SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CADUET® 5 mg/10 mg film-coated tablet

CADUET® 5 mg/20 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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

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 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CADUET is indicated for:

- Patients at increased cardiovascular risk due to concomitant hypertension and dyslipidaemia.
- Patients with angina and concomitant dyslipidaemia.

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

4.2 Posology and method of administration

Posology

General considerations

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 individualised 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.

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 titration of 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 (see section 4.5)

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 sections 4.4 and 4.5).

Special populations

Use in patients with impaired renal function

No dose adjustment is required in patients with impaired renal function (see section 4.4).

Use in patients with impaired hepatic function

CADUET should not be used in patients with hepatic impairment (see sections 4.3 and 4.4).

Use in the elderly population

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

regimens are recommended.

Paediatric population

Safety and efficacy of CADUET has not been established in children and adolescents.

Use in combination with other medicines

Studies with atorvastatin

Use with ciclosporin

In cases where co-administration of atorvastatin with ciclosporin is necessary, the dose of atorvastatin should not exceed 10 mg (see sections 4.4 and 4.5).

Method of administration

For oral use.

Doses may be taken at any time of day with or without food.

4.3 Contraindications

CADUET is contraindicated in patients who:

- Have known hypersensitivity to dihydropyridines*, amlodipine, atorvastatin or to any of the excipients of CADUET (listed in section 6.1).

  *Amlodipine is a dihydropyridine calcium channel blocker.
- Have active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- Are pregnant, breastfeeding their infants, or of childbearing potential not using appropriate contraceptive measures (see section 4.6).
- Have severe hypotension.
- Have shock (including cardiogenic shock).
- Have left ventricular outflow tract obstruction (e.g. severe aortic stenosis).
- Have haemodynamically unstable heart failure after acute myocardial infarction.
- Dose combinations of CADUET where the atorvastatin component is higher than 10 mg are contraindicated in patients taking the HIV protease inhibitors tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir (see section 4.5, *Protease inhibitors*).

- CADUET is contraindicated in patients taking the hepatitis C antivirals glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

Use in patients with heart failure

In patients with NYHA II and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema.

Use in patients with impaired hepatic function (see section 4.3)

Hepatic effects

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

Elevations (> 3 x upper limit of normal [ULN]) of serum transaminases have been reported following therapy with atorvastatin.

Persistent increases in serum transaminases (> 3 x ULN on two or more occasions) occurred in 0,7 % of patients who received atorvastatin. The incidence of these abnormalities was 0,2 %, 0,2 %, 0,6 %, and 2,3 % for 10, 20, 40 and 80 mg respectively. When the dosage of atorvastatin was interrupted or discontinued, transaminase levels usually returned to pre-treatment levels.

Liver function tests should be performed before initiation of treatment with CADUET and repeated as clinically indicated. If liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with CADUET, promptly interrupt therapy. If an alternate aetiology is not found, do not restart CADUET.

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 (see section 4.3).

Skeletal muscle effects

Myalgia has been reported in CADUET (atorvastatin component) treated patients (see section 4.8). 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 CADUET is increased with concurrent administration of ciclosporin, fibric acid derivatives, erythromycin, niacin, azole antifungals, colchicine, hepatitis C protease inhibitors (telaprevir, boceprevir, elbasvir/grazoprevir), combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir and atazanavir plus ritonavir. Many of these medicines inhibit cytochrome P450 3A4 metabolism and/or medicine-transport. Atorvastatin is biotransformed by CYP 3A4. Medical practitioners considering combined therapy with CADUET and fibric acid derivatives, erythromycin, immunosuppressive medicines, azole antifungals, lipid lowering doses of niacin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir should regularly 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 medicine. Therefore, lower starting and maintenance doses of the atorvastatin component should also be considered when taken concomitantly with the aforementioned medicines.

CADUET should be discontinued throughout the duration of fusidic acid therapy. CADUET may be re-introduced seven days after the last dose of fusidic acid. 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 section 4.5). CADUET may cause an elevation of creatine phosphokinase due to the atorvastatin component (see section 4.8).

Cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. 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, 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 – 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.
- CADUET 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 CADUET is administered concomitantly with certain medicines such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivates or HIV-protease inhibitors (see sections 4.5 and 4.8). Many of these medicines inhibit cytochrome P450 3A4 metabolism and/or medicine transport. Atorvastatin is biotransformed by CYP3A4. Medical practitioners considering combined therapy with these medicines should regularly 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 medicine.

Haemorrhagic stroke

CADUET increases the risk of recurrent stroke and transient ischaemic attack.

Endocrine function

Increases in HbA1c and fasting serum glucose levels have been reported with the atorvastatin component of CADUET. Some evidence suggests that statins as a class raise blood glucose and, in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients taking CADUET who are at risk (fasting glucose 5,6 – 6,9 mmol/L, BMI > 30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines for a deterioration of their glycaemic control.

4.5 Interaction with other medicines and other forms of interaction

No medicine interaction studies have been conducted with CADUET and other medicines, although studies have been conducted in the individual amlodipine and atorvastatin components as described

below.

Amlodipine interactions

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 medicines, antibiotics, and oral hypoglycaemic medicines.

CYP3A4 inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 – 87 years of age) resulted in a 57 % increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers (18 – 43 years of age) did not significantly change amlodipine systemic exposure (22 % increase in AUC). Although the clinical relevance of these findings is uncertain, the pharmacokinetic variations may be more pronounced in the elderly.

Strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) increase the plasma concentrations of amlodipine to a greater extent than diltiazem. CADUET should be used with caution together with CYP3A4 inhibitors.

CYP3A4 inducers

There are no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

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 amlodipine on other medicines

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.

Ciclosporin

No interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients. Various studies in renal transplant patients report that amlodipine co-administration with ciclosporin affect trough concentrations of ciclosporin from no change up to an average increase of 40 %. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on CADUET.

Warfarin

Co-administration with amlodipine does not significantly alter the effect of warfarin on prothrombin response time or the International Normalised Ratio (INR).

Medicine/laboratory test interactions

None known.

Special studies: effect of other medicines 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. 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 CADUET with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

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 medicine independently exerted its own blood pressure lowering effects.

Atorvastatin interactions

The risk of myopathy during treatment with atorvastatin is increased with concurrent administration of ciclosporin, fibric acid derivatives, niacin or cytochrome P450 3A4 inhibitors (nefazodone, macrolide antibiotics e.g. erythromycin and azole antifungals) and has resulted

in rhabdomyolysis with renal dysfunction secondary to myoglobinuria (see below and section 4.4, *Skeletal muscle effects*).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolised by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Transporter inhibitors

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. ciclosporin) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and ciclosporin 5,2 mg/kg/day resulted in a 870 % increase in exposure to atorvastatin (see section 4.2, *Use in combination with other medicines*).

Erythromycin/clarithromycin

Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin (see section 4.4, *Skeletal muscle effects*).

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin. Plasma concentrations of atorvastatin increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In cases where co-administration with CADUET is necessary, doses above 10 mg atorvastatin daily are contraindicated (see section 4.3).

Concomitant administration of atorvastatin 10 mg single dose with tipranavir 500 mg twice daily plus ritonavir 200 mg twice daily for, seven days, resulted in a 940 % increase in atorvastatin AUC and 860 % increase in atorvastatin C_{max}. Atorvastatin did not result in a change in pharmacokinetics of tipranavir plus ritonavir.

Concomitant administration of atorvastatin 20 mg single dose with telaprevir 750 mg every eight hours, for 10 days, resulted in a 790 % increase in atorvastatin AUC and 1 060 % increase in atorvastatin C_{max}.

In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. Concomitant administration of atorvastatin 20 mg single dose for 4 days with lopinavir 400 mg twice a daily plus ritonavir 100 mg twice daily for 14 days resulted in a 690 % increase in atorvastatin AUC and 570 % increase in atorvastatin C_{max}.

In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg and should be used with caution. Concomitant administration of atorvastatin 40 mg once a day for 4 days with saquinavir 400 mg twice daily plus ritonavir 400 mg twice daily for 15 days resulted in a 390 % increase in atorvastatin AUC and 430 % increase in atorvastatin C_{max}. The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used. Concomitant administration of atorvastatin 10 mg once a day for 4 days with darunavir 300 mg twice daily plus ritonavir 100 mg twice daily for 9 days resulted in a 340 % increase in atorvastatin AUC and 230 % increase in atorvastatin C_{max}. Concomitant administration of atorvastatin 10 mg once a day for 4 days with fosamprenavir 1 400 mg twice a day for 14 days resulted in a 230 % increase in atorvastatin AUC and 400 % increase in atorvastatin C_{max}. Atorvastatin resulted in a 27 % decrease in fosamprenavir. Concomitant administration of atorvastatin 10 mg once a day for 4 days with fosamprenavir 700 mg twice a day plus ritonavir 100 mg twice a day for 14 days resulted in a 250 % increase in atorvastatin AUC and 280 % increase in atorvastatin C_{max}. Atorvastatin did not result in a change in pharmacokinetics of

fosamprenavir 700 mg plus ritonavir.

In patients taking nelfinavir, the dose of atorvastatin should not exceed 40 mg daily. Concomitant administration of atorvastatin 10 mg once a day for 28 days with nelfinavir 1 250 mg twice a day for 14 days resulted in a 74 % increase in atorvastatin AUC and 220 % increase in atorvastatin C_{max}.

Concomitant administration of atorvastatin 40 mg single dose with boceprevir 800 mg three times a day for 7 days resulted in a 2,3-fold increase in atorvastatin AUC and 2,66-fold increase in atorvastatin C_{max} (see section 4.4, *Skeletal muscle effects*).

Diltiazem hydrochloride

Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin (51 % increase in AUC).

Cimetidine

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

Itraconazole

Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC (230 % increase in AUC).

Grapefruit juice

Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (> 1,2 litres per day).

Inducers of cytochrome P450 3A

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampicin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampicin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacids

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and

aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approximately 35 %. However, LDL-C reduction was not altered.

Antipyrine

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

Colestipol

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

Azithromycin

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

Oral contraceptives

Co-administration with an oral contraceptive containing norethindrone and ethinyl oestradiol increased AUC values for norethindrone and ethinyl oestradiol by approximately 30 % and 20 %, respectively. 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 and INR during the first days of dosing which returned to normal within 15 days of atorvastatin treatment. Nevertheless, patients receiving warfarin should be regularly monitored when atorvastatin is added to their therapy.

Fusidic acid

Severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. CADUET treatment should be discontinued throughout treatment with fusidic acid. CADUET therapy may be re-introduced seven days after the last dose of fusidic acid.

Colchicine

Cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

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 is 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 lead to increased plasma levels of atorvastatin (see section 4.4, *Skeletal muscle effects*).

Other concomitant therapy

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

4.6 Fertility, pregnancy and lactation

CADUET is contraindicated in patients who are pregnant, breastfeeding their infants, or of childbearing potential not using appropriate contraceptive measures. CADUET should only be used in women of childbearing potential who are using appropriate contraceptive measures.

4.7 Effects on ability to drive and use machines

CADUET may cause dizziness and syncope or muscle events that can impair a patient's ability to drive or use machinery.

4.8 Undesirable effects

Summary of the safety profile

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 those that were reported previously with amlodipine and/or atorvastatin (please see respective adverse event tables below).

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.

Tabulated summary of adverse events

Frequency key: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Amlodipine experience

System organ class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Very rare	Leukopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reaction
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, altered mood
Nervous system disorders	Common	Somnolence, dizziness, headaches
	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Tinnitus

Cardiac disorders	Common	Palpitations
	Very rare	Myocardial infarction, dysrhythmia (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, change in 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 discolouration, hyperhidrosis, pruritus, rash
	Very rare	Angioedema, erythema multiforme, urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, myalgia, muscle spasms, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, pollakiuria
Reproductive system and breast disorders	Uncommon	Erectile dysfunction, gynaecomastia
General disorders and administration site conditions	Common	Oedema, fatigue
	Uncommon	Chest pain, asthenia, pain, malaise
Investigations	Uncommon	Increased weight, decreased weight

Atorvastatin experience

In the atorvastatin placebo-controlled clinical trial database of 16 066 (8 755 atorvastatin vs. 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.

System organ class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia
Immune system disorders	Common	Allergic reaction (including anaphylaxis)
Infections and infestations	Common	Nasopharyngitis
Metabolism and nutrition disorders	Uncommon	Hypoglycaemia, hyperglycaemia, anorexia, weight gain
Respiratory, thoracic and mediastinal disorders	Common	Pharyngolaryngeal pain, epistaxis
Psychiatric disorders	Common	Insomnia
	Uncommon	Nightmare
Eye disorders	Uncommon	Blurred vision
Nervous system disorders	Common	Hypoaesthesia, paraesthesia, dizziness, headache
	Uncommon	Peripheral neuropathy, amnesia, dysgeusia
Ear and labyrinth disorders	Uncommon	Tinnitus
Gastrointestinal disorders	Common	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence
	Uncommon	Vomiting, abdominal discomfort, eructation
	Rare	Pancreatitis
Hepatobiliary disorders	Rare	Hepatitis, cholestatic jaundice
	Uncommon	Cholestasis
Injury and poisoning	Uncommon	Tendon rupture
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, pain in extremity, musculoskeletal pain, muscle spasms, joint swelling
	Uncommon	Muscle fatigue, neck pain
	Rare	Myositis, muscle cramps
	Very rare	Rhabdomyolysis, myopathy
Investigations	Common	Abnormal liver function test, increased blood creatine phosphokinase
	Uncommon	White blood cells urine positive
Reproductive system and breast disorders	Uncommon	Impotence
General disorders and administration site conditions	Common	Asthenia, chest pain, fatigue
	Uncommon	Malaise, pyrexia
	Rare	Peripheral oedema

Post-marketing reports

There have been post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with CADUET use. These events may be reversible upon discontinuation of CADUET. Times to symptom onset are variable (1 day to years). Immune mediated necrotizing myopathy has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no information on overdosage with CADUET in humans.

Amlodipine

Amlodipine overdosage could result in excessive peripheral vasodilatation and reflex tachycardia. Marked and prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to amlodipine overdosage requires active cardiovascular support and monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. 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.

Atorvastatin

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 atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.0 Vascular medicines and A 7.6 Other

Atorvastatin/amlodipine 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 inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

Amlodipine pharmacodynamics

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.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm 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.

Atorvastatin pharmacodynamics

Atorvastatin is a 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).

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 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 atorvastatin dose than it does with systemic atorvastatin concentration.

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.

5.2 Pharmacokinetic properties

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 circulating amlodipine 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 – 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent substance) 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 atorvastatin 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 C_{max} and AUC) following evening administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of 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 atorvastatin

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, atorvastatin 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.

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.

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 active substance 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of 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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

CADUET tablets are available in silver aluminium foil/foil blister packs containing 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

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Isando

Gauteng, 1609

Tel.: +27(011) 451 1300 / +27(071) 281 2503 (24 hours)

Manufacturer: Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany

8. REGISTRATION NUMBERS

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

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

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

9. DATE OF FIRST AUTHORISATION

17 February 2006

10. DATE OF REVISION OF THE TEXT

05 August 2022

BOTSWANA: S2

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

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

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 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