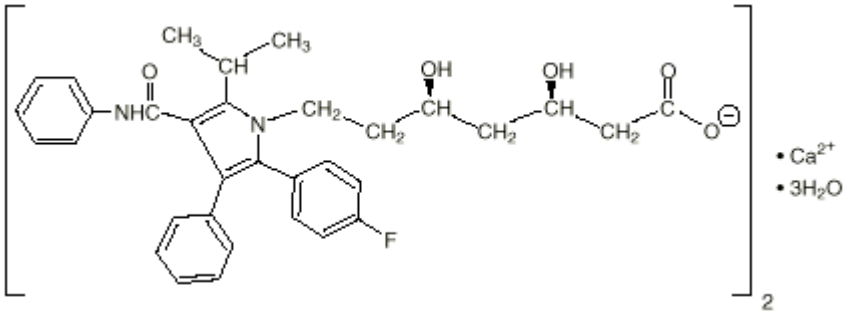
Empirical Formula:

$(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$

Molecular Mass

1209.42

Structural Formula



Physical Form

Atorvastatin calcium is a white to off-white crystalline powder.

Solubility

Atorvastatin calcium is practically 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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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 8 dose combinations of amlodipine besylate and atorvastatin calcium (5/10 mg, 5/20 mg, 5/40 mg, 5/80 mg, 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg), amlodipine alone (5 mg and 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, 80 mg) or placebo. At 8 weeks, all 8-combination treatment groups of amlodipine and atorvastatin demonstrated statistically significant dose-related reductions in systolic blood pressure and LDL-C compared to placebo, with no overall modification of effect of either component on SBP and LDL-C

In a double-blind, placebo-controlled study, a total of 847 patients with co-morbid hypertension and dyslipidemia received once daily placebo, 5 mg amlodipine, 10 mg of atorvastatin or the combination of 5 mg amlodipine and 10 mg atorvastatin. The primary objective of the study was the percentage of patients on the combination of amlodipine and atorvastatin reaching JNC VI and NCEP III goals compared to atorvastatin, amlodipine and placebo alone. Significantly more patients treated with the combination (45.5%) reached both their BP and LDL-C goals compared to amlodipine or atorvastatin alone.

CADUET

Clinical studies in patients with 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 8 dose combinations of amlodipine besylate and atorvastatin calcium (5/10 mg, 5/20 mg, 5/40 mg, 5/80 mg, 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg), amlodipine alone (5 mg and 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, 80 mg) or placebo. At 8 weeks, all 8-combination treatment groups of amlodipine and atorvastatin demonstrated statistically significant dose-related reductions in systolic blood pressure and LDL-C compared to placebo, with no overall modification of effect of either component on SBP and LDL-C (Table 3).

Table 3 - Primary Efficacy Analysis: Efficacy of the Combined Treatments in Reducing SBP and LDL-C

Efficacy of the Combined Treatments in Reducing Systolic BP						
Parameter / Analysis		**Placebo**	**ATO 10 mg**	**ATO 20 mg**	**ATO 40 mg**	**ATO 80 mg**
Placebo	LS mean change mmHg	-2.9	-4.3	-6.1	-6.2	-6.6
AML 5 mg	LS mean change mmHg	-12.6	-13.6	-15.3	-12.8	-12.6
	95% CIs		-12.3/ -6.3	-12.2/ -6.2	-9.7/ -3.6	-9.0/ -3.0
AML 10 mg	LS mean change mmHg	-16.5	-15.9	-16	-16.5	-17.5
	95% CIs		-14.6/ -8.5	-12.9/ -6.8	-13.3/ -7.2	-14.0/ -7.9

Efficacy of the Combined Treatments in Reducing LDL-C						
Parameter / Analysis		**Placebo**	**ATO 10 mg**	**ATO 20 mg**	**ATO 40 mg**	**ATO 80 mg**
Placebo	LS mean % chg	-1.2	-33.5	-39.5	-43.1	-47
AML 5 mg	LS mean % chg	-0.1	-39	-42.2	-44.9	-48.2
	95% CIs		-42.9/ -34.9	-46.2/ -38.2	-48.8/ -40.8	-52.2/ -44.2
AML 10 mg	LS mean % chg	-2.6	-36.6	-38.6	-43.2	-49.2
	95% CIs		-38.1/ -30.0	-40.0/ -32.0	-44.6/ -36.7	-50.6/ -42.6
ATO: Atorvastatin, AML: Amlodipine, LDL-C: Low density lipoprotein cholesterol, SBP: Systolic Blood						

Pressure Comparisons described above were between each individual combination treatment group and the corresponding amlodipine treatment group. BASELINE LDL-C= 182.0mg/dL SBP=148.4mmHg

In a double-blind, placebo-controlled study, a total of 847 patients with co-morbid hypertension and dyslipidemia received once daily placebo, 5 mg amlodipine, 10 mg of atorvastatin or the combination of 5 mg amlodipine and 10 mg atorvastatin. The primary objective of the study was the percentage of patients on the combination of amlodipine and atorvastatin reaching JNC VI and NCEP III goals compared to atorvastatin, amlodipine and placebo alone. The results following 8 weeks of treatment are summarized in Table 4. Significantly more patients treated with the combination (45.5%) reached both their BP and LDL-C goals compared to amlodipine or atorvastatin alone.

Table 4 - Results of efficacy end-points in placebo-controlled study of amlodipine/atorvastatin in patients with hypertension and dyslipidemia

	Placebo N = 239	**ATO 10 mg N = 200**	**AML 5 mg N = 201**	**ATO 10 mg & AML 5 mg N= 207**
JNC VI* Blood Pressure goals	29.7%	32.3%	54%	51%[†]
NCEP ATP III LDL-C goals	6.6%	78.2%	12.4%	82.1%**
Both JNC VI and NCEP ATP III* goals	3.5%	28.6%	8.3%	45.5%*[†]
Change in BP mmHg	-5.4/-3.3	-5.9/-4.2	-14.3/ -8.9	-12.7/ -8.2 [+]
Change in LDL-C -%	0.2	-33.9	-1.8	-37.2 [a]

ATO: Atorvastatin AML: Amlodipine LDL-C: Low density lipoprotein cholesterol SBP: Systolic Blood Pressure

[**] *P*<0.001 versus amlodipine

[†] *P*<0.001 versus atorvastatin

+ p< 0.001 vs. atorvastatin and NS vs. amlodipine

a p=0.07 vs Atorvastatin & <0.001 vs amlodipine

BASELINE LDL-C = 163.5 mg/dL, SBP = 146.9mmHg

***** BP goals in JNC VII for this population are consistent with JNC VI BP goals

Amlodipine

Effects in Hypertension: 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.

Effects in 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).

Atorvastatin

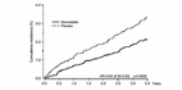
Prevention of Cardiovascular Disease

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 ≤6.5 mmol/L. Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age ≥55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL ≥6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin 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 LIPITOR group) or nonfatal MI (108 events in the placebo group vs 60 events in the LIPITOR group)] with an absolute risk reduction of 1.1% and a relative risk reduction of 36% (based on incidences of 1.9% for atorvastatin vs 3.0% for placebo), p=0.0005 (see figure 1)]. This risk reduction yields a Number Needed to Treat of 311 patients per year. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

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



Hypercholesterolemia

Atorvastatin has been shown to significantly improve lipid profiles in a variety of dyslipidemic conditions. Atorvastatin has been shown to be highly effective in reducing total and LDL-cholesterol, and triglycerides and apolipoprotein B in patients with primary hypercholesterolemia, familial and non-familial hypercholesterolemia, and mixed dyslipidemia, including familial combined dyslipidemia and patients with non-insulin dependent diabetes mellitus (NIDDM).

In 2 multicenter, placebo-controlled, double-blind, dose-response studies in patients with mild to moderate hypercholesterolemia (Fredrickson Types IIa and IIb), atorvastatin given as a single daily dose over 6 weeks reduced total-C, LDL-C, apo B, and TG; HDL was increased (Table 5). A therapeutic response was evident within 2 weeks, and the maximum response was usually achieved within 2-4 weeks.

Table 5 - Dose-Response in Patients With Mild to Moderate Hypercholesterolemia (Fredrickson Types IIa and IIb) (Mean Percent Change From Baseline)[a]

atorvastatin Dose (mg/day)	N	Total-C	LDL-C	Apo B	TG	HDL-C
Placebo	21	+4	+4	+3	+10	-3
10	22	-29	-39	-32	-19	+6
20	20	-33	-43	-35	-26	+9
40	21	-37	-50	-42	-29	+6
80	23	-45	-60	-50	-37	+5

[a] Results are pooled from 2 dose-response studies

In a pooled data set from 24 controlled clinical trials in patients with primary hypercholesterolemia (Type IIa) and mixed (combined) dyslipidemia (Type IIb), atorvastatin increased HDL-C by 5% to 8% from baseline at each dose tested (10, 20, 40, and 80 mg QD) (Table 7). In patients with HDL-C < 0.9 mmol/L (a condition often observed in persons with the metabolic syndrome) (see 1 INDICATIONS), atorvastatin raised HDL-C 7% to 14%. These changes were independent of the dose administered. Atorvastatin also

decreased total-C/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C ratios from baseline in a dose-dependent manner (Table 6). Atorvastatin (10, 20, 40 and 80 mg QD) increased HDL-C levels from baseline for both men and women.

Table 6 – Adjusted[a] Mean Percent Changes from Baseline in HDL-C, Total-C/HDL-C, LDL-C/HDL-C, Non-HDL-C/HDL-C, and HDL-C ≤ 0.9 mmol/L for Patients[b] With Mild to Moderate Hypercholesterolemia (Fredrickson Types IIa and IIb)

atorvastatin Dose (mg/day)	N (all patients)	HDL-C	Total-C/ HDL-C	LDL-C/ HDL-C	Non HDL-C/ HDL-C	HDL-C (baseline ≤ 0.9 mmol/L) (N)
Placebo	250	+0.2‡	+2.8‡	+3.8‡	+3.5‡	+6.2* (17)
10	1871	+6.4	-29.3†	-37.0†	-35.5†	+13.8 (248)
20	147	+7.8	-36.0†	-44.1†	-43.0†	+8.3 (20)
40	115	+7.1	-38.9†	-49.6†	-47.1†	+8.6 (8)
80	318	+5.0	-43.5†	-55.3†	-52.4†	+7.1 (58)

[a] Least squares means from ANCOVA model with study, treatment and baseline
[b] Data pooled from 24 controlled studies
†significant linear dose trend
‡ significantly different from atorvastatin 10 mg (p<0.01)
* signficantly different from atorvastatin 10 mg (p<0.05)

In another multicenter, placebo-controlled, double-blind trial in patients with hypertriglyceridemia, atorvastatin lowered triglycerides in a dose-related manner, without causing a redistribution of triglycerides into various lipoprotein fractions (Table 7).

Table 7 - Efficacy in Patients With Hypertriglyceridemia (Mean Percent Change From Baseline)

atorvastatin Dose (mg/day)	N	VLDL-C	Total-C	VLDL-TG	LDL-C	TG	HDL-C	Apo B
Placebo	12	-2	+0.3	-6.6	+1.4	-5.3	+2.4	+2.7
5	11	-34.0*	-19.9*	-28.7	-12.7*	-27.3	+7.1	-15.4*
20	12	-46.0*	-33.1*	-35.7*	-31.1*	-33.7*	+10.6	-32.7*
80	11	-54-2*	-41.3*	-43.6*	-36.1*	-42.4*	+11.8*	-38.7*

* Significantly different from placebo, p<0.05

Comparison of pooled data by Fredrickson types shows similar reductions for Type IIa and IIb patients in total-C, LDL-C and apo B; however, Type IIb patients, and Types IV patients experience a greater percent decrease in VLDL-C and TG levels (Table 8).

Table 8 - Efficacy in Patients by Fredrickson Type[a] (Mean Percent Change from Baseline)

Lipid Parameter	atorvastatin 10 mg/day		
	Type IIa (N = 935)	Type IIb (N = 550)	Type IV (N = 29)
LDL-C	-36	-35	-26
Apo B	-28	-28	-25
Total-Cl	-27	-27	-25
TG	-14	-24	-29
VLDL-C	-15	-28	-41
HDL-C	+6	+10	+13
Apo B/HDL-C	-31	-34	-33
Non-HDL-C/HDL-C	-37	-38	-38

[a] Pooled dataset

A comparison of results in patients with heterozygous familial and non-familial hypercholesterolemia shows similar magnitudes of reductions in LDL-C, apo B and non-HDL-C/HDL-C ratio, in both patient populations (Table 9).

Table 9 - Efficacy in Heterozygous FH and Non FH Patients[†] (Mean Percent Change from Baseline)

Lipid Parameter	Phenotype	atorvastatin	
		10 mg/day	80 mg/day
LDL-C	Heterozygous FH Non FH	-36 (N=140) -36 (N=1215)	-53 (N=154) -52 (N=166)
Apo B	Heterozygous FH Non FH	-27 (N=134) -28 (N=1149)	-46 (N=153) -46 (N=144)
Non HDL-C/HDL-C Ratio	Heterozygous FH Non FH	-37 (N=140) -37 (N=1215)	-53 (N=132) -54 (N=166)

[†] Data from several studies

Comparison of results in patients with and without familial combined dyslipidemia (FCH) demonstrated that atorvastatin lowered LDL-C, apo B, total-C, VLDL-C, TG, and the non HDL-C/HDL-C ratio to a similar extent in both patient populations (Table 10).

Table 10 - Efficacy in Patients With and Without FCH[†],[a] (Mean Percent Change from Baseline)

Lipid Parameter	atorvastatin 10 mg/day	
	FCH (N = 78-84)	Non-FCH (N = 1084-1224)
Total-C	-26%	-27%
LDL-C	-34%	-36%
TG	-21%	-17%
HDL-C	+8%	+7%
Apo B	-26%	-28%
VLDL-C	-25%	-18%
Non HDL-C/HDL-C Ratio	-36%	-37%
LDL-C/Apo B ratio	-9%	-11%

[†] Data from several studies

[a] The following criteria were used to define patients with FCH: first degree relative with lipid disorder, TG >250 mg/dL (>2.8 mmol/L), VLDL >45 mg/dL (>1.16 mmol/L), HDL <35 mg/dL (<0.9 mmol/L) (men) or <45 mg/dL (<1.16 mmol/L) (women).

In 3, double-blind, multicenter studies in patients with mild to moderate hypercholesterolemia, the number of patients meeting NCEP target LDL-C levels on atorvastatin was assessed over a 1-year period. After 16 weeks, between 46-74% of patients receiving 10 mg/day atorvastatin reached target LDL-C levels. The efficacy of atorvastatin (10 or 20 mg/day) was maintained over 52 weeks, with between 50-78% of patients achieving their LDL-C target levels.

The effect of atorvastatin was evaluated in comparative clinical trials with lovastatin, simvastatin and pravastatin.

For more detailed clinical trial information please refer to the individual Product Monographs for NORVASC and LIPITOR.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General toxicity

Amlodipine

Amlodipine (as maleate unless otherwise indicated)

SPECIES	SEX	ROUTE	LD_{50}	Range of Lethal Doses (mg/kg)	
			base/mg/kg	No Deaths	All Dead
Mice	M	p.o.	N.D.	10	40
	F	p.o.	N.D.	10	40
	M	i.v.	N.D.	2.5	10
	F	i.v.	N.D.	2.5	10
Rats	M	p.o.	150	2/10 at 100	400
	F	p.o.	140	2/10 at 100	250
	M	i.v.	N.D.	1	10
	F	i.v.	N.D.	1	10
Rats*	M	p.o.	393**		
	F	p.o.	686**		

* Sprague Dawley Rats from Shizouka Lab Animal Centre, Hamamatsu, Japan
** Besylate Salt
+ Dogs from Interfauna, France
++ Dogs from Japan
N.D. Not Determined: The result did not permit calculations of LD50 values. Thus, range of lethal doses is given.

The main clinical signs in the oral studies were somnolence, decreased spontaneous movement and for rats salivation, dyspnea, ptosis, lacrimation, blanching, cyanosis, rough coat, abdominal distension, and eventually coma. After i.v. injection, the animals died rapidly showing only somnolence, tachypnea or ptosis.

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
MAXIMUM TOLERATED DOSE (SINGLE)					
Dog	Oral (gavage)	4 8 16	2 M	Single Dose	At all dose levels: Vasodilation and increases in plasma aldosterone levels. At 4 mg/kg: Compensatory tachycardia. At 8 mg/kg: In 1 of 2 dogs vomiting, sedation, respiratory distress and diarrhea 48 hr post-dose; normal at day 5. Compensatory tachycardia. At 16 mg/kg: Moribund with hyperthermia within 24 hours; low blood pressure returned to normal over 2-6 days; transient raise in heart rate. Histological examination showed congestion, edema and hemorrhage of the right atrial wall in the 2 dogs at 16 mg/kg. The hemorrhage in the right atrial wall corresponds to the right atrial lesions seen in long-term studies with amlodipine and other vasodilators (see long-term toxicity). One of 2 dogs at each dose showed fibrosis of the left ventricle in the subendocardial region and the posterior papillary muscle. The maximum tolerated dose was not determined.
Dog (Japanese Study)	Oral	3.5 7	1 M 1 F	Single Dose	Mortality: 1 male dog at 7 mg/kg. Decreased spontaneous movement and flushing of palpebral conjunctiva and buccal cavity. At 7 mg/kg: 1 female vomiting; 1 male hypothermia, lying prone. Hematology/Clinical Chemistry: Increase in WBC and BUN at 10 and 5 mg/kg (males). The maximum tolerated dose was not determined.

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Mouse	Oral (diet)	0 2.5 5 10	10 M 10 F	2 Months	At 10 mg/kg/day: Mice died during week 2 of the study. At 5 mg/kg/day (males and females) and 2.5 mg/kg/day (males): Increase in water consumption. At 5 mg/kg/day - Pathology: Drug-related increases in heart and liver weights.
Rat (Japanese Study)	Oral (gavage)	0 4 16 32 64	12 M 12 F	1 Month	At 64 mg/kg/day: All rats died within 9 days. At 32 mg/kg/day: 12/24 rats died; decreased food consumption, growth inhibition, ptosis, decreased spontaneous movement. At 16 and 32 mg/kg/day: The pattern of results on heart weights, increased urinary volume, effect on electrolyte balance and the adrenals was similar to that of the 6 month study below; increase in BUN at 16 mg/kg (males) and at 32 mg/kg (males and females).
Rat (Japanese Study)	Oral (gavage)	0 2 7 21	16 M 16 F	3 Months followed by 1 Month drug withdrawal	21 mg/kg/day: Salivation, growth inhibition, increased BUN, increased urinary volume, effect on electrolyte balance and adrenals was similar to that of the 6 month study below. Also post-mortem dilation of small intestine without morphological lesions. At 7 mg/kg/day: Alterations in urinary electrolytes excretion. No drug related effects at the end of 1 month drug withdrawal phase.
Rat	Oral (gavage)	0 2.5 5 10	20 M 20 F	6 Months	At all dose levels: Renal effects: increased urinary volume and/or Na/K/Cl excretion, decreased plasma Na/K and/or Ca/Cl and increased urea; Post-mortem: Increase in heart weights. At 10 mg/kg/day: Renal effects: increased kidney weight. Histopathology: Thickening of zona glomerulosa at 5 and 10 mg/kg/day.

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Rat (Japanese Study)	Oral (gavage)	1.4 7 18	30 M 30 F	12 Months	(interim sacrifice 5/sex/group after 6 months) Mortality: 3 rats (2 males and 1 female) at 18 mg/kg/day. At 18 mg/kg/day: Salivation, growth inhibition; Renal effects: increase in urinary volume with increased electrolytes excretion and decreased serum electrolytes; increase in BUN. At 7 mg/kg/day: Growth inhibition (males); Renal effects: increases of urinary volume and electrolyte excretion. Post-mortem: Increases of adrenal weights (at 18/mg/kg), increases of relative heart weight (18 and 7 mg/kg), dilated small intestines without morphological change (18 mg/kg). Histopathology - Main Finding: Enlargement of the zona glomerulosa of the adrenals (18 and 7 mg/kg).
Dog	Oral (gavage)	0.5 to 4	2 M 2 F	10 Days	Supplementary Dose Escalation Study (0.5 mg/kg/day) At 4 mg/kg: Death of all (4/4) dogs preceded in 3 dogs by low systolic blood pressure, bradycardia, disturbances of heart rhythm and conduction. Clinical signs included pale skin, hypothermia and prostration. Histopathology: Showed foci of myocyte necrosis and sarcoplasmic vacuolation in the left ventricle, papillary muscle and left and right atria. Congestion and/or edema in several organs (i.e., gastrointestinal tract/gall bladder wall and surrounding tissues as well as the connective tissue surrounding both kidneys).

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Dog	Oral	0 0.25 0.5 1	3 M 3 F	6 Months	At all dose levels: Increase in urinary volume and urinary excretion of electrolytes (not dose-related). Reduction in blood pressure and increases in heart rate. At 1 mg/kg/day - Pathology: Increase in relative heart weights in 4/6 dogs, inflammatory lesion of the right atrial wall was seen which was considered to be consequence of excessive hemodynamic changes.
Dog	Oral	0 0.125 0.25 0.5	4 M 4 F	12 Months	At 0.5 mg/kg/day: Reduction in blood pressure and increases in heart rate; increase in urinary volume and urinary excretion of electrolytes (females). At 0.5 mg/kg/day - Pathology: Showed inflammatory lesions of the right atrial wall in 1/8 dogs, similar to that of the 6 month study above, and diffuse gingival hyperplasia.

Atorvastatin

The acute toxicity of atorvastatin following single doses was evaluated in mice, rats and dogs by oral and intravenous routes, and the results are summarized below:

Table 11 - Acute Oral and Intravenous Toxicity Studies with Atorvastatin

Species	Sex	Route	Dose Range (mg/kg)	Results
Mouse	Male/Female	Oral	200-5000	No Deaths
Mouse	Male/Female	IV	0.4 - 4	No Deaths
Rat	Male/Female	Oral	200-5000	No Deaths
Rat	Male/Female	IV	0.4 - 4	No Deaths
Dog	Male/Female	Oral	10 - 400	No Deaths
Dog	Male/Female	IV	0.4 - 4	No Deaths

The acute toxicity of atorvastatin in rodents and dogs is low. Oral median lethal doses in mice and rats are greater than 5000 mg/kg.

The target organs affected by atorvastatin in multiple dose toxicity studies in rats (2 weeks to 52 weeks), and dogs (2 weeks to 104 weeks) are summarized in the table below. The spectrum of effects observed is not unexpected in view of the magnitude of the dose levels used, potency of atorvastatin in inhibiting mevalonate synthesis and the essential role of HMG-CoA reductase in maintaining cellular homeostasis.

Table 12 - Atorvastatin: Target Organs Affected in Animal Studies

Rat	Dog
Liver	Liver
Stomach (non-glandular)	Gallbladder
Skeletal Muscle	Skeletal Muscle
	Intestine
	Brain/Optic Nerve*

* Occurred after administration of high, intolerable doses (280 mg/kg)

Table 13 - Atorvastatin: Significant Adverse Changes in Chronic Studies

Species/Results	Minimal Toxic Dose (mg/kg/day)	No-Effect Dose (mg/kg/day)
RAT		
Hepatocellular atypia	70	5
Bile Duct hyperplasia[1]	125	70
Nonglandular stomach acanthosis	125	70
DOG		
Death[2]	120	40
Hepatocellular granulomata[3]	10	ND
Hepatocellular necrosis[3]	120	40
Gallbladder edema/hemorrhage[3]	120	40
Bile duct hyperplasia[3]	120	10
Intestinal ulcers and single cell necrosis[3]	120	40
Skeletal muscle (tongue) necrosis[2]	120	40

[1] Present only at Week 26; not observed at Week 52.

[2] Findings occurred in Week 7 or 9.

[3] Findings occurred at Week 52 or in moribund dogs, were less pronounced after a 12-week withdrawal period (Week 64), and were not observed after 104 weeks of dosing.

ND = Not determined

The results of the long-term toxicology studies with atorvastatin indicated that similar to other HMG-CoA reductase inhibitors, the liver is the primary target organ. This is expected since the liver is the primary site of the pharmacologic action of atorvastatin and it is subject to the greatest drug exposure following oral administration. In both the rat and dog studies, the hepatic changes diminished with time (i.e., effects were less pronounced at the end of the 52-week and 104-week studies) suggesting an adaptive response.

Brain hemorrhage, optic nerve degeneration, lenticular opacities and testicular degeneration were not seen in dogs treated for 104-weeks with atorvastatin up to 120 mg/kg/day.

Genotoxicity

Amlodipine

Study	Test Organism	Dose	Route	Major Findings
Ames Test (modified) Quantitative Plate Assay (QAP) and Metabolic Activation (MA) with Hepatic Microsomes	salmonella typhimurium: Strains TA 1535, TA 1537, TA 98 and TA 100	10-0.02 mg/plate (QAP) 0.2-0.0005 mg/plate (MA)	In-vitro	No evidence of mutation frequency.
In-vivo Cytogenetic Tests	mouse bone marrow	20 mg/kg single dose 10 mg/kg/day for 5 days	In-vivo p.o. s.c.	No indication of chromosome breakage or mutagenicity observed.
In vitro Cytogenetic Tests with or without metabolic activation [rat liver microsomal enzymes (S-9)]	human lymphocytes	Without metabolic activation: 0.01 to 1000 :g/Ml of culture medium With metabolic activation: 1.0 to 25 :g/Ml of culture medium.	In-vitro	Non-activation: No evidence of induced chromosome breakage observed at levels of 1.0 :g/mL and below. At levels higher that 1.0 :g/mL, compound produced mitotic inhibition. Activation: No drug induced clastogenic activity observed at levels up to 10 :g/mL. Higher levels produced mitotic inhibition.
Quantitative Plate Assay (QAP) of Mouse Urine	Salmonella typhimurium Strains: TA 1535, TA 1537, TA 98 and TA 100.	0, 1, 10 and 20 mg/kg	In-vivo p.o.	No incidence of an excreted mutagen.
L 5178Y/TK +/- Gene Mutation Assay with and without liver S-9 fraction	mouse lymphoma cells	1.2 - 38 :g/mL	In-vitro	No evidence of gene mutational activity.

Atorvastatin

Atorvastatin did not demonstrate mutagenic or clastogenic potential in four in vitro tests with and without metabolic activation or in one in vivo assay. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the in vitro HGPRT forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the in vitro Chinese hamster lung cell assay and was negative in the in vivo mouse micronucleus test.

Carcinogenicity

Amlodipine

There was no evidence of a carcinogenic effect when amlodipine was administered in the diet for up to 24 months to rats up to 2.5 mg/kg/day. Amlodipine was also administered for up to 24 months of dietary administration to mice at doses up to 2.5 mg/kg/day and no evidence of carcinogenicity was observed.

Atorvastatin

Atorvastatin was not carcinogenic in rats given 10, 30 or 100 mg/kg/day for 2 years. The 100 mg/kg dose is 63-fold higher than the maximum recommended human dose of 80 mg (1.6 mg/kg, based on a 50 kg human) and AUC (0-24 hr) values were 8- to 16-fold higher.

In a 2-year study in mice given 100, 200 or 400 mg/kg/day, incidences of hepatocellular adenoma in males and hepatocellular carcinoma in females were increased at 400 mg/kg. This dose is 250 times the maximum recommended human dose on a mg/kg basis and systemic exposure based on AUC (0-24 hr) was 6 to 11 times higher. There was no evidence of treatment-related increases in tumor incidences at the lower doses of 100 and 200 mg/kg/day (i.e., up to 125 times the maximum recommended human dose on a mg/kg basis and systemic exposures of 3 times higher based on AUC (0-24 hr).

Reproductive and Developmental Toxicology

Amlodipine

Species	Route	Dose base/mg/kg/day	Animal per Dose Level	Duration	Findings
Fertility					
Rat (SD) (Japanese Study)	Oral (gavage)	0 1.4 7 18	24 M + 24 F	Males 71 days prior to and during mating. Females 14 days prior to and during mating and up to 7 days of gestation.	At 18 mg/kg: Impairment of body weight gain (females). There were no effects of the drug on copulation or pregnancy rates, nor any evidence of embryotoxicity or teratogenicity.
Teratology					
Rat (Charles River CD/SD)	Oral (gavage)	0 2 5 10	20 F	Days 6-15 post insemination. Hysterectomies on day 20 of gestation.	No effects were observed.
Rat (SD) Japanese Study	Oral (gavage)	3 7 18	34 F	Days 7-17 post-insemination. b of dams sacrificed on day 21 of gestation. F_1 generation	No effects were observed except in the dams. At 18 mg/kg: Reduction in food

Species	Route	Dose base/mg/kg/day	Animal per Dose Level	Duration	Findings
				followed.	intake and body weight gain.
Rabbit (Japanese White) Japanese Study	Oral	3 7 18	18 or 19 F	Day 6 to day 18 of gestation.	At 18 and 7 mg/kg: Decrease in maternal body weight (18 mg/kg) decrease in food consumption (18 and 7 mg/kg). No evidence of drug induced fetotoxicity or teratogenicity.
Peri- and Post-Natal					
Rat (SD) Japanese Study	Oral (gavage)	0 1.4 2.8 7.0	25 F	Day 17 of gestation to day 21 post-partum.	As in the combined Fertility/Perinatal Study above; at the high dose level (7.0 mg/kg/day) adverse effects were observed on parturition and number of viable pups at birth and day 4 post-partum.

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 8 times greater than the maximum recommended dosage for humans.

Impairment of fertility

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 ≤ 10 mg amlodipine/kg/day (about 8 times the maximum recommended human dose of 10 mg/day on a mg/m^2 basis, for a 50 kg human).

In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Atorvastatin

No adverse effects on fertility or reproduction were observed in male rats given doses of atorvastatin up to 175/mg/kg/day or in female rats given doses up to 225 mg/kg/day. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg basis.

Atorvastatin did not cause any adverse effects on sperm or semen parameters, or in reproductive organ histopathology in dogs given doses of 10, 40 or 120 mg/kg for 2 years. Atorvastatin was not teratogenic in either rats or rabbits.

17 SUPPORTING PRODUCT MONOGRAPHS

1. LIPITOR 10 mg, 20 mg, 40 mg and 80 mg tablets, submission control number 241951, Product Monograph, Upjohn Canada ULC. December 10, 2020

2. NORVASC 2.5 mg, 5 mg and 10 mg tablets, submission control number 236351, Product Monograph, Upjohn Canada ULC. May 27, 2020

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCADUET®

Amlodipine besylate and atorvastatin calcium tablets

Read this carefully before you start taking **CADUET** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CADUET**.

What is CADUET used for?
CADUET contains two active ingredients, amlodipine and atorvastatin. CADUET is used in adults who need both active ingredients.

CADUET is used to:
- Treat high blood pressure (hypertension).
- Prevent chest pain attacks (angina).
- Lower cholesterol or other fats in the blood such as triglycerides.

How does CADUET work?
CADUET contains two active ingredients, amlodipine and atorvastatin. Amlodipine belongs to a group of medications called calcium channel blockers. They block the transfer of calcium into the heart and blood vessels. This relaxes the blood vessels which improves blood flow, making it easier for the heart to pump blood.

Atorvastatin belongs to a group of medicines called HMG-CoA reductase inhibitors, or "statins". Atorvastatin decreases "bad" cholesterol (low-density lipoprotein) and triglyceride levels, while increasing "good" cholesterol (high-density lipoprotein). High levels of cholesterol and other fats can cause heart disease by clogging the blood vessels that feed blood and oxygen to the heart.

What are the ingredients in CADUET?
Medicinal ingredients: amlodipine besylate and atorvastatin calcium.

Non-medicinal ingredients: calcium carbonate, colloidal silicon dioxide (anhydrous), croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, opadry II white or opadry II blue, polysorbate 80, pregelatinized starch, and purified water.

CADUET comes in the following dosage forms:
Tablets:

- 5mg/10mg (white)
- 5mg/20mg (white)
- 5mg/40mg (white)
- 5mg/80mg (white)
- 10mg/10mg (blue)
- 10mg/20mg (blue)
- 10mg/40mg (blue)
- 10mg/80mg (blue)

Do not use CADUET if:

- you are allergic to amlodipine besylate, atorvastatin calcium or any of the other ingredients in CADUET.
- you have been diagnosed with low blood pressure.
- you have active liver disease or unexplained increases in liver enzymes.
- you are pregnant or breast-feeding. If you become pregnant, tell your doctor right away.
- you are taking medication containing glecaprevir/pibrentasvir (MAVIRET™), elbasvir/grazoprevir, velpatasvir/sofosbuvir, or ledipasvir/sofosbuvir.
- you are taking medication containing cyclosporine (SANDIMMUNE®, NEORAL®).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CADUET. Talk about any health conditions or problems you may have, including if you:

- have had a stroke or a mini stroke called a transient ischemic attack (TIA)
- regularly drink *three or more* alcoholic drinks daily
- have kidney or liver problems
- are 65 years of age or older
- are taking fusidic acid.
- Are taking medicines containing digoxin, ketoconazole, clarithromycin or ritonavir
- Have a narrowed heart valve (aortic stenosis)
- Are at a risk for developing myopathy (muscle aching or weakness). Risk factors include if you:
    - have ever had muscle problems or have a family history of muscle problems
    - have ever had muscle problems during treatment with statins, such as atorvastatin (LIPITOR®), fluvastatin, lovastatin, pravastatin, rosuvastatin (CRESTOR®) or simvastatin (ZOCOR®)
    - are taking other medicines to lower cholesterol such as fibrates (gemfibrozil, fenofibrate) or niacin
    - Have thyroid problems
    - Drink large amounts of alcohol
    - Do excessive physical exercise
    - Are 65 years of age or older
    - Have kidney or liver problems
    - Have diabetes with hepatic fatty change
    - Recently had surgery or suffered a trauma

Other warnings you should know about:

CADUET can cause serious side effects, including:

- Worsened angina (chest pain) and heart attacks.
- Hypotension (low blood pressure). Your blood pressure should be carefully monitored.
- Hypersensitivity (allergic reaction). This has been seen with other statins. If you have allergic reactions, your healthcare professional may stop your treatment.
- Hyperglycaemia (high blood sugar). Slightly increased blood sugar can occur when you take CADUET. Discuss with your healthcare professional your risk of developing diabetes.
- Jaundice. If during treatment you develop jaundice, tell your doctor right away. Your treatment with CADUET may need to be stopped.
- Myalgia (muscle pain) and Rhabdomyolysis (muscle tenderness or weakness). Tell your doctor right away if you have muscle pain, tenderness or weakness especially if you are also feeling unwell or have a fever. Your healthcare professional will perform tests and your treatment with CADUET may need to be stopped.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Liver Disease: If during treatment you develop liver problems, tell your doctor right away. Your treatment with CADUET may need to be stopped.

Laboratory Testing: CADUET can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CADUET:

- Medicines that reduce inflammation such as corticosteroids and colchicine
- Medicines used to suppress the immune system such as tacrolimus, sirolimus, and everolimus
- Medicines used to treat cancer such as temsirolimus
- Medicine used to regulate cholesterol levels such as gemfibrozil, fenofibrate, bezafibrate, and niacin (nicotinic acid)
- Medicine used to treat heartburn called cimetidine
- Medicines used to treat bacterial, fungal, or viral infections such as letermovir, fusidic acid, rifampin, erythromycin, clarithromycin, ketoconazole and itraconazole
- Medicine used to treat depression called nefazodone
- Medicine used to treat heart failure called digoxin
- Medicines used to treat blood pressure such as spironolactone, diltiazem and beta-blockers
- Medicines used to treat HIV such as efavirenz, tipranavir/ritonavir, ritonavir, lopinavir/ritonavir, fosamprenavir, nelfinavir mesylate, and darunavir
- Medicine used to treat erectile dysfunction called sildenafil (VIAGRA®)
- Medicines used to treat stomach acidity called antacids
- Medicine used to relax muscles called dantrolene
- Oral contraceptives
- Herbal medicines such as St. John's Wort
- Grapefruit or grapefruit juice

How to take CADUET:

- Take CADUET exactly as your healthcare professional has told you. Do not increase, decrease or stop taking CADUET without first talking to your healthcare professional. Check with your healthcare professional if you are not sure.
- Take one tablet daily with or without food. Swallow tablet with water.
- Continue to take your medicine even if you do not feel better. It may take a number of weeks for your medicine to start working.

CADUET is just part of the treatment your healthcare professional will plan with you to help keep you healthy. Depending on the condition of your health and your lifestyle, your doctor may recommend:

- a change in your diet to control your weight, reduce your cholesterol, reduce intake of saturated fats and increase fiber
- exercise that is right for you
- quitting smoking or avoiding smoky places
- giving up alcohol or drinking less

Follow the plan that you and your doctor make.

Usual dose:

Your healthcare professional will determine which dose is right for you. Based on your response and tolerability your healthcare professional may increase your dose. If you are elderly or have liver or kidney problems your healthcare professional may prescribe a lower dose.

Overdose:

If you think you have taken too much CADUET, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your nest dose, skip the missed dose and continue with your next scheduled dose. Do not double dose.

What are possible side effects from using CADUET?

These are not all the possible side effects you may feel when taking CADUET. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:

- stomach pain or upset, vomiting or throwing up, loss of appetite and inability to eat, or malaise (general feeling of being unwell), burping
- gas, constipation, diarrhea
- headache, neck pain
- fever
- hair loss
- skin rash, hives, itchiness

- insomnia (difficulty sleeping), drowsiness, fatigue, nightmares
- erectile dysfunction (inability to develop or maintain an erection of the penis)
- blurred vision, ringing in the ears
- breathing problems including persistent cough and/or shortness of breath or fever
- mood related disorders including depression
- poor memory, confusion and memory loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff	✓		
RARE			
Abnormal vision		✓	
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			✓
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		✓	
Asthenia (lack or loss of strength)		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)	✓		
Increased frequency, severity, duration of angina (chest pains)		✓	
Jaundice (build up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool, itching all over your body		✓	
Myalgia (muscle pain): aching muscles, tenderness or weakness		✓	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper			✓

abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen		✓	
Paraesthesia (pins and needles): sensation of tingling, pain or numbness in hands, fingers and toes	✓		
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine		✓	
Shortness of breath		✓	
UNKNOWN			
Extrapyramidal symptoms: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want			✓
Hyperglycaemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue	✓		
Liver Disease (worsening of liver function): confusion, coma, death			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep your medicine at 15-30°C (room temperature)

Keep out of reach and sight of children.

If you want more information about CADUET:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html, the manufacturer's website http://www.viatris.ca, or by calling 1-844-596-9526.

This leaflet was prepared by BGP Pharma ULC.

Last Revised AUG 16, 2023

BGP Pharma ULC
Etobicoke, Ontario M8Z 2S6

® PFIZER PFE US HOLDINGS 4 LLC
BGP Pharma ULC, a Viatris company, Licensee