SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

CADUET® 5 mg/10 mg Film Coated Tablet

CADUET® 5 mg/20 mg Film Coated Tablet

CADUET® 5 mg/40 mg Film Coated Tablet

CADUET® 5 mg/80 mg Film Coated Tablet

CADUET® 10 mg/10 mg Film Coated Tablet

CADUET® 10 mg/20 mg Film Coated Tablet

CADUET® 10 mg/40 mg Film Coated Tablet

CADUET® 10 mg/80 mg Film Coated Tablet

COMPOSITION:

Each film coated tablet contains two active ingredients: amlodipine besylate and atorvastatin calcium available as 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg amlodipine besylate/atorvastatin calcium dosage strengths respectively.

Excipients: calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinised starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicone dioxide (anhydrous), magnesium stearate, Opadry II White or Opadry Blue.

CADUET tablets do not contain sugar.

PHARMACOLOGICAL CLASSIFICATION:

A 7.0 Vascular Medicines and A 7.6 Other

PHARMACOLOGICAL ACTION:

CADUET has a dual mechanism of action; the dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) 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 –03-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

In a double-blind, placebo-controlled study of 1 660 patients with co-morbid hypertension and dyslipidaemia, once daily treatment with eight dose combinations of amlodipine and atorvastatin (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, or 10/80 mg) was compared versus amlodipine alone (5 mg or 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, or 80 mg), and placebo. In addition to concomitant hypertension and dyslipidaemia, 15 % of the patients had diabetes mellitus, 22 % were smokers and 14 % had a positive family history of cardiovascular disease. At eight weeks, all eight combination-treatment groups demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP and LDL-C.

In an open-label trial, 1 220 patients with comorbid hypertension and dyslipidaemia received elective dose-titration with amlodipine/atorvastatin over a 14-week period. Patients were required to have uncontrolled blood pressure to enter the trial (whether or not they were using antihypertensive medications at enrolment; patients were allowed to continue on previous antihypertensives, other than calcium channel blockers, during the 14-week dose-titration period) but could enter with either controlled or uncontrolled LDL-C. As a result, no patient entered the trial with both blood pressure and LDL-C controlled, and neither was controlled in 62 % of patients. Treatment with amlodipine/atorvastatin reduced mean blood pressure -17,1 mmHg systolic and -9,6 mmHg diastolic, and reduced mean LDL-C by -32,7 %, resulting in control of both blood pressure and LDL-C for 58 % of these patients (controlled blood pressure and LDL-C were defined, respectively, as < 140/90 mmHg and < 160 mg/dL for patients with comorbid hypertension and dyslipidaemia only; < 140/90 mmHg and < 130 mg/dL for patients with comorbid hypertension and dyslipidaemia plus 1 additional cardiovascular risk factor, excluding known coronary heart disease or diabetes mellitus; and < 130/85 mmHg and < 100 mg/dL for patients with comorbid hypertension and dyslipidaemia plus known coronary heart disease, diabetes mellitus, or other atherosclerotic disease). Only 13 % of the patients in this trial used amlodipine/atorvastatin as initial therapy for comorbid hypertension and dyslipidaemia, whereas the amlodipine component of amlodipine/atorvastatin comprised add-on therapy for hypertension in 56 % of patients, including patients for whom the atorvastatin component of amlodipine/atorvastatin comprised initial therapy for

dyslipidaemia (20 %), a substitution for atorvastatin taken previously (18 %), or a switch from another statin (18 %). When evaluated according to use of antihypertensive and lipid-lowering medications at enrolment, results showed that both blood pressure and LDL-C were brought under control for 65 % of patients who used amlodipine/atorvastatin as initial therapy for comorbid hypertension and dyslipidaemia and for 55 % to 64 % of patients for whom the amlodipine component of amlodipine/atorvastatin constituted add-on therapy for hypertension (55 % for such patients who had previously used lipid-lowering medications other than atorvastatin, 58 % for such patients who had previously used atorvastatin, and 64 % for such patients who had not previously used lipid-lowering medications).

Amlodipine pharmacodynamic properties:

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking induced coronary vasoconstriction.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

In vitro studies have shown that approximately 97,5 % of circulating amlodipine is bound to plasma proteins.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and

is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with Coronary Artery Disease (CAD):

The effects of amlodipine on cardiovascular morbidity and mortality, the progression of coronary atherosclerosis, and carotid atherosclerosis were studied in the Prospective Randomized Evaluation of the Vascular Effects of NORVASC Trial (PREVENT). This multicentre, randomized, double blind, placebo-controlled study followed 825 patients with angiographically defined coronary artery disease for three years. The population included patients with previous myocardial infarction (MI) (45 %), percutaneous transluminal coronary angioplasty (PTCA) at baseline (42 %), or history of angina (69 %). Severity of CAD ranged from 1-vessel disease (45 % of patients) to 3+ vessel disease (21 %). Patients with uncontrolled hypertension (DBP > 95 mm Hg) were excluded from the study. Major cardiovascular events were adjudicated by a blinded endpoint committee. Although there were no demonstrable effects on the rate of progression of coronary artery lesions, amlodipine arrested the progression of carotid intima-media thickening. A significant reduction (-31 %) was observed in the amlodipine-treated patients in the combined endpoint of cardiovascular death, MI, stroke, PTCA, coronary artery bypass graft (CABG), hospitalization for unstable angina, and worsening congestive heart failure (CHF). A significant reduction (-42 %) in revascularization procedures (PTCA and CABG) was also seen in the amlodipine-treated patients. Fewer hospitalizations (-33 %) were seen for unstable angina in amlodipine patients than in the placebo group.

Use in patients with heart failure:

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo-controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or

cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Atorvastatin pharmacodynamic properties:

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In patients with homozygous and heterozygous familial hypercholesterolaemia (FH), nonfamilial forms of hypercholesterolaemia, and mixed dyslipidaemia, atorvastatin reduces total-C (total cholesterol), LDL-C (low-density lipoprotein cholesterol), and apo B (apolipoprotein B). Atorvastatin also reduces VLDL-C (very-low-density lipoprotein cholesterol) and TG (triglycerides) and produces variable increases in HDL-C (high-density lipoprotein cholesterol).

Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Like LDL, cholesterol-enriched triglyceride-rich 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. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

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 production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL in patients with homozygous familial hypercholesterolaemia, a population that has not normally responded to lipid-lowering medication.

Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration.

Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND DIRECTIONS FOR USE).

In a dose-response study, atorvastatin (10 – 80 mg) reduced total-C (30 % – 46 %), LDL-C (41 % – 61 %), apo B (34 % – 50 %), and TG (14 % – 33 %). These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with non-insulin-dependent diabetes mellitus.

In patients with isolated hypertriglyceridaemia, atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C. In patients with dysbetalipoproteinaemia, atorvastatin reduces IDL-C (intermediate density lipoprotein cholesterol).

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinaemia pooled from 24 controlled trials, the median percent increases from baseline in HDL-C for atorvastatin (10 – 80 mg) were 5,1 – 8,7 % in a non-dose-related manner. Additionally, analysis of this pooled data demonstrated significant dose related decreases in total-C/HDL-C and LDL-C/HDL-C ratios, ranging from -29 to -44 % and -37 to -55 %, respectively.

The effects of atorvastatin on ischaemic events and total mortality were studied in the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering study (MIRACL). This multi-centre, randomized, double-blind, placebo-controlled study followed 3 086 patients with acute coronary syndromes; unstable angina or non-Q wave myocardial infarction. Patients were treated with standard care, including diet, and either atorvastatin 80 mg daily or placebo for a median duration of 16 weeks. The final LDL-C, total-C, HDL-C and TG levels were 72, 147, 48, 139 mg/dL in the atorvastatin group, respectively, and 135, 217, 46, and 187 mg/dL, respectively, in the placebo group. Atorvastatin significantly reduced the risk of ischaemic events and death by 16 %. The risk of experiencing re-hospitalization for angina pectoris with documented evidence of myocardial ischaemia was significantly reduced by 26 %. Atorvastatin reduced the risk of ischaemic events and death to a similar extent across the range of baseline LDL-C. In addition, atorvastatin reduced the risk of ischaemic events and death to similar extents in patients with non-Q wave MI and unstable angina, as well as in males and females and in patients ≤ 65 years of age and > 65 years of age.

Pharmacokinetic properties: CADUET data:

Following oral administration, two distinct peak plasma concentrations were observed. The first within 1

to 2 hours of administration is attributable to atorvastatin, the second between 6 and 12 hours after dosing is attributable to amlodipine. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from CADUET are not significantly different from the bioavailability of amlodipine and atorvastatin from co-administration of 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 CADUET was not affected under the fed state as assessed by C_{max}: 105 % (90 % CI: 99, 111) and AUC: 101 % (90 % CI: 97, 105) relative to the fasted state. Although food decreases the rate and extent of absorption of atorvastatin from CADUET by approximately 32 % and 11 %, respectively, as assessed by C_{max}: 68 % (90 % CI 60, 79) and AUC: 89 % (90 % CI 83, 95), relative to the fasted state, similar reductions in plasma concentrations in the fed state have been seen with atorvastatin without a reduction in LDL-C effect (see below).

Amlodipine data:

Absorption:

After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 – 12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. The volume of distribution is approximately 21 L/kg. The bioavailability of amlodipine is not altered by the presence of food.

Biotransformation/elimination:

The terminal plasma elimination half-life is about 35 – 50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7 – 8 days of consecutive dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10 % of the parent compound and 60 % of metabolites excreted in the urine.

Distribution:

In vitro studies with amlodipine have shown that approximately 97,5 % of the circulating drug is bound to plasma proteins in hypertensive patients. The terminal plasma elimination half-life of amlodipine is about 35 – 50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7 – 8 days of consecutive dosing.

Metabolism:

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

Excretion:

Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 – 50 hours. 10 % of the parent amlodipine compound and 60 % of the metabolites of amlodipine are excreted in the urine.

Atorvastatin data:

Absorption:

Atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14 % and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30 %. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25 % and 9 %, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30 % for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution:

The mean volume of distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥ 98 % bound to plasma proteins. A blood/plasma ratio of approximately 0,25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk.

Metabolism:

Atorvastatin is extensively metabolised to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70 % of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion:

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation.

Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2 % of dose of atorvastatin is recovered in urine following oral administration.

Data on amlodipine and atorvastatin in special populations:

Elderly:

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied. Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated.

Plasma concentrations of atorvastatin are higher (approximately 40 % for C_{max} and 30 % for AUC) in healthy elderly subjects (age ≥ 65 years) than in young adults. The ACCESS study specifically evaluated elderly patients with respect to reaching their NCEP treatment goals. The study included 1 087 patients under 65 years of age, 815 patients over 65 years of age, and 185 patients over 75 years of age. No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Paediatric:

Pharmacokinetic data in the paediatric population are not available.

Gender:

Concentrations of atorvastatin in women differ (approximately 20 % higher for C_{max} and 10 % lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal insufficiency:

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Therefore, patients with renal failure can receive the usual initial amlodipine dose. Amlodipine is not dialysable.

In studies with atorvastatin: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary.

Hepatic insufficiency:

Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40 – 60 %. Therapeutic response to atorvastatin is unaffected in patients with moderate to severe hepatic dysfunction, but exposure to the drug is greatly increased. 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 (Childs-Pugh B).

INDICATIONS:

CADUET is indicated for:

1) Patients at increased cardiovascular risk due to concomitant hypertension and dyslipidaemia.

and/or

2) Patients with angina and concomitant dyslipidaemia.

CADUET may be used either alone or in combination with other anti-hypertensive or anti-anginal drugs.

CONTRAINDICATIONS:

CADUET is contraindicated in patients who have:

1. Known hypersensitivity to dihydropyridines, amlodipine, atorvastatin or any component of this medication,
2. Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, myopathy,
3. Or in patients who are pregnant, breastfeeding, or of childbearing potential not using appropriate contraceptive measures. 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 to the foetus.

WARNINGS AND SPECIAL PRECAUTIONS:

Effects on ability to drive and use machines:

Clinical experience with amlodipine and atorvastatin indicates that CADUET is unlikely to impair a patient's ability to drive or use machinery.

Use in patients with heart failure:

In a long-term placebo-controlled study (PRAISE–2) of amlodipine treated patients with NYHA II and IV heart failure of non-ischaemic etiology, amlodipine was associated with increased reports pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Use in patients with impaired hepatic function (see also CONTRAINDICATIONS):

Hepatic effects:

Due to the atorvastatin component, CADUET should be administered with caution in patients with impaired liver function.

As with other lipid-lowering agents of the HMG-CoA reductase inhibitor class, moderate (> 3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin given at doses of 10, 20, 40 and 80 mg.

Persistent increases in serum transaminases (> 3 x ULN on two or more occasions) occurred in 0,7 % of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0,2 %, 0,2 %, 0,6 %, and 2,3 % for 10, 20, 40 and 80 mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Liver tests should be performed before initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in ALT or AST of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of CADUET is recommended.

CADUET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of CADUET.

Skeletal muscle effects:

Myalgia has been reported in atorvastatin-treated patients (see SIDE EFFECTS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK)

values > 10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. Atorvastatin is biotransformed by CYP 3A4. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy (see INTERACTIONS). CADUET may cause an elevation of creatine phosphokinase due to the atorvastatin component (see SIDE EFFECTS).

As with other drugs in the class of HMG-CoA reductase inhibitors, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported. 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 (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures). Control of hypertension may be continued with the appropriate dose of amlodipine.

Before treatment:

CADUET should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine phosphokinase (CPK) level should be measured before starting statin treatment in the following situations:

- Renal impairment.
- Hypothyroidism.

- Personal or familial history of hereditary muscular disorders.
- Previous history of muscular toxicity with a statin or fibrate.
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed.
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

If CPK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine phosphokinase measurement:

Creatine phosphokinase (CPK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK levels are significantly elevated at baseline (> 5 times ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Whilst on treatment:

Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

- If such symptoms occur whilst a patient is receiving treatment, their CPK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CPK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Atorvastatin must be discontinued if clinically significant elevation of CPK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicaments such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivates or HIV-protease inhibitors (see INTERACTIONS and SIDE EFFECTS). Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug transport.

Atorvastatin is biotransformed by CYP3A4. Physicians considering combined therapy with these drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.

INTERACTIONS:

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

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

In studies with amlodipine:

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Special studies: Effect of other agents on amlodipine:

Digoxin:

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

Ethanol (alcohol):

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Cyclosporin:

Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Warfarin:

Co-administration with amlodipine does not significantly alter the effect of warfarin on prothrombin response time.

Drug/laboratory test interactions:

None known.

Special studies: Effect of other agents on amlodipine:

Cimetidine:

Co-administration of cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice:

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

Aluminium/magnesium:

Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil:

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

Studies with atorvastatin:

The risk of myopathy during treatment with HMG CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, macrolide antibiotics, including erythromycin, azole antifungals, or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed (see WARNINGS AND SPECIAL PRECAUTIONS).

Antacid:

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites by approx. 35 %. However, LDL-C reduction was not altered.

Antipyrine:

Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol:

Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25 %) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

Digoxin:

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20 % following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. Patients taking digoxin should be monitored appropriately.

Erythromycin, clarithromycin:

Co-administration of atorvastatin 10 mg OD and erythromycin (500 mg QID), or atorvastatin 10 mg OD and clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin. Clarithromycin increased the C_{max} and AUC of atorvastatin by 56 % and 80 % respectively.

Azithromycin:

Co-administration of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

Itraconazole:

Concomitant administration of atorvastatin 40 mg and itraconazole 200 mg daily resulted in a 3-fold increase in atorvastatin AUC.

Oral contraceptives:

Co-administration with an oral contraceptive containing norethindrone and ethinyl estradiol increased AUC values for norethindrone and ethinyl estradiol by approximately 30 % and 20 %. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin:

Co-administration of atorvastatin and warfarin caused a small decrease in prothrombin time during the

first days of dosing which returned to normal within 15 days of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.

Cimetidine:

An interaction study with cimetidine and atorvastatin was conducted, and no clinically significant interaction was seen.

Protease inhibitors:

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Inducers of cytochrome P450 3A4:

The effect of inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) on atorvastatin is unknown. The possible interaction with other substrates of this isozyme is unknown but should be considered for other drugs with a narrow therapeutic index, for example, antiarrhythmic agents Class III including amiodarone.

Inhibitors of cytochrome P450 3A4:

Atorvastatin is metabolised by cytochrome P450 3A4. Interaction may occur when atorvastatin is administered with inhibitors of cytochrome P450 3A4 (e.g. cyclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Concomitant administration can lead to increased plasma concentrations of atorvastatin. Therefore, special caution should be exercised when atorvastatin is used in combination with such medicinal agents (see also WARNINGS AND SPECIAL PRECAUTIONS).

Inhibitors of P-glycoprotein:

Atorvastatin and atorvastatin-metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. cyclosporin) can increase the bioavailability of atorvastatin.

Phenazone:

Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

Gemfibrozil/fibric acid derivatives:

The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibric acid derivatives. According to results of in vitro studies the metabolic pathway of atorvastatin via

glucuronidation is inhibited by gemfibrozil. This may possibly lead to increased plasma levels of atorvastatin (see also WARNINGS AND SPECIAL PRECAUTIONS).

Other concomitant therapy:

In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and oestrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

PREGNANCY AND LACTATION:

CADUET is contraindicated in pregnancy and while breastfeeding. CADUET should only be used in women of childbearing potential who are using appropriate contraceptive measures.

DOSAGE AND DIRECTIONS FOR USE:

CADUET is a combination product targeting concomitant cardiovascular conditions, hypertension/angina and dyslipidaemia.

The dosage range for CADUET is 5 mg/10 mg to a maximum dose of 10 mg/80 mg once daily. The starting dose and maintenance dose should be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and dyslipidaemia. Current treatment guidelines should be consulted to establish treatment goals for patients based on their baseline values. Doses may be taken at any time of day with or without food.

As a component of multiple-risk factor intervention, CADUET should be used in addition to non-pharmacological measures, including an appropriate diet, exercise and weight reduction in obese patients, smoking cessation, and to treat underlying medical problems, when the response to these measures have been inadequate.

Following initiation and/or CADUET, lipid levels should be analysed, and blood pressure measured within 2 – 4 weeks, and dosage of the amlodipine and atorvastatin components should be adjusted accordingly. Titration for blood pressure response may proceed more rapidly if clinically warranted.

Initial therapy:

CADUET may be used to initiate treatment in patients with hyperlipidaemia and either hypertension or angina. The recommended starting dose of CADUET should be based on the appropriate combination

of recommendations for the amlodipine and atorvastatin components considered separately. The maximum dose of the amlodipine component of CADUET is 10 mg once daily. The maximum dose of the atorvastatin component of CADUET is 80 mg once daily.

Substitution therapy:

CADUET may be substituted for its individually titrated components. Patients may be given the equivalent dose of CADUET or a dose of CADUET with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, blood pressure lowering, or lipid lowering effect. CADUET may be used to provide additional therapy for patients already on one of its components. As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of amlodipine/atorvastatin should be selected based on continuation of the component being used previously and on the recommended starting dose for the component being added.

Concomitant medication:

The amlodipine component of CADUET has been safely co-administered with thiazide diuretics, ACE inhibitors, alpha-blockers, beta-blockers, long-acting nitrates, and or/sublingual nitroglycerine. CADUET has also been safely administered with the above medicines.

The atorvastatin component of CADUET may be used in combination with a bile acid binding resin for additive effect on lipid lowering. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS AND SPECIAL PRECAUTIONS, and INTERACTIONS).

Special populations and special considerations for dosing:

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia (atorvastatin studies):

The majority of patients are controlled with 10 mg atorvastatin once a day. A therapeutic response is evident within two weeks, and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.

Homozygous familial hypercholesterolaemia (atorvastatin studies):

In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to 80 mg of atorvastatin with a greater than 15 % reduction in LDL-C (18 % – 45 %).

Use in patients with impaired renal function:

No dose adjustment is required in patients with impaired renal function.

Use in patients with impaired hepatic function:

CADUET should not be used in patients with hepatic impairment (see CONTRAINDICATIONS).

Use in children:

Safety and effectiveness of CADUET has not been established in children.

Use in the elderly:

CADUET is well tolerated at similar doses in elderly or younger patients. Therefore, normal dosage regimens are recommended.

SIDE EFFECTS:

CADUET has been evaluated for safety in 1 092 patients in double-blind placebo-controlled studies treated for concomitant hypertension and dyslipidaemia. In clinical trials with CADUET, no adverse events peculiar to this combination have been observed. Adverse events have been limited to those that were reported previously with amlodipine and/or atorvastatin (please see respective adverse event tables below).

In general, treatment with CADUET was well tolerated. For the most part, adverse events have been mild or moderate in severity. In controlled clinical trials, discontinuation of therapy due to clinical adverse events or laboratory abnormalities was only required in 5,1 % of patients treated with both amlodipine and atorvastatin compared to 4,0 % of patients given placebo.

The following adverse events, listed according to the MedDRA system organ class and frequencies, are for amlodipine and atorvastatin individually. These adverse events may also be associated with the underlying disease and concomitant medications.

Frequency key: Very common: ≥ 1/10, Common: ≥ 1/100 and < 1/10, Uncommon: ≥ 1/1 000 and < 1/100, Rare: ≥ 1/10 000 and < 1/1 000, Very rare: < 1/10 000.

Amlodipine experience

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Blood and the lymphatic system disorders	Very rare	Leucopenia, thrombocytopaenia
Immune system disorders	Very rare	Allergic reaction

Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes
Nervous system disorders	Common	Somnolence, dizziness, headache
	Uncommon	Tremor, taste perversion, syncope, hypoaesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Uncommon	Visual disturbances
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, rhinitis
	Very rare	Coughing
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Uncommon	Vomiting, dyspepsia, altered bowel habits, dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discoloration, increased sweating, pruritus, rash
	Very rare	Angioedema, erythema multiforme, urticaria
Musculoskeletal and connective	Uncommon	Arthralgia, myalgia, muscle cramps, back pain

tissue disorders		
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Common	Oedema, fatigue
	Uncommon	Chest pain, asthenia, pain, malaise
Investigations	Uncommon	Weight increase, weight decrease

Atorvastatin experience:

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Blood and the lymphatic system disorders	Uncommon	Thrombocytopaenia
Immune system disorders	Common	Allergic reaction
Metabolism and nutrition disorders	Uncommon	Hypoglycaemia, hyperglycaemia, anorexia, weight gain
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Common	Hypoaesthesia, paraesthesia, dizziness, headache
	Uncommon	Peripheral neuropathy, amnesia
Ear and labyrinth disorders	Uncommon	Tinnitus
Gastrointestinal disorders	Common	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence
	Uncommon	Vomiting
	Rare	Pancreatitis
Hepatobiliary disorders	Rare	Hepatitis, cholestatic jaundice
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Uncommon	Alopecia, urticaria
	Rare	Bullous rashes

	Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia, back pain
	Rare	Myositis, muscle cramps
	Very rare	Rhabdomyolysis, myopathy
Reproductive system and breast disorders	Uncommon	Impotence
General disorders and administration site conditions	Common	Asthenia, chest pain
	Uncommon	Malaise
	Rare	Peripheral oedema

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no information on overdosage with CADUET in humans.

For amlodipine, experience with intentional overdose in humans is limited. Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for 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 may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Specific treatment is not available for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically, and supportive measures instituted, as required. Liver function tests and serum CPK levels should be monitored. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

IDENTIFICATION:

CADUET 5 mg/10 mg: White oval shaped film coated tablet, marked “Pfizer” on one side and CDT 051” on the other side.

CADUET 5 mg/20 mg: White oval shaped film coated tablet, marked “Pfizer” on one side and CDT 052” on the other side.

CADUET 5 mg/40 mg: White oval shaped film coated tablet, marked “Pfizer” on one side and CDT 054” on the other side.

CADUET 5 mg/80 mg: White oval shaped film coated tablet, marked “Pfizer” on one side and CDT 058” on the other side.

CADUET 10 mg/10 mg: Blue oval shaped film coated tablet, marked “Pfizer” on one side and CDT 101” on the other side.

CADUET 10 mg/20 mg: Blue oval shaped film coated tablet, marked “Pfizer” on one side and CDT 102” on the other side.

CADUET 10 mg/40 mg: Blue oval shaped film coated tablet, marked “Pfizer” on one side and CDT 104” on the other side.

CADUET 10 mg/80 mg: Blue oval shaped film coated tablet, marked “Pfizer” on one side and CDT 108” on the other side.

PRESENTATION:

CADUET tablets are available in clear aluminium/PVC blister packs containing 30 film coated tablets.

STORAGE INSTRUCTIONS:

Store at room temperature, below 25 °C. Protect from light.

STORE ALL MEDICINES OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

CADUET 5 mg/10 mg: A39/7.0/0326

CADUET 5 mg/20 mg: A39/7.0/0327

CADUET 5 mg/40 mg: A39/7.0/0328

CADUET 5 mg/80 mg: A39/7.0/0329

CADUET 10 mg/10 mg: A39/7.0/0330

CADUET 10 mg/20 mg: A39/7.0/0331

CADUET 10 mg/40 mg: A39/7.0/0332

CADUET 10 mg/80 mg: A39/7.0/0333

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

17 February 2006

BOTSWANA: S2

CADUET 5 mg/10 mg – Reg. No.: BOT0801488

CADUET 5 mg/20 mg – Reg. No.: BOT1202067

CADUET 5 mg/40 mg – Reg. No.: BOT1202068

CADUET 10 mg/10 mg – Reg. No.: BOT0801489

CADUET 10 mg/20 mg – Reg. No.: BOT1202069

CADUET 10 mg/40 mg – Reg. No.: BOT1202070

NAMIBIA: NS2

CADUET 5 mg/10 mg – Reg. No.: 06/7.0/0256

CADUET 5 mg/20 mg – Reg. No.: 06/7.0/0257

CADUET 5 mg/40 mg – Reg. No.: 08/7.0/0091

CADUET 5 mg/80 mg – Reg. No.: 08/7.0/0092

CADUET 10 mg/10 mg – Reg. No.: 06/7.0/0258

CADUET 10 mg/20 mg – Reg. No.: 06/7.0/0259

CADUET 10 mg/40 mg – Reg. No.: 08/7.0/0093

CADUET 10 mg/80 mg – Reg. No.: 08/7.0/0094