

CADIVAST[®]

Amlodipine (as besilate) and atorvastatin (as calcium trihydrate) tablets

1 NAME OF THE MEDICINE

Amlodipine (as besilate) and atorvastatin (as calcium trihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredients in Cadivast are amlodipine besilate and atorvastatin calcium trihydrate.

Excipients with known effect: Soya bean products

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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| Cadivast 5/10 tablets | : A white to off-white, film-coated, oval, biconvex tablet debossed with “AA 4” on one side of the tablet and “M” on the other side. |
| Cadivast 5/20 tablets | : A white to off-white, film-coated, round, biconvex tablet debossed with “AA 5” on one side of the tablet and “M” on the other side. |
| Cadivast 5/40 tablets | : A white to off-white, film-coated, capsule shaped, biconvex tablet debossed with “AA 6” on one side of the tablet and “M” on the other side. |
| Cadivast 5/80 tablets | : A white to off-white, film-coated, oval, biconvex tablet debossed with “AA 7” on one side of the tablet and “M” on the other side |
| Cadivast 10/10 tablets | : A blue, film-coated, barrel shaped, biconvex tablet debossed with “AA 8” on one side of the tablet and “M” on the other side. |
| Cadivast 10/20 tablets | : A blue, film-coated, oval, biconvex tablet debossed with “AA 9” on one side of the tablet and “M” on the other side. |
| Cadivast 10/40 tablets | : A blue, film-coated, round, biconvex tablet debossed with “AA 10” on one side of the tablet and “M” on the other side. |
| Cadivast 10/80 tablets | : A blue, film-coated, capsule shaped, biconvex tablet debossed with “AA 11” on one side of the tablet and “M” on the other side. |

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Amlodipine besilate and atorvastatin calcium trihydrate tablet is indicated for patients in whom treatment with amlodipine and atorvastatin is appropriate at the doses presented.

The indications for amlodipine are:

1. Hypertension: Amlodipine is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of amlodipine, which has been used

in combination with a thiazide diuretic, beta adrenoceptor blocking agent or an angiotensin converting enzyme inhibitor.

2. Angina: Amlodipine is indicated for the first line treatment of chronic stable angina. Amlodipine may be used alone, as monotherapy or in combination with other antianginal drugs.

The indications for atorvastatin are:

1. Atorvastatin is indicated as an adjunct to diet for the treatment of patients with hypercholesterolaemia. Prior to initiating therapy with atorvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, and alcoholism) should be identified and treated.
2. Atorvastatin is indicated in hypertensive patients with multiple risk factors for coronary heart disease (CHD) which may include diabetes, history of stroke or other cerebrovascular disease, peripheral vascular disease or existing asymptomatic CHD (see Section 5.1 Pharmacodynamic Properties, Clinical Trials, Prevention of Cardiovascular Disease) to reduce the risk of nonfatal myocardial infarction and non-fatal stroke.

These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.

4.2 DOSE AND METHOD OF ADMINISTRATION

Amlodipine besilate and atorvastatin calcium trihydrate tablet is a combination product targeting two distinct cardiovascular risk factors, hypertension and dyslipidaemia.

The starting dose and maintenance doses of amlodipine besilate and atorvastatin calcium trihydrate tablet should be individualised according to goals consistent with current treatment guidelines and patient response.

Amlodipine besilate and atorvastatin calcium trihydrate tablet is available in eight strengths ranging from amlodipine besilate/atorvastatin calcium trihydrate 5 mg/10 mg to amlodipine besilate/atorvastatin calcium trihydrate 10 mg/80 mg to allow the physician maximum flexibility in titrating patients to treatment targets.

Amlodipine besilate and atorvastatin calcium trihydrate tablet is to be taken once-daily and may be taken at any time of the day with or without food.

After initiation of amlodipine besilate and atorvastatin calcium trihydrate tablet, lipid levels should be analysed and blood pressure measured after approximately 4 to 6 weeks, and dosage adjusted accordingly. Titration for blood pressure response may proceed more rapidly if clinically warranted.

In patients requiring additional blood pressure lowering and/or angina treatment, amlodipine besilate and atorvastatin calcium trihydrate tablet may be added to existing therapies.

Special Patient Populations

Small, Fragile or Elderly

Amlodipine besilate and atorvastatin calcium trihydrate tablet can be used in this patient population provided titration to 5 mg of amlodipine has been achieved (see Section 4.4 Special Warnings and Precautions for Use).

Children

There are no studies to date to determine the safety or efficacy of amlodipine besilate and atorvastatin calcium trihydrate tablet in children.

Use in Renal Impairment

No dosage adjustment is necessary in patients taking amlodipine besilate and atorvastatin calcium trihydrate tablet (see Section 4.4 Special Warnings and Precautions for Use).

Use in Hepatic Impairment

Plasma concentrations of atorvastatin are markedly increased in patients with chronic alcoholic liver disease (Childs-Pugh B). The half-life of amlodipine is prolonged in patients with impaired liver function and dosage recommendations have not been established. Therefore, amlodipine besilate and atorvastatin calcium trihydrate tablet should be administered with caution in patients with impaired liver function or history of liver disease, and in patients who consume substantial quantities of alcohol (see Section 4.4 Special Warnings and Precautions for Use, Liver Dysfunction).

Concomitant Medications

The amlodipine component of amlodipine besilate and atorvastatin calcium trihydrate tablet has been safely administered with thiazides, ACE inhibitors, beta-blockers, long acting nitrates, and/or sublingual nitroglycerin. No dose adjustment of amlodipine is required.

The atorvastatin component of amlodipine besilate and atorvastatin calcium trihydrate tablet was used concomitantly with antihypertensive agents in clinical studies without evidence of clinically significant adverse interactions. Interaction studies with all specific agents have not been conducted.

The atorvastatin component of amlodipine besilate and atorvastatin calcium trihydrate tablet may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle). For other interactions, see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions.

In cases where co-administration of atorvastatin with ciclosporin, telaprevir or the combination of tipranavir/ritonavir is necessary, the dose of atorvastatin should not exceed 10 mg.

Use of atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin.

When atorvastatin and letermovir are administered concomitantly, do not exceed 20 mg atorvastatin daily (see Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, Effects of Other Medicines on Atorvastatin, Transporter Inhibitors). Appropriate clinical assessment is recommended to ensure that the lowest dose of atorvastatin necessary is used.

Caution should be used when co-prescribing atorvastatin with medicinal compounds that result in an increase in systemic concentrations of atorvastatin, such as elbasvir/grazoprevir and simeprevir, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed (see Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.3 CONTRAINDICATIONS

Amlodipine besilate and atorvastatin calcium trihydrate tablet is contraindicated in patients with a known hypersensitivity to any component of this medication.

Amlodipine besilate and atorvastatin calcium trihydrate tablet contains atorvastatin calcium trihydrate and is, therefore, contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases (see Section 4.4 Special Warnings and Precautions for Use, Liver Dysfunction).

Amlodipine besilate and atorvastatin calcium trihydrate tablet is contraindicated during pregnancy, while breastfeeding and in women of child-bearing potential, unless on an effective contraceptive and highly unlikely to conceive (see Section 4.6 Fertility, Pregnancy and Lactation, Use in Pregnancy and Use in Lactation).

Concomitant use with fusidic acid hemihydrate is also contraindicated due to the atorvastatin component (see Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Amlodipine besilate and atorvastatin calcium trihydrate tablet is contraindicated in patients being treated with the Hepatitis C antivirals, glecaprevir/pibrentasvir.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Amlodipine besilate and atorvastatin calcium trihydrate tablet is a combination of atorvastatin, a HMG-CoA reductase inhibitor (statin) and amlodipine, a calcium channel blocker (CCB). Adverse events may result from either component of this medicine.

As amlodipine besilate and atorvastatin calcium trihydrate tablet contains amlodipine and atorvastatin the precautions applying to both these medicines are applicable and are detailed below:

Precautions Relating to the Amlodipine Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet

Increased Angina

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

Outflow Obstruction (Aortic Stenosis)

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

Use in Patients with Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

Hypotension

The use of amlodipine in patients where there is a risk of hypotension (e.g. in normotensive, small, elderly or fragile patients) is not recommended unless titration to 5 mg amlodipine has been achieved (see Section 4.2 Dose and Method of Administration).

Beta-Blocker Withdrawal

Amlodipine is not a beta-blocker and therefore provides no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Use in Hepatic Impairment

See Section 5.2 Pharmacokinetic Properties, Special Populations.

Use in Renal Impairment

See Section 5.2 Pharmacokinetic Properties, Special Populations.

Peripheral Oedema

Mild to moderate peripheral oedema was the most common adverse event in amlodipine clinical trials (see Section 4.8 Adverse Effects (Undesirable Effects)). The incidence of peripheral oedema was dose dependent and ranged in frequency from 3.0% to 10.8% in the 5 mg to 10 mg dose range. Care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.

Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet**Liver Dysfunction**

Amlodipine besilate and atorvastatin calcium trihydrate tablet should be administered with caution in patients with impaired liver function. Following therapy with other lipid-lowering agents of the same class as atorvastatin, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported.

Persistent increases in serum transaminases >3 x ULN occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6% and 2.3% for 10 mg, 20 mg, 40 mg 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 function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in alanine transaminase (ALT) or aspartate transaminase (AST) of >3 x ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin 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 atorvastatin (see Section 4.3 Contraindications).

Skeletal Muscle

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see Sections 4.8 Adverse Effects (Undesirable Effects)). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine kinase (CK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of CK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis is increased with concurrent administration of drugs that increase the systemic concentration of atorvastatin (see Section 4.2 Dose and Method of Administration, and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs (i.e.: ciclosporin), colchicine, azole antifungals, human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors (e.g. telaprevir, boceprevir), HCV non-structural protein

5A (NS5A)/5B (NS5B) inhibitors, letermovir or the combination of tipranavir/ritonavir, 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 weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. When atorvastatin and letermovir are administered concomitantly, do not exceed 20 mg atorvastatin daily (see Section 4.2 Dose and Method of Administration, Concomitant Medications and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, Effects of Other Medicines on Atorvastatin, Transporter Inhibitors). Appropriate clinical assessment is recommended to ensure that the lowest dose of atorvastatin necessary is used. Lower starting and maintenance doses of atorvastatin component should also be considered when taken concomitantly with the other aforementioned drugs (see Section 4.2 Dose and Method of Administration, Concomitant Medications).

There have been reports of rhabdomyolysis (including some fatalities) in patients receiving concomitant fusidic acid hemihydrate and statins (see Section 4.3 Contraindications and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). In patients where the use of systemic fusidic acid hemihydrate is considered essential, statin treatment should be discontinued throughout the duration of the fusidic acid hemihydrate treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid hemihydrate.

Periodic creatine kinase (CK) determinations may be considered in such situations, although there is no assurance that such monitoring will prevent the occurrence of severe myopathy (see Section 4.4 Special Warnings and Precautions for Use, Effects on Laboratory Tests).

As with other drugs in this class, rhabdomyolysis with acute renal failure has 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. Atorvastatin 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).

Immune Mediated Necrotizing Myopathy

There have been rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatinine kinase, which persists despite discontinuation of statin treatment.

Haemorrhagic Stroke

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or transient ischaemic attack (TIA), showed a higher incidence of haemorrhagic stroke in patients on atorvastatin 80 mg (55/2365, 2.3%) compared to placebo (33/2366, 1.4%), ($p=0.02$). Throughout the study, all-cause mortality was numerically higher in the atorvastatin arm than the placebo arm. At study end all-cause mortality was 9.1% on atorvastatin vs. 8.9% on placebo.

The increased risk of haemorrhagic stroke was observed in patients who entered the study with prior haemorrhagic stroke (15.6% for atorvastatin vs. 4.2% for placebo, hazard ratio [HR] 4.06; 95% CI 0.84-19.57) or prior lacunar infarct (2.8% for atorvastatin vs. 0.6% for placebo, HR 4.99; 95% CI 1.71-14.61). All-cause mortality was also increased in these patients with prior haemorrhagic stroke (15.6% for atorvastatin vs. 10.4% for placebo) or prior lacunar infarct (10.9% for atorvastatin vs. 9.1% for placebo). The potential risk of haemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1 to 6 months) stroke or TIA.

In 68% of patients who entered the study with neither a haemorrhagic stroke nor lacunar infarct, the risk of haemorrhagic stroke on atorvastatin vs. placebo was 2% vs. 1.8 % (large vessel), 1.7% vs. 1.6 % (TIA), 1.6% vs. 1.7 % (unknown cause).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically may blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration nor impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary gonadal axis in pre-menopausal women are unknown. Caution should be exercised if a HMG-CoA reductase inhibitor is administered concomitantly with other drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone and cimetidine.

Increases in glycated haemoglobin (HbA1c) and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Effect on Ubiquinone Levels (COQ₁₀)

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term, statin-induced deficiency of ubiquinone has not been established.

Effect on Lipoprotein (a)

Like other HMG-CoA reductase inhibitors, atorvastatin has variable effects on lipoprotein(a) (Lp(a)). It is unclear whether the beneficial effects of lowering LDL-C and total cholesterol in some patients may be blunted by raised Lp(a) levels.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see Section 4.8 Adverse Effects (Undesirable Effects)). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Use in the Elderly

Amlodipine

In elderly patients (≥ 65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials, the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (< 65 years). Adverse events include oedema, muscle cramps and dizziness. Amlodipine should be used with caution in the elderly.

Atorvastatin

The safety and efficacy of atorvastatin in patients ≥ 70 years of age were similar to those of patients < 70 years of age.

Paediatric Use

There have been no studies conducted on the safety and efficacy of amlodipine besilate and atorvastatin calcium trihydrate tablet in paediatric populations.

Effects on Laboratory Tests

The atorvastatin component of amlodipine besilate and atorvastatin calcium trihydrate tablet can cause elevations in ALT/AST, alkaline phosphatase, GGT, bilirubin and creatine kinase.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There have been two studies (one single and one multiple dose) to examine possible pharmacokinetic interaction between amlodipine and atorvastatin in healthy volunteers.

The single dose study was a randomised, open-label, 3 treatment, 3 period, crossover study in 27 healthy male volunteers (only 24 could be evaluated due to drop-out of 3 subjects). Study treatments included atorvastatin 80 mg alone, amlodipine 10 mg alone, or both treatments co-administered, with a 2 week washout period between each dose. In this study, the geometric mean of the atorvastatin AUC was 18% greater when amlodipine was co-administered; however, this was not accompanied by any statistically significant increase in C_{max} . An analysis using an estimation approach based on the point estimate and the 90% confidence interval indicated no clinically significant pharmacokinetic interaction.

The multiple-dose study was a randomised, open-label, crossover study in 16 healthy male volunteers. Study treatments included atorvastatin 80 mg alone, amlodipine 10 mg alone, or both treatments co-administered, with a 2-week washout period between each 7 day dosing period. In this study, the geometric mean AUC of atorvastatin was 16% greater when amlodipine was co-administered. Also in this study, an analysis using an estimation approach based on the point estimate and the 95% confidence interval failed to show a clinically significant pharmacokinetic interaction.

Medicines affected by or affecting the individual components are outlined below followed by those where no interaction has been observed with either amlodipine or atorvastatin and other medicines.

Atorvastatin

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 depend on the variability of effect on cytochrome P450 3A4. Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have also been noted with HIV protease inhibitors (fosamprenavir and combinations of lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir), hepatitis C (HCV) protease inhibitors (boceprevir, elbasvir/grazoprevir, simeprevir), HCV NS5A/NS5B inhibitors, clarithromycin, itraconazole and letermovir. Based on experience with other HMG-CoA reductase inhibitors, caution should be exercised when atorvastatin is administered with inhibitors of cytochrome P450 3A4 (e.g. ciclosporin, macrolide antibiotics including erythromycin and azole antifungals including itraconazole). The risk of myopathy during treatment with other HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, erythromycin, azole antifungals or niacin (see Section 4.2 Dose and Method of Administration, Concomitant Medications and Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle).

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampicin, phenytoin) 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 on atorvastatin plasma concentrations.

Fusidic Acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid hemihydrate with statins. Co-administration of this combination may cause increased

plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown.

Although interaction studies with atorvastatin and fusidic acid hemihydrate have not been conducted, there have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid hemihydrate is necessary, statin treatment should be discontinued throughout the duration of the fusidic acid hemihydrate treatment (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle).

Colchicine

Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine (see Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle).

Effects of Other Medicines on Atorvastatin

The following drugs have been shown to have an effect on the pharmacokinetics or pharmacodynamics of atorvastatin:

Antacid: Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides with atorvastatin decreased atorvastatin plasma concentrations by approximately 35%; however, LDL-C reduction was not altered.

Colestipol: Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

Transporter Inhibitors: Atorvastatin is a substrate of the hepatic transporters (See section 5.2 Pharmacokinetic properties).

Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin. Ciclosporin is an inhibitor of organic anion-transporting polypeptide 1B1 (OATP1B1), OATP1B3, multi-drug resistance protein 1 (MDR1), and breast cancer resistance protein (BCRP) as well as CYP3A4, thus it increases exposure to atorvastatin. Do not exceed 10 mg atorvastatin daily (see Section 4.2 Dose and Method of Administration, Concomitant Medications).

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Co-administration of atorvastatin with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3 Contraindications).

Concomitant administration of atorvastatin (20 mg single dose) and letermovir (480 mg once daily) for 10 days resulted in an increase in exposure to atorvastatin (ratio of AUC: 3.29; ratio of C_{max} : 2.17). The ratio of AUC or C_{max} is calculated by dividing the AUC or C_{max} of co-administered letermovir plus atorvastatin by that of atorvastatin alone, respectively. Letermovir inhibits efflux transporters P-gp, BCRP, MRP2, OAT2 and hepatic transporter OATP1B1/1B3, thus it increases exposure to atorvastatin. Do not exceed 20 mg atorvastatin daily (see Section 4.2 Dose and Method of Administration, Concomitant Medications).

The magnitude of CYP3A- and OATP1B1/1B3-mediated drug interactions on co-administered drugs may be different when letermovir is co-administered with ciclosporin. Use of atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin.

Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary (see Section 4.2 Dose and Method of Administration, Concomitant Medications).

Erythromycin/Clarithromycin: In healthy individuals, co-administration of atorvastatin (10 mg once-daily) and erythromycin (500 mg four times a day), or clarithromycin (500 mg twice-daily), known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin (see Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle).

Protease Inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin (see Section 4.4 Special Warnings and Precautions for Use, Precautions Relating to the Atorvastatin Component of Amlodipine Besilate and Atorvastatin Calcium Trihydrate Tablet, Skeletal Muscle).

Diltiazem Hydrochloride: Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin.

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

Grapefruit Juice: Contains one or more components that inhibit cytochrome P450 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L per day).

Effects of Atorvastatin on Other Medicines

The following medicines have been shown to have their pharmacokinetics or pharmacodynamics affected by atorvastatin.

Digoxin: When multiple doses of digoxin (0.25 mg once-daily) and 10 mg of atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, steady-state plasma digoxin concentrations increased by approximately 20% following administration of digoxin with 80 mg of atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives: Co-administration of atorvastatin with an oral contraceptive containing norethisterone and ethinylestradiol increased AUC values for norethisterone and ethinylestradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Medicines Shown Not to Interact with Atorvastatin

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

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

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

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

Amlodipine

Amlodipine has been safely administered with thiazide diuretics, beta-blockers, ACE inhibitors, long acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycaemic drugs.

Special studies have indicated that the co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers, that coadministration of cimetidine did not alter the pharmacokinetics of amlodipine; and that coadministration with warfarin did not change the warfarin prothrombin response time.

In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indometacin).

Grapefruit Juice: Grapefruit juice is known to inhibit the cytochrome P450 system in the gastrointestinal mucosa, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

CYP3A4 Inhibitors: With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients, the plasma concentration of amlodipine was increased. The clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution when administered with CYP3A4 inhibitors.

Clarithromycin: Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

CYP3A4 Inducers: There are no data available regarding the effect of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum (St John's Wort)) may decrease the plasma concentration of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers.

Aluminium/Magnesium (Antacid): 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 16 patients 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.

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

Ciclosporin: No drug 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 co-administration of amlodipine with ciclosporin affects the trough concentrations of ciclosporin, and consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors: mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. Concomitant use of mTOR inhibitors and amlodipine may increase exposure of mTOR inhibitors.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The potential effect of the amlodipine/atorvastatin combination on fertility has not been evaluated in animal studies.

Amlodipine

There was no effect on fertility of rats treated with amlodipine at oral doses up to 18 mg/kg/day.

Atorvastatin

The effects of atorvastatin on spermatogenesis and human fertility have not been investigated in clinical studies. Dietary administration of 100 mg atorvastatin/kg/day to rats caused a decrease in spermatid concentration in the testes, a decrease in sperm motility and an increase in sperm abnormalities. Similar effects, however, were not observed in male rats dosed by gavage to 175 mg/kg/day (plasma AUC for HMG-CoA reductase inhibitory activity 14 times higher than in humans dosed at 80 mg/day) and male fertility was not affected in either study. No adverse events on fertility or reproduction were observed in female rats given doses up to 225 mg/kg/day (plasma AUC for enzyme inhibitory activity 56 times higher than in humans dosed at 80 mg/day). Atorvastatin caused no adverse events on sperm or semen parameters or on reproductive organ histopathology in dogs given doses of 10 mg/kg/day, 40 mg/kg/day, or 120 mg/kg/day for 2 years (Plasma AUC for enzyme inhibitory activity 13 times higher than in humans).

Use in Pregnancy

Pregnancy Category: D

The definition of Pregnancy Category D is drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Amlodipine besilate and atorvastatin calcium trihydrate tablet is contraindicated in pregnancy due to the atorvastatin component (see Section 4.3 Contraindications).

Atorvastatin

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary dyslipidaemia. Cholesterol and other products of cholesterol biosynthesis are essential components for foetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause foetal harm when administered to pregnant women. Amlodipine besilate and atorvastatin calcium trihydrate tablet should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the foetus (see Section 4.3 Contraindications).

Atorvastatin crosses the rat placenta and reaches a level in foetal liver equivalent to that in maternal plasma. Animal reproduction studies showed no evidence of teratogenic activity in rats or rabbits at oral doses up to 300 mg/kg/day and 100 mg/kg/day respectively. Increased post-implantation foetal loss, decreased foetal weight and increased skeletal variations were observed in rats dosed at 100 to 300 mg/kg/day and rabbits dosed at 50 to 100 mg/kg/day. In a peri/post natal study, rats dosed at 225 mg/kg/day showed an

increased incidence of stillbirths, decreases in birth weight, an increased incidence of dilated renal pelvis, increased postnatal mortality, suppression of pup growth, retardation of physical development and abnormal behavioural development; some of these effects were also observed at the non-maternotoxic dose of 100 mg/kg/day; the plasma AUC for HMG-CoA reductase inhibitory activity at the no effect dose level of 20 mg/kg/day was similar to that in humans dosed at 80 mg/day.

HMG-CoA reductase inhibitors are contraindicated in pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

In two series of 178 and 143 cases where pregnant women took HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy, serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant woman exposed to HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to HMG-CoA inhibitors is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Amlodipine

Amlodipine besilate and atorvastatin calcium trihydrate tablet contains amlodipine, a calcium channel blocker. This class of medicines carry the potential to produce foetal hypoxia associated with maternal hypotension. Amlodipine was not teratogenic in rats (18 mg/kg/day) or rabbits (10 mg/kg/day). Oral doses of amlodipine (7 mg/kg/day) given to rats at or near parturition induced a prolongation of gestation time, an increase in the number of stillbirths and a decrease in postnatal survival.

Use in Lactation

Experience in humans indicates that amlodipine is transferred into human breast milk. The median amlodipine concentration ratio of milk/plasma in 31 lactating women with pregnancy induced hypertension was 0.85 following amlodipine administration at an initial dose of 5 mg once daily which was adjusted as needed (mean daily dose and body weight adjusted daily dose: 6 mg and 98.7 mcg/kg respectively). The estimated daily dose of amlodipine in the infant via breast milk was 4.17 mcg/kg.

It is not known whether atorvastatin is excreted in human milk. In rats, plasma concentrations of atorvastatin are similar to those in milk. Because of the potential for adverse reactions in nursing infants, women taking amlodipine besilate and atorvastatin calcium trihydrate tablets should not breast-feed (see Section 4.3 Contraindications).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Amlodipine besilate and atorvastatin calcium trihydrate tablet has been evaluated in 1092 patients in double-blind, placebo-controlled studies who were treated for concomitant hypertension and dyslipidaemia. In clinical trials with amlodipine besilate and atorvastatin calcium trihydrate tablet, no adverse events peculiar to this combination have been observed.

In general, treatment with amlodipine besilate and atorvastatin calcium trihydrate tablet was well tolerated and adverse events were mild to moderate in severity. In controlled clinical trials, discontinuation of therapy due to adverse events or laboratory abnormalities was 5.1% of patients treated with the amlodipine/atorvastatin component vs 4% in the placebo-treated patients.

Adverse events reported in more than 1% of patients who took concomitant amlodipine and atorvastatin in the AVALON and RESPOND studies are provided in the table below.

Table 1: Adverse Events Reported in >1% of Patients Who Took Amlodipine + Atorvastatin (Double-Blind Phases of AVALON and RESPOND Combined) [Number (%) of Patients]				
<i>Body System</i>	Placebo	AMLO Alone	ATOR Alone	AMLO + ATOR
COSTART Preferred Term	N = 350	Any Dose N = 422	Any Dose N = 643	Any Dose N = 1092
Body as a Whole	74 (21.1)	70 (16.6)	120 (18.7)	183 (16.8)
Abdominal Pain	6 (1.7)	8 (1.9)	13 (2.0)	24 (2.2)
Accidental Injury	6 (1.7)	9 (2.1)	13 (2.0)	15 (1.4)
Allergic Reaction	1 (0.3)	5 (1.2)	2 (0.3)	3 (0.3)
Asthenia	14 (4.0)	10 (2.4)	16 (2.5)	26 (2.4)
Back Pain	11 (3.1)	8 (1.9)	12 (1.9)	16 (1.5)
Flu Syndrome	7 (2.0)	2 (0.5)	10 (1.6)	13 (1.2)
Headache	35 (10.0)	25 (5.9)	54 (8.4)	61 (5.6)
Pain	5 (1.4)	7 (1.7)	5 (0.8)	11 (1.0)
Cardiovascular	18 (5.1)	26 (6.2)	32 (5.0)	72 (6.6)
Hypertension	0	0	10 (1.6)	5 (0.5)
Palpitation	4 (1.1)	7 (1.7)	8 (1.2)	18 (1.6)
Vasodilatation	6 (1.7)	4 (0.9)	3 (0.5)	19 (1.7)
Digestive	44 (12.6)	38 (9.0)	66 (10.3)	101 (9.2)
Constipation	3 (0.9)	7 (1.7)	9 (1.4)	19 (1.7)
Diarrhoea	12 (3.4)	4 (0.9)	6 (0.9)	19 (1.7)
Dyspepsia	4 (1.1)	8 (1.9)	7 (1.1)	12 (1.1)
Flatulence	6 (1.7)	4 (0.9)	9 (1.4)	7 (0.6)
GGT Increased	0 (0.0)	1 (0.2)	6 (0.9)	16 (1.5)
Nausea	13 (3.7)	10 (2.4)	10 (1.6)	13 (1.2)
Metabolic and Nutritional	19 (5.4)	44 (10.4)	23 (3.6)	145 (13.3)
Peripheral Oedema	8 (2.3)	38 (9.0)	6 (0.9)	99 (9.1)
ALT (SGPT) Increased	0	1 (0.2)	5 (0.8)	15 (1.4)
AST (SGOT) Increased	1 (0.3)	1 (0.2)	3 (0.5)	13 (1.2)
Musculoskeletal	27 (7.7)	31 (7.3)	41 (6.4)	57 (5.2)
Arthralgia	12 (3.4)	12 (2.8)	7 (1.1)	14 (1.3)
Leg Cramps	5 (1.4)	4 (0.9)	5 (0.8)	4 (0.4)
Myalgia	7 (2.0)	8 (1.9)	13 (2.0)	24 (2.2)
Nervous	44 (12.6)	33 (7.8)	47 (7.3)	59 (5.4)
Depression	4 (1.1)	0	3 (0.5)	3 (0.3)
Dizziness	18 (5.1)	16 (3.8)	11 (1.7)	25 (2.3)
Hypesthesia	6 (1.7)	2 (0.5)	1 (0.2)	0
Insomnia	2 (0.6)	0	10 (1.6)	3 (0.3)

Paresthesia	5 (1.4)	4 (0.9)	0	5 (0.5)
Vertigo	5 (1.4)	2 (0.5)	1 (0.2)	1 (0.1)
Respiratory	46 (13.1)	40 (9.5)	50 (7.8)	94 (8.6)
Pharyngitis	5 (1.4)	1 (0.2)	4 (0.6)	10 (0.9)
Respiratory Tract Infection	22 (6.3)	24 (5.7)	29 (4.5)	58 (5.3)
Rhinitis	5 (1.4)	4 (0.9)	10 (1.6)	3 (0.3)
Skin and Appendages	14 (4.0)	12 (2.8)	13 (2.0)	46 (4.2)
Rash	4 (1.1)	5 (1.2)	6 (0.9)	19 (1.7)
Urogenital	5 (1.4)	20 (4.7)	13 (2.0)	30 (2.7)
Urinary Frequency	1 (0.3)	6 (1.4)	3 (0.5)	6 (0.5)
COSTART = Coding symbols for thesaurus of adverse reaction terms; AMLO = Amlodipine; ATOR = Atorvastatin				

The safety profile of the combination product is consistent with the adverse events previously reported for amlodipine and/or atorvastatin that are detailed below.

Amlodipine

In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1,730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total TG, total-C, HDL-C, uric acid, blood urea nitrogen or creatinine or liver function tests.

The most common adverse events are headache and oedema. The incidence (%) of side effects that occurred in a dose-related manner was as follows:

Adverse Event	2.5 mg N=275	5 mg N=296	10 mg N=268	Placebo N=520
Oedema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose-related but which were reported with an incidence greater than 1.0% in placebo controlled clinical trials include the following:

Placebo Controlled Studies

Adverse Event	Amlodipine (%) (N=1730)	Placebo (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9

Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

The following events occurred in $\leq 1\%$ but $>0.1\%$ of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: hypotension, peripheral ischaemia, syncope, tachycardia, postural dizziness, postural hypotension, angioedema.

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

Gastrointestinal: anorexia, constipation, dyspepsia*, dysphagia, diarrhoea, flatulence, vomiting, altered bowel habits, pancreatitis, gingival hyperplasia.

General: allergic reactions, asthenia*, back pain, hot flushes, malaise, pain, rigors, weight gain.

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

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

Respiratory System: dyspnoea*, epistaxis.

Skin and Appendages: alopecia, pruritus*, rash*, rash erythematous, rash maculopapular, vasculitis.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: thirst, hyperglycaemia.

Haemopoietic: purpura, leucopenia, thrombocytopenia.

Endocrine: gynaecomastia.

*These events occurred in less than 1% in placebo-controlled trials, but the incidence of these adverse events was between 1% and 2% in all multiple-dose studies.

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

As with other calcium channel blockers, the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

There have been infrequent, post-marketing reports of hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

There have been post-marketing reports of extrapyramidal disorder in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus and abnormal lipid profiles.

Atorvastatin

Atorvastatin is generally well-tolerated. Adverse events have usually been mild and transient.

Clinical Adverse Events

In the atorvastatin placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin; 7,311 placebo), 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.

The most frequent ($\geq 1\%$) adverse effects associated with atorvastatin therapy reported, in patients participating in placebo-controlled clinical studies include

Gastrointestinal disorders: dyspepsia, nausea, flatulence, diarrhoea

Infections and infestations: nasopharyngitis

Investigations: liver function test abnormal¹, blood creatine phosphokinase increased

Metabolism and nutrition disorders: hyperglycaemia

Musculoskeletal and connective tissue disorders: myalgia, arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, joint swelling

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis

Additional Adverse Events

The following have been reported in clinical trials of atorvastatin, however, not all the events listed have been causally associated with atorvastatin therapy.

Common ($\geq 1\%$ and $< 10\%$)

Gastrointestinal disorders: constipation

Infections and infestations: urinary tract infection

Nervous system disorders: headache

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Ear and labyrinth disorders: deafness

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal discomfort, abdominal pain, vomiting

General disorders and administration site conditions: asthenia, malaise

Infections and infestations: infection, influenza

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: back pain, neck pain

Nervous system disorders: paraesthesia

Psychiatric disorders: insomnia, nightmare

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: asthma

¹ Refers to the following preferred terms: hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, liver function test abnormal and transaminases increased.

Skin and subcutaneous tissue disorders: rash, pruritus, urticaria

Rare ($\geq 0.01\%$ and $< 0.1\%$)

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: pancreatitis, eructation

General disorders and administration site conditions: pyrexia

Hepatobiliary disorders: hepatitis, cholestasis

Immune system disorders: hypersensitivity (including anaphylaxis)

Infections and infestations: sinusitis, pharyngitis

Injury, poisoning and procedural complications: injury

Investigations: white blood cells urine positive

Metabolism and nutrition disorders: hypoglycaemia

Musculoskeletal and connective tissue disorders: myositis, myopathy, muscle fatigue

Nervous system disorders: peripheral neuropathy

Skin and subcutaneous tissue disorders: angioedema, alopecia

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed an increased risk of haemorrhagic stroke in patients with prior haemorrhagic stroke or prior lacunar infarct (see Section 4.4 Special Warnings and Precautions for Use).

In ASCOT (see Section 5.1 Pharmacodynamic Properties, Clinical trials, Prevention of Cardiovascular Disease) involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow up.

Post-Marketing Experience

Rare adverse events that have been reported post-marketing which are not listed above, regardless of causality, include the following:

Blood and lymphatic system disorders: thrombocytopenia

General disorders and administration site conditions: chest pain, fatigue, peripheral oedema

Hepatobiliary disorders: hepatic failure

Injury, poisoning and procedural complications: tendon rupture

Investigations: weight increased

Musculoskeletal and connective tissue disorders: lupus-like syndrome, muscle rupture, immune-mediated necrotising myopathy, rhabdomyolysis which may be fatal² (see Section 4.3 Contraindications, Section 4.4 Special Warnings and Precautions for Use and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions)

Nervous system disorders: hypoaesthesia, dizziness, amnesia, dysgeusia

Reproductive system and breast disorders: gynaecomastia

² examples of signs and symptoms are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure and cardiac arrhythmia

Skin and subcutaneous tissue disorders: bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis)

The following adverse events have been reported with some statins: Exceptional cases of interstitial lung disease, especially with long term therapy (see **Section 4.4 Special Warnings and Precautions for Use**).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

There is no information on overdoses with amlodipine besilate and atorvastatin calcium trihydrate tablet.

Available data suggest that amlodipine besilate and atorvastatin calcium trihydrate tablet overdose, due to its CCB component, might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonist. Hypotension and bradycardia are usually seen within 1 to 5 hours following amlodipine overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to 7 days. Marked and probably prolonged systemic hypotension, up to and including shock with fatal outcome, have been reported.

Treatment

If massive amlodipine besilate and atorvastatin calcium trihydrate tablet overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support, including elevation of the extremities, and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors should be considered with attention to circulating volume and urine output. Intravenous calcium may help to reverse the effects of calcium entry blockade. In symptomatic patients, monitor serum creatinine, BUN, creatinine kinase, urine myoglobin for indications of renal impairment secondary to rhabdomyolysis and liver function tests.

If there has been significant ingestion, consider administration of activated charcoal. Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecac-emesis is not recommended since haemodynamic instability and CNS depression may rapidly develop. As both amlodipine and atorvastatin are highly protein bound, dialysis is not likely to be of benefit. For atorvastatin induced rhabdomyolysis, administer sufficient 0.9% saline to maintain urine output of 2 to 3 mL/kg/hr. Diuretics may be necessary to maintain urine output. Urinary alkalisation is not routinely recommended.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Amlodipine besilate and atorvastatin calcium trihydrate tablet has a dual mechanism of action consisting of the dihydropyridine calcium ion antagonist, amlodipine and the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor, atorvastatin.

Studies have been conducted in which placebo, amlodipine alone, atorvastatin alone, and the eight dose combinations of amlodipine and atorvastatin have been administered once-daily, in patients with comorbid hyperlipidaemia and hypertension. Analyses of changes in systolic blood pressure demonstrated that there was no overall modification of amlodipine's effect on systolic blood pressure when the drug was taken in combination with atorvastatin compared to amlodipine alone. Analyses of changes in low density lipoprotein cholesterol (LDL-C) demonstrated that there was no overall modification of atorvastatin's effect on LDL-C when the drug was taken in combination with amlodipine compared with atorvastatin alone (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

Antihypertensive/Anti-anginal Action of Amlodipine

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionised compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterised by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces the total ischaemic burden by the following two actions:

1. 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.
2. Amlodipine has been shown to block constriction in main coronary arteries and coronary arterioles, induced by calcium, potassium, adrenaline, serotonin and thromboxane A₂ analogue both in normal and in ischaemic regions.

Haemodynamics

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreased arterial blood pressure and increased heart rate in haemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once-daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.

The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation, thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

The Dyslipidaemic Action of Atorvastatin

Atorvastatin is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. Low density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a marked and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

A variety of clinical and pathologic studies have demonstrated that elevated cholesterol and lipoprotein levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

The atorvastatin component reduces total-C, LDL-C, and apo B in both healthy volunteers and in patients with homozygous and heterozygous forms of familial hypercholesterolaemia (FH), non-familial forms of hypercholesterolaemia, and mixed dyslipidaemia. Atorvastatin also reduces very low density lipoprotein cholesterol (VLDL-C) and TG and produces variable increases in HDL-C and apolipoprotein A1 (apo A1). Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B and TG, and increases HDL-C in patients with isolated hypertriglyceridaemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinaemia. In animal models, atorvastatin limits the development of lipid-enriched atherosclerotic lesions and promotes the regression of pre-established atheroma.

Atorvastatin and its metabolites are responsible for pharmacological activity in humans. The liver is its primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dose rather

than systemic drug concentration correlates better with LDL-C reduction. Individualisation of drug dose should be based on therapeutic response (see Section 4.2 Dose and Method of Administration).

Clinical Trials

Amlodipine/Atorvastatin Combination

Studies in Patients with Hypertension and Dyslipidaemia

In the RESPOND double-blind, placebo-controlled study, a total of 1,660 patients with comorbid hypertension and dyslipidaemia received once-daily treatment with eight dose combinations of amlodipine and atorvastatin (5 mg/10 mg, 10 mg/10 mg, 5 mg/20 mg, 10 mg/20 mg, 5 mg/40 mg, 10 mg/40 mg, 5 mg/80 mg, 10 mg/80 mg), amlodipine alone (5 mg and 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, 80 mg) or placebo. At 8 weeks, all eight combination treatment groups of amlodipine and atorvastatin demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP and LDL-C (Table 2).

Table 2: Primary Efficacy Analysis: Efficacy of the Combined Treatments in Reducing SBP and LDL-C						
Efficacy of the Combined Treatments in Reducing SBP						
Parameter/Analysis		Placebo	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
Placebo	LS mean change mmHg	-2.9	-4.3	-6.1	-6.2	-6.6
AML 5 mg	LS mean change mmHg	-12.6	-13.6	-15.3	-12.8	-12.6
	95% CIs		-12.3/-6.3	-12.2/-6.2	-9.7/-3.6	-9.0/-3.0
AML 10 mg	LS mean change mmHg	-16.5	-15.9	-16.0	-16.5	-17.5
	95% CIs		-14.6/-8.5	-12.9/-6.8	-13.3/-7.2	-14.0/-7.9
Efficacy of the Combined Treatments in Reducing LDL-C						
Parameter/Analysis		Placebo	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
Placebo	LS mean change mmHg	-1.2	-33.5	-39.5	-43.1	-47.0
AML 5 mg	LS mean change mmHg	-0.1	-39.0	-42.2	-44.9	-48.2
	95% CIs		-42.9/-34.9	-46.2/-38.2	-48.8/-40.8	-52.2/-44.2
AML 10 mg	LS mean change mmHg	-2.6	-36.6	-38.6	-43.2	-49.2
	95% CIs		-38.1/-30.0	-40.0/-32.0	-44.6/-36.7	-50.6/-42.6
ATO: Atorvastatin, AML: Amlodipine, LDL-C: Low density lipoprotein cholesterol, SBP: Systolic Blood Pressure Comparisons described above were between each individual combination treatment group and the corresponding amlodipine treatment group. BASELINE LDL-C= 4.70 mmol/L (182.0 mg/dL) SBP=148.4 mmHg						

In the AVALON double blind, placebo-controlled study, a total of 847 patients with comorbid hypertension and dyslipidaemia received once-daily placebo, 5 mg amlodipine, 10 mg of atorvastatin or

the combination of 5 mg amlodipine and 10 mg atorvastatin. The primary objective of the study was the percentage of patients on the combination of amlodipine and atorvastatin reaching JNC VI and NCEP III goals compared to atorvastatin, amlodipine and placebo alone. The results following 8 weeks of treatment are summarised in Table 3. Significantly more patients treated with the combination (45.5%) reached both their blood pressure (BP) and LDL-C goals compared to amlodipine or atorvastatin alone. Amlodipine besilate and atorvastatin calcium trihydrate tablet was not studied in patients with decompensated chronic cardiac failure or post myocardial infarction (within 3 to 6 months).

Table 3: Results of Efficacy End Points in AVALON, a Placebo-Controlled Study of Amlodipine/Atorvastatin in Patients with Hypertension and Dyslipidaemia				
	Placebo N=239	ATO 10 mg N=200	AML 5 mg N=201	ATO 10 mg & AML 5 mg N=207
JNC VI* B P Goals	29.7%	32.3%	54%	51% [†]
NCEP ATP III LDL-C Goals	6.6%	78.2%	12.4%	82.1% ^{**}
Both JNC VI and NCEP ATP III* Goals	3.5%	28.6%	8.3%	45.5% ^{*†}
Change in BP mmHg	-5.4/-3.3	-5.9/-4.2	-14.3/ -8.9	-12.7/ -8.2 ⁺
Change in LDL- C -%	+0.2	-33.9	-1.8	-37.2 ^a
ATO: Atorvastatin, AML: Amlodipine, LDL-C: Low density lipoprotein cholesterol, BP: Blood Pressure **P<0.001 vs amlodipine, †P<0.001 vs atorvastatin, +p< 0.001 vs. atorvastatin and NS vs .amlodipine, ap=0.07 vs. atorvastatin & <0.001 vs. amlodipine Baseline LDL-C = 4.23 mmol/L (163.5 mg/dL), SBP = 146.9 mmHg *BP goals in JNC VII for this population are consistent with JNC VI BP goals				

Amlodipine Component

Studies in Patients with Congestive Heart Failure

Amlodipine has been compared to placebo in four 8 to 12 week studies of male and female patients with New York Heart Association (NYHA) class II-IV heart failure, involving a total of 697 patients. Primary endpoints for these studies were: Symptom Limiting Exercise Time, Pulmonary Capillary Wedge Pressure (PCWP) and Cardiac Index (CI). Secondary endpoints varied from study to study and included Functional Status (NYHA classification), Cardiopulmonary Exam (including symptomatic status), Left Ventricular Ejection Fraction (LVEF), and Gas Exchange Measurement.

Although efficacy in regard to the primary and secondary endpoints was not demonstrated, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Table 4: Results of Primary Endpoints in Placebo-Controlled Studies of Amlodipine in Patients with NYHA Class II-IV Heart Failure								
	Pulmonary Capillary Wedge Pressure (mmHg)			Cardiac Index (L/min/m ²)				
Study 053-176	Change from baseline	Change from baseline	Change from baseline	Change from baseline	Change from baseline	Change from baseline	Change from baseline	
	5 mg Aml-Pbo (n=40)	10 mg Aml-Pbo (n=36)	Aml-Pbo (n=40)	5 mg Aml-Pbo (n=40)	10 mg Aml-Pbo (n=36)	Aml-Pbo (n=40)		
Acute	0.69	0.87	0.78	0.09	0.18	0.13		
Chronic	0.09	0.70	0.39	0.18	0.27	0.22		
Study		Amlodipine			Placebo			P value
		Baseline	Final	Change	Baseline	Final	Change	
053-121 (n = 50 Active; 54 Pbo)	Exercise time (sec)	522	NR	73.7	571	NR	17.3	NR
053-174 (n = 91 Active; 95 Pbo)	Exercise time (sec)	495.0	552.2	57.2	514.7	562.9	48.2	0.497
053-175 (n = 111 Active; 117 Pbo)	Exercise time (sec)	508.2	552.8	44.6	501.4	559.9	58.4	0.716
Aml: amlodipine, Pbo: placebo								

In a long term (follow up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine 5 to 10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin and angiotensin-converting enzyme (ACE) inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life threatening arrhythmia, acute myocardial infarction, or hospitalisation for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo: the cardiac morbid events represented about 25% of the endpoints in the study.

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

Electrophysiologic Effects

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg of amlodipine and a further 10 mg of amlodipine after a 30 minute interval produced peripheral vasodilation and afterload reduction, but did not significantly alter A-H and H-V conduction and sinus node recovery time after

pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse events on electrocardiographic parameters were observed.

In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Effects in Hypertension

In patients with hypertension once-daily dosing provides clinically significant reductions in blood pressure in both the supine and standing positions throughout the 24-hour interval post dose. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. The blood pressure effect is maintained over the 24-hour dosing interval, with little difference in peak and trough effect. Tolerance has not been demonstrated in patients studied for up to 1 year. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure.

Effects in Chronic Stable Angina

In patients with angina, once-daily administration of amlodipine increases total exercise time to angina onset and total work time to 1 mm ST segment depression and decreases both angina attack frequency and nitroglycerine tablet consumption. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Other

In clinical trials amlodipine has shown no harmful effect on lipid levels. Dihydropyridine calcium channel blockers have not been associated with any adverse metabolic effects and are suitable for use in patients with asthma, diabetes and gout.

Atorvastatin Component

In a multicentre, placebo-controlled, double-blind dose response study in patients with hypercholesterolaemia, atorvastatin was given as a single daily dose over 6 weeks. Atorvastatin (10 mg-80 mg) reduced total-C (30%-46%), LDL-C (41%-61%), apo B (34%-50%) and TG (14%-33%) while producing variable increases in HDL-C and apolipoprotein A (Table 5). A therapeutic response was seen within 2 weeks, and maximum response achieved within 4 weeks.

Atorvastatin	N	Total-C	LDL-C	Apo B	TG	HDL-C
Dose (mg)						
Placebo	12	4.8	7.6	5.8	-0.7	-2.5
10	11	-30.3	-41.0	-34.4	-14.2	4.5
20	10	-34.5	-44.3	-36.3	-33.2	12.1
40	11	-37.8	-49.7	-40.9	-24.9	-2.6
80	11	-45.7	-61.0	-50.3	-27.2	3.4

^aAdjusted mean % change from baseline

In three further trials, 1,148 patients with either heterozygous familial hypercholesterolaemia, non-familial forms of hypercholesterolaemia, or mixed dyslipidaemia were treated with atorvastatin for one year. The

results were consistent with those of the dose response study and were maintained for the duration of therapy.

In patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb), data pooled from 24 controlled trials demonstrated that the adjusted mean percent increases from baseline in HDL-C for atorvastatin (10-80 mg) were 5.0% to 7.8% in a non-dose related manner.

Clinical studies demonstrate that a dose of 10 mg atorvastatin is more effective than simvastatin 10 mg and pravastatin 20 mg in reducing LDL-C, total-C, TG and apo B. In several multicentre, double-blind studies in patients with hypercholesterolaemia, atorvastatin was compared to other HMG-CoA reductase inhibitors. After randomisation, patients were treated with atorvastatin 10 mg per day or the recommended starting dose of the comparative agent. At week 16 a greater proportion of atorvastatin treated patients than those treated with simvastatin (46% vs. 27%) or pravastatin (65% vs. 19%) reached their target LDL-C levels. Increasing the dosage of atorvastatin resulted in more patients reaching target LDL-C goals.

Prevention of Cardiovascular Disease

In the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium trihydrate on the composite endpoint of fatal coronary heart disease and non-fatal myocardial infarction (MI) was assessed in 10,305 hypertensive patients, 40 to 79 years of age, without a history of symptomatic coronary heart disease and with total-C levels ≤ 6.5 mmol/L. Additionally, all patients were at moderate risk of coronary heart disease, having at least 3 of the predefined cardiovascular risk factors [male gender (81%), age ≥ 55 years (84%), smoking (33%), non insulin dependent diabetes mellitus (25%), history of CHD in a first-degree relative (26%), plasma total-C to HDL-C ratio ≥ 6 (14%), peripheral vascular disease (5%), left ventricular hypertrophy on echocardiography (14%), past history of cerebrovascular event (10%), specific ECG abnormality (14%), proteinuria/albuminuria (62%)]. Patients with a history of previous myocardial infarction or angina were excluded.

In this randomised, double-blind, placebo-controlled study, patients were treated with antihypertensive therapy (goal BP $< 140/90$ mmHg for non-diabetic patients, $< 130/80$ mmHg for diabetic patients) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137) and followed for a median duration of 3.3 years. At baseline, in the atorvastatin group, 38 patients (0.7%) had total-C levels less than 3.5 mmol/L; 2,340 patients (45.3%) had total-C levels greater than or equal to 3.5 mmol/L and less than 5.5 mmol/L; 2,304 patients (44.6%) had total-C levels greater than or equal to 5.5 mmol/L and less than 6.5 mmol/L; and 486 patients (9.4%) had total-C levels greater than or equal to 6.5 mmol/L. At baseline, 457 patients (9.8%) in the atorvastatin group had LDL-C levels less than or equal to 2.5 mmol/L; 1,731 patients (37%) had LDL-C levels greater than 2.5 mmol/L and less than 3.4 mmol/L; and 2,495 patients (53.3%) had LDL-C levels greater than or equal to 3.4 mmol/L. Median (25th & 75th percentile) changes from baseline after 1 year of atorvastatin treatment in total-C, LDL-C, TG and HDL-C were -1.40 mmol/L ($-1.80, -0.90$), -1.27 mmol/L ($-1.66, -0.84$), -0.20 mmol/L ($-0.60, 0.10$) and 0.00 mmol/L ($-0.10, 0.10$). Blood pressure control throughout the trial was similar in patients assigned to atorvastatin and placebo.

Table 6: Summary of Risk Reductions in Primary Prevention Patients						
Endpoint	Atorvastatin 10 mg N (%)	Placebo N (%)	Absolute Risk Reduction^a % (95% CI)	Number Needed to Treat Per Year	Relative Risk Reduction % (95% CI)	P Value
Primary						
Fatal CHD and Non-fatal MI	100 (1.9)	154 (3.0)	1.07 (0.47 to 1.67)	310.5	36 (17 to 50)	0.0005

Secondary						
Total Cardiovascular Events Including Revascularisation Procedures	389 (7.6)	483 (9.5)	1.9 (0.80 to 2.96)	176.0	20 (9 to 30)	0.0008
Total Coronary Events	178 (3.5)	247 (4.8)	1.4 (0.60 to 2.14)	241.9	29 (14 to 41)	0.0006
Fatal and Non-fatal Stroke ^b	89 (1.7)	119 (2.3)	0.6 (0.05 to 1.14)	555.2	26 (2 to 44)	0.0332
Non-fatal MI (excluding Silent MI) and Fatal CHD	86 (1.7)	137 (2.7)	1.0 (0.42 to 1.56)	329.1	38 (19 to 53)	0.0005
^a Based on difference in crude events rates occurring over a median follow-up of 3.3 years.						
^b Although the reduction of fatal and non-fatal strokes did not reach a predefined significance level (p=0.01), a favourable trend was observed with a 26% relative risk reduction.						

The primary endpoint examined in ASCOT was the rate of fatal coronary heart disease or non-fatal myocardial infarction over 3.3 years. These coronary events occurred in 1.9% of atorvastatin treated patients compared to 3% of placebo-treated patients, a relative risk reduction of 36% (p = 0.0005) (Table 6). Although this difference was statistically significant for the whole trial population, this difference was not statistically significant in specified subgroups such as diabetes, patients with left ventricular hypertrophy (LVH), previous vascular disease or metabolic syndrome.

There was no statistically significant reduction in the rate of total mortality, cardiovascular mortality or heart failure in the atorvastatin treated group compared to placebo.

Non Insulin Dependent Diabetes Mellitus (NIDDM)

A 26-week randomised, double-blind, comparator study in NIDDM subjects showed that atorvastatin is effective in dyslipidaemic patients with NIDDM. A 10 mg dose of atorvastatin produced a 34% reduction in LDL-C, a 27% reduction in total-C, a 24% reduction in TG and a 12% rise in HDL-C.

Homozygous Familial Hypercholesterolaemia

Atorvastatin has also been shown to reduce LDL-C in patients with homozygous familial hypercholesterolaemia (FH), a population that has not usually responded to other lipid lowering medication. In an uncontrolled compassionate use study, 29 patients aged 6 to 37 years with homozygous FH received maximum daily doses of 20 mg to 80 mg of atorvastatin. The mean LDL reduction in this study was 18%. Twenty five patients with a reduction in LDL-C had a mean response of 20% (range 7%-53%, median 24%). 5 of the 29 patients had absent LDL receptor function, 3 of whom responded to atorvastatin with a mean LDL-C reduction of 22%. Experience in paediatric patients has been limited to patients with homozygous FH.

Hypertriglyceridaemia

In patients with hypertriglyceridaemia (baseline TG \geq 2.26 mmol/L and LDL-C $<$ 4.14 mmol/L) atorvastatin (10 to 80 mg) reduced serum TG by 31% to 40%. In patients with severe hypertriglyceridaemia (baseline TG $>$ 5.7 mmol/L), atorvastatin (10 to 80 mg) reduced serum TG by 30% to 56%.

In a randomised, placebo controlled, double blind, multicentre study in patients with hypertriglyceridaemia (TG \geq 3.95 mmol/L, LDL-C \leq 4.1 mmol/L), atorvastatin 20 mg/day and 80 mg/day produced significantly greater reductions in TG levels than placebo (Table 7).

Atorvastatin Dose (mg)	N	TG	Total-C	LDL-C	VLDL-C	Apo B	HDL-C
Placebo	12	-5.3	+0.3	+1.4	-2.0	+2.7	+2.4
20	13	-33.6*	-33.1*	-31.1*	-46.0*	-32.7*	+10.6
80	11	-42.4*	-41.3*	-36.1*	-54.2*	-38.7*	+11.8*

^a Adjusted mean % change from baseline
* significantly different from placebo, p<0.05

Dysbetalipoproteinaemia

In patients with dysbetalipoproteinaemia, atorvastatin (10 to 80 mg) reduced IDL-C (range 28% to 52%) and IDL-C + VLDL-C (range 34% to 58%).

In an open-label, randomised, crossover study in patients with dysbetalipoproteinaemia, treatment with atorvastatin 80 mg/day resulted in significantly greater mean percent decreases in IDL-C + VLDL-C, IDL-C, total-C, VLDL-C and Apo B than either simvastatin 40 mg/day or gemfibrozil 1200 mg/day and significantly greater mean percent decreases in TG than simvastatin 40 mg/day (Table 8).

Treatment	N	IDL-C + VLDL-C	IDL-C	Total-C	TG	VLDL-C	Apo B	HDL-C
Atorvastatin 10 mg/day	15	-34	-28	-40	-40	-32	-47	+3
Atorvastatin 80 mg/day	16	-58	-50	-57	-56	-59	-66	+13
Gemfibrozil 1200 mg/day	15	-33*	-13 ⁺	-34*	-52 ⁺	-35*	-53*	+11
Simvastatin 40 mg/day	16	-28*	-27*	-41*	-36*	-26*	-52*	+1*

^a Adjusted mean % change from baseline
^b Comparisons other than atorvastatin 80 mg/day vs simvastatin 40 mg/day were ad hoc
*significantly different from atorvastatin 80 mg/day, p<0.05
+ significantly different from atorvastatin 10 mg/day, p<0.05

5.2 PHARMACOKINETIC PROPERTIES

Amlodipine besilate and atorvastatin calcium trihydrate tablet

Following oral administration of amlodipine besilate and atorvastatin calcium trihydrate tablet, peak plasma concentrations are observed within 1 to 2 hours for atorvastatin and between 6 and 12 hours for amlodipine. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from amlodipine besilate and atorvastatin calcium trihydrate tablet are not significantly different from the bioavailability of amlodipine and atorvastatin from coadministration of amlodipine and atorvastatin tablets as assessed by C_{max} and AUC for the amlodipine component and C_{max} and AUC for the atorvastatin component in healthy volunteers.

The bioavailability of amlodipine from amlodipine besilate and atorvastatin calcium trihydrate tablet was not affected by food as assessed by C_{max}: 105% (90% CI: 99%-111%) and AUC: 101% (90% CI: 97%-105%). Although food decreases the rate and extent of absorption of atorvastatin from amlodipine besilate and atorvastatin calcium trihydrate tablet by approximately 32% and 11% respectively, as assessed by C_{max}: 68% (90% CI 60%-79%) and AUC: 89% (90% CI: 83%-95%), similar reductions in plasma concentrations in the fed state have been seen with atorvastatin without a reduction in LDL-C effect.

Co-administration of multiple 10 mg doses of amlodipine with 80 mg atorvastatin in healthy subjects resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin compared to when the two drugs were given independently. The individual pharmacokinetic profile of amlodipine and atorvastatin are outlined below:

Amlodipine

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 and 12 hours post-dose. This may reflect significant initial uptake by the liver, followed by a phase of redistribution. This interval is shorter (2 to 8 hours) in patients with hepatic insufficiency. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Distribution

The volume of distribution is approximately 20 L/kg. 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 to 8 days of consecutive dosing in healthy volunteers.

Metabolism and Excretion

Amlodipine is extensively metabolised by the liver to inactive metabolites, with 10% of the parent compound and 60% of metabolites excreted in the urine.

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Atorvastatin

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. A constant proportion of atorvastatin is absorbed intact. The absolute bioavailability is 14%. The low systemic availability is attributed to pre-systemic 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 C_{max} and AUC) following evening drug administration compared to morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see Section 4.2 Dose and Method of Administration).

Distribution

The mean volume of distribution of atorvastatin is about 400 L. Atorvastatin is $\geq 98\%$ bound to plasma proteins. A red blood cell /plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see Section 4.6 Fertility, Pregnancy and Lactation, Use in Lactation).

Metabolism

In humans, atorvastatin is extensively metabolised to ortho- and para-hydroxylated derivatives. *In vitro* inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-

administration with erythromycin, a known inhibitor of this isozyme (see Section 4.4 Special Warnings and Precautions for Use). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

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

Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special Populations

No studies have been conducted with amlodipine besilate and atorvastatin calcium trihydrate tablet in special populations. Information is provided below on the individual components of amlodipine besilate and atorvastatin calcium trihydrate tablet.

Elderly (≥ 65 years)

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

Atorvastatin: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥ 65 years) than in young adults. Lipid effects are comparable to that seen in younger patient populations given equal doses of atorvastatin.

Gender

Atorvastatin: Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men; however, there is no clinically significant difference in lipid effects with atorvastatin between men and women.

Renal Impairment

Amlodipine: Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses. Amlodipine is not dialysable.

Atorvastatin: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary. While studies have not been conducted in patients with end stage renal disease, haemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Impairment

See Sections 4.2 Dose and Method of Administration, 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There are no genotoxicity or carcinogenicity studies with the amlodipine/atorvastatin combination.

Amlodipine

Amlodipine did not induce gene mutation in bacteria and mouse lymphoma cells; nor did it induce chromosome aberrations in human lymphocytes or Chinese hamster V79 fibroblast cells (*in vitro*) and in mouse bone marrow cells (*in vivo*).

Atorvastatin

Atorvastatin did not demonstrate mutagenic or clastogenic potential in an appropriate battery of assays. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* hypoxanthine-guanine phosphoribosyltransferase (HGPRT) forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test.

Carcinogenicity

There are no carcinogenicity studies with amlodipine/ atorvastatin combination.

Amlodipine

The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in mice or rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to or below those achieved clinically.

Atorvastatin

In a 2-year study in rats given 10 mg/kg/day, 30 mg/kg/day or 100 mg/kg/day, the incidence of hepatocellular adenoma was marginally, although not significantly, increased in females at 100 mg/kg/day. The maximum dose used was 11 times higher than the highest human dose (80 mg/day) based on AUC (0-24) values. In a 2-year study in mice given 100 mg/kg, 200 mg/kg or 400 mg/kg, incidences of hepatocellular adenoma in males and hepatocellular carcinoma in females were increased at 400 mg/kg/day. The maximum dose used was 14 times higher than the highest human dose (80 mg/day) based on AUC (0-24) values. Other HMG-CoA reductase inhibitors have been reported to induce hepatocellular tumours in mice and rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

In addition to the active ingredients amlodipine besilate and atorvastatin calcium trihydrate, each Cadivast tablet contains the following inactive ingredients:

- colloidal anhydrous silica
- sodium carbonate
- microcrystalline cellulose
- arginine
- pregelatinised maize starch
- croscarmellose sodium
- hypolose
- magnesium stearate

- Opadry AMB white OY-B-28920 (ARTG no. 4271) [5 mg/ 10 mg, 5 mg/20 mg, 5 mg/40 mg and 5 mg/80 mg]
- Opadry AMB blue 80W10932 (ARTG no. 106951) [10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg]

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

- Cadivast 5/10 tablets** : Available in [OPA/Al/PVC or PVC/Aclar] blister packs of 10 or 30 tablets and HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.
- Cadivast 5/20 tablets** : Available in [OPA/Al/PVC or PVC/Aclar] blister packs of 10 or 30 tablets and HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.
- Cadivast 5/40 tablets** : Available in [OPA/Al/PVC or PVC/Aclar] blister packs of 10 or 30 tablets and HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.
- Cadivast 5/80 tablets** : HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.
- Cadivast 10/10 tablets** : Available in [OPA/Al/PVC or PVC/Aclar] blister packs of 10 or 30 tablets and HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.
- Cadivast 10/20 tablets** : Available in [OPA/Al/PVC or PVC/Aclar] blister packs of 10 or 30 tablets and HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.
- Cadivast 10/40 tablets** : Available in [OPA/Al/PVC or PVC/Aclar] blister packs of 10 or 30 tablets and HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.
- Cadivast 10/80 tablets** : HDPE bottles of 30 or 90 tablets. HDPE bottles of 500 tablets for dispensing only. Not for individual patient supply.

Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

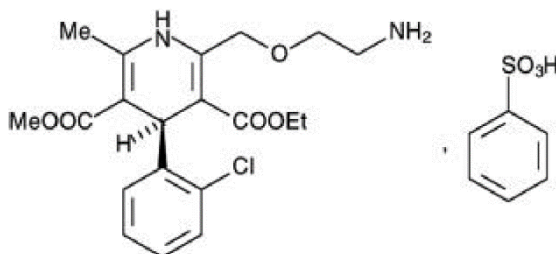
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Amlodipine

Chemical Structure

Structural formula :



Chemical name : 3-ethyl, 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene sulfonate

Molecular formula : $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

Molecular weight : 567.1

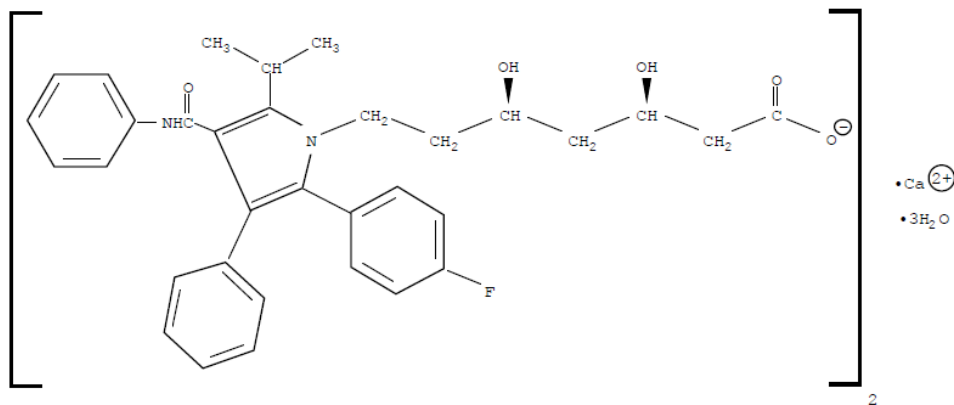
CAS Number

CAS registry no. : 111470-99-6

Atorvastatin calcium trihydrate

Chemical Structure

Structural formula :



Chemical name : (3*R*, 5*R*)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate calcium trihydrate

Molecular formula : $C_{66}H_{68}CaF_2N_4O_{10} \cdot 3H_2O$

Molecular weight : 1209.39

CAS Number

CAS registry no. : 344423-98-9

Amlodipine besilate is white or almost white powder. Atorvastatin calcium trihydrate is white or almost white powder. Amlodipine besilate is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol. Atorvastatin calcium trihydrate slightly soluble in water, slightly soluble in ethanol (96%), and practically insoluble in methylene chloride.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd

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30 – 34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

09/01/2014

10 DATE OF REVISION

10/05/2021

Summary Table of Changes

Section Changed	Summary of New Information
4.2, 4.4, 4.5	Updated with additional information on drug interaction with letermovir
4.4, 4.5	Safety update on skeletal muscle effects for drug interaction with HCV NS5A/NS5B inhibitors
4.4, 4.5, 5.3, 8	Editorial changes

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