CADUET
(Amlodipine besilate/Atorvastatin calcium)

1. NAME OF THE MEDICINAL PRODUCT

CADUET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: amlodipine besilate, atorvastatin calcium.

The tablets for oral administration contain amlodipine besilate and atorvastatin calcium equivalent to 5 mg/10 mg, 5 mg/20 mg, amlodipine/atorvastatin dosage strengths, respectively.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

The amlodipine/atorvastatin combination product (henceforth in this document termed "amlodipine/atorvastatin") is indicated for the following patient populations:

1. Patients at increased cardiovascular risk due to the presence of the two modifiable risk factors hypertension and dyslipidemia; and/or

2. Patients at increased cardiovascular risk due to the presence of symptomatic Coronary Heart Disease (CHD) expressed as angina with the additional modifiable risk factor of dyslipidemia; and/or

3. Prevention of cardiovascular complications in hypertensive patients (see below - *Prevention of Cardiovascular Complications*).

In these patients with multiple cardiovascular risk factors, amlodipine/atorvastatin is indicated for:

Hypertension[1]

The amlodipine component is indicated for the first-line treatment of hypertension and can be used as the sole agent to control blood pressure (BP) in the majority of patients. Patients not adequately controlled on a single antihypertensive agent (other than amlodipine) may benefit from the addition of the amlodipine component of amlodipine/atorvastatin, in the same manner as they would benefit from the addition of amlodipine alone.

Amlodipine is also indicated to reduce the risk of fatal CHD and non-fatal myocardial infarction (MI), and to reduce the risk of stroke.

Coronary Artery Disease[1]

The amlodipine component is indicated to reduce the risk of coronary revascularization procedures and the need for hospitalization due to angina in patients with coronary artery disease (CAD).[2]

Chronic Stable Angina[1]

The amlodipine component is indicated for the first-line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. Amlodipine/atorvastatin may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine/atorvastatin may be used alone or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.

Dyslipidemia[2]

The atorvastatin component is indicated as an adjunct to diet for the treatment of patients with elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial hypercholesterolemia), combined (mixed) hyperlipidemia (*Fredrickson* Types IIa and IIb), elevated serum TG levels (*Fredrickson* Type IV), and in patients with dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet.

The atorvastatin component is also indicated for the reduction of total C and LDL-C in patients with homozygous familial hypercholesterolemia (FH).

Prevention of Cardiovascular Complications

In patients without clinically evident cardiovascular disease (CVD), and with or without dyslipidemia, but with multiple risk factors for CHD such as smoking, hypertension, diabetes, low HDL-C, or a family history of early CHD, atorvastatin is indicated to:

- Reduce the risk of fatal CHD and non-fatal MI
- Reduce the risk of stroke
- Reduce the risk of revascularization procedures and angina pectoris

In patients with clinically evident CHD, atorvastatin is indicated to:

- Reduce the risk of non-fatal MI
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for congestive heart failure (CHF)
- Reduce the risk of angina

Pediatric Patients (10-17 years of age)

Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous FH if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥190 mg/dL or

b. LDL-C remains ≥160 mg/dL and

- There is a positive family history of premature CVD or
- Two or more other CVD risk factors are present in the pediatric patient.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

General Considerations[1,2]

Amlodipine/atorvastatin is a combination product targeting concomitant cardiovascular conditions, hypertension/angina and dyslipidemia.

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

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

Following initiation and/or titration of amlodipine/atorvastatin, lipid levels should be analyzed and BP measured within 2 to 4 weeks, and dosage of amlodipine and atorvastatin components should be adjusted accordingly. Titration for BP response may proceed more rapidly if clinically warranted.

Initial Therapy[1,2]

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

Substitution Therapy[1,2]

Amlodipine/atorvastatin may be substituted for its individually titrated components. Patients may be given the equivalent dose of amlodipine/atorvastatin or a dose of amlodipine/atorvastatin with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, BP lowering, or lipid-lowering effect.

Amlodipine/atorvastatin may be used to provide additional therapy for patients already on one of its components. As initial therapy for one indication and continuation of treatment of the other, the

recommended starting dose of amlodipine/atorvastatin should be selected based on continuation of the component being used previously and on the recommended starting dose for the component being added.

Concomitant Medication (See also **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction)**

The amlodipine component of amlodipine/atorvastatin has been safely co-administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, long-acting nitrates, and with sublingual nitroglycerine.[1] Amlodipine/atorvastatin has also been safely administered with the aforementioned medicines.[3]

The atorvastatin component of amlodipine/atorvastatin may be used in combination with a bile acid-binding resin for additive effect on lipid lowering.[2] The combination of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrates should generally be avoided[2] (see **section 4.4. Special Warnings and Precautions for Use** and **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**).

Special Populations and Special Considerations for Dosing

Coronary Artery Disease (Amlodipine Studies)[1]

For patients with CAD, the recommended dosage range is 5 mg to 10 mg of amlodipine once daily. In clinical studies, the majority of patients required 10 mg once daily (see **section 5.1. Pharmacodynamic Properties - Amlodipine/Atorvastatin Pharmacodynamics** - Use in Patients with Coronary Artery Disease).

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia (Atorvastatin Studies)[2]

The majority of patients are controlled with 10 mg of atorvastatin once daily. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Homozygous Familial Hypercholesterolemia (Atorvastatin Studies)[2]

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

Use in Patients with Impaired Hepatic Function[1,2]

Amlodipine/atorvastatin should not be used in patients with hepatic impairment (see **section 4.3. Contraindications** and **section 4.4. Special Warnings and Precautions for Use)**.

Use in Patients with Impaired Renal Function[2]

No adjustment of the dose is required in patients with impaired renal function (see **section 4.4. Special Warnings and Precautions for Use**).

Use in the Elderly

No adjustment of the dose is required in elderly patients.

Use in Children

There have been no studies conducted to determine the safety or effectiveness of amlodipine/atorvastatin (combination product) in pediatric populations. However, there have been studies in pediatric populations with amlodipine alone and atorvastatin alone (see below).

Studies with amlodipine[1]

The recommended antihypertensive oral dose in pediatric patients aged 6 to 17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients (see **section 5.1. Pharmacodynamic Properties** and **section 5.2. Pharmacokinetic Properties**).

The effect of amlodipine on BP in patients less than 6 years of age is not known.

Studies with atorvastatin[2]

Use in Pediatric Patients with Severe Dyslipidemias[13,14,31]

For patients aged 10 years and above, the recommended starting dose is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy (see **section 4.1. Therapeutic Indications** and **section 5.1. Pharmacodynamic Properties**). Adjustments should be made at intervals of 4 weeks or more.

Experience in pediatric patients younger than 10 years of age is derived from open-label studies (see **section 4.8. Undesirable Effects**, **section 5.1. Pharmacodynamic Properties**, and **section 5.2. Pharmacokinetic Properties - Special Populations**).

Use in Combination with Other Medicinal Compounds

Studies with atorvastatin[2]

In cases where co-administration of atorvastatin with cyclosporine, telaprevir[24], the combination tipranavir/ritonavir[24], or glecaprevir/pibrentasvir[40] is necessary, the dose of atorvastatin should not exceed 10 mg.

Use of atorvastatin is not recommended in patients taking letermovir co-administered with cyclosporine.[41]

Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have also been noted with other human immunodeficiency virus (HIV) protease inhibitors (lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir, fosamprenavir/ritonavir and nelfinavir), hepatitis C (HCV) protease inhibitors (boceprevir[26], elbasvir/grazoprevir[40], simeprevir[40]), clarithromycin, itraconazole, and letermovir[41]. Caution should be used when co-prescribing atorvastatin, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed[26] (see **section 4.4. Special Warnings and Precautions for Use – Skeletal Muscle Effects** and **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction).**

4.3. CONTRAINDICATIONS

Amlodipine/atorvastatin is contraindicated in patients who:

1. Have known hypersensitivity to dihydropyridines,* amlodipine, atorvastatin, or any component of this medication,

2. Have active liver disease or unexplained persistent elevations of serum transaminases >3 × the upper limit of normal [ULN],

3. Are pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. Amlodipine/atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.

* Amlodipine is a dihydropyridine calcium channel blocker.[25]

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in Patients with Heart Failure[1]

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine-treated patients with New York Heart Association (NYHA) class III-IV heart failure of nonischemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see **section 5.1. Pharmacodynamic Properties**).

Use in Patients with Impaired Hepatic Function (See also **section 4.3. Contraindications)**

Hepatic Effects[2]

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

Persistent increases in serum transaminases (>3 × ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10 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 any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve(s). Should an increase in alanine transaminase (ALT) or aspartate transaminase (AST) >3 × ULN persist, reduction of dose or withdrawal of amlodipine/atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases (see **section 4.8. Undesirable Effects**).

Amlodipine/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 amlodipine/atorvastatin (see **section 4.3. Contraindications**).

Skeletal Muscle Effects[2]

Myalgia has been reported in atorvastatin-treated patients (see **section 4.8. Undesirable Effects**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 × ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Amlodipine/atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy is increased with concurrent administration of drugs that increase the systemic concentration of atorvastatin (see **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction** and **section 5.2 Pharmacokinetic Properties**).[24,26,40] Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug transport. CYP3A4 is the primary hepatic isozyme known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, HIV/HCV protease inhibitors, HCV NS5A/NS5B inhibitors[42], letermovir[41], or lipid-modifying 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. Therefore, lower starting and maintenance doses of the atorvastatin component should also be considered when taken concomitantly with the aforementioned drugs. (see **section 4.2. Posology and Method of Administration**). The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin is advised during fusidic acid therapy (see **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**). Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Amlodipine/atorvastatin may cause an elevation of CPK due to the atorvastatin component (see **section 4.8. Undesirable Effects**).

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins (see **section 4.8. Undesirable Effects**). IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, positive anti-HMG CoA reductase antibody and improvement with immunosuppressive agents.[43]

As with other drugs in the class of HMG-CoA reductase inhibitors, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.[19] Amlodipine/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). Control of hypertension may be continued with the appropriate dose of amlodipine.

Hemorrhagic Stroke[2]

A post-hoc analysis of a clinical study in 4731 patients without CHD who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and were initiated on atorvastatin 80 mg revealed a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo (55 atorvastatin vs. 33 placebo). Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo). However, in patients treated with atorvastatin 80 mg there were fewer strokes of any type (265 atorvastatin vs. 311 placebo) and fewer CHD events (123 atorvastatin vs. 204 placebo) (see **section 5.1. Pharmacodynamic Properties – Recurrent Stroke**).

Endocrine Function

Increases in glycated haemoglobin (HbA1c) and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.[24]

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are co-administered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the C_{max}: 91% (90% confidence interval [CI]: 80% -103%), but the AUC of atorvastatin increased by 18% (90% CI: 109% -127%) in the presence of amlodipine.[4]

No drug interaction studies have been conducted with amlodipine/atorvastatin and other drugs, although studies have been conducted using the individual amlodipine and atorvastatin components, as described below:

Amlodipine Interactions[1]

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

CYP3A4 Inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg of amlodipine in elderly hypertensive patients (69-87 years of age) resulted in a 57% increase in amlodipine systemic exposure.[22] Erythromycin co-administration in healthy volunteers (18-43 years of age) did not significantly change amlodipine systemic exposure (22% increase in AUC).[21] Although the clinical relevance of these findings is uncertain, the pharmacokinetic variations may be more pronounced in the elderly.

Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors.[25]

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.[28]

CYP3A4 Inducers

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

Grapefruit Juice

Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased BP-lowering effects.[23,25]

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 indomethacin).

In the following studies, there were no significant changes in the pharmacokinetics of either amlodipine or another drug within the study, when co-administered.

Special Studies: Effect of Other Agents on Amlodipine[1]

Cimetidine

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

Aluminum/Magnesium (antacid)

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

Sildenafil

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

Special Studies: Effect of Amlodipine on Other Agents.

Digoxin

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

Ethanol (alcohol)

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

Warfarin

Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients. Various studies in renal transplant patients report that amlodipine co-administration with cyclosporine affect trough concentrations of cyclosporine from no change up to an average increase of 40%. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine.[27]

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.[28]

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.[38]

Drug/Laboratory Test Interactions

None known.

Atorvastatin Interactions[2]

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4/transporter inhibitors[40] (e.g., erythromycin and azole antifungals). (see below and also **section 4.2. Posology and Method of Administration – Use in Combination with Other Medicinal Compounds** and **section 4.4. Special Warnings and Precautions for Use– Skeletal Muscle Effects**).

Inhibitors of Cytochrome P450 3A4

Atorvastatin is metabolized 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.

Erythromycin/Clarithromycin

Co-administration of atorvastatin and erythromycin (500 mg four times daily) or clarithromycin (500 mg twice daily), known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin (see **section 4.4. Special Warnings and Precautions for Use – Skeletal Muscle Effects** and **section 5.2. Pharmacokinetic Properties**).

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 5.2. Pharmacokinetic Properties**).

Diltiazem Hydrochloride

Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin (see **section 5.2. Pharmacokinetic Properties**).

Cimetidine

An atorvastatin interaction study with cimetidine was conducted, and no clinically significant interactions were seen (see **section 5.2. Pharmacokinetic Properties**).

Itraconazole

Concomitant administration of atorvastatin (20-40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC (see **section 5.2. Pharmacokinetic Properties**).

Grapefruit Juice

Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L/day) (see **section 5.2. Pharmacokinetic Properties**).

Transporter Inhibitors[40]

Atorvastatin is a substrate of the hepatic transporters (see **section 5.2. Pharmacokinetic Properties**).

Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of AUC: 8.7; see **section 5.2. Pharmacokinetic Properties**). Cyclosporine 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. Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Do not exceed 10 mg atorvastatin daily (see **section 4.2. Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).

Concomitant administration of atorvastatin 20 mg and letermovir 480 mg daily resulted in an increase in exposure to atorvastatin (ratio of AUC: 3.29; see **section 5.2 Pharmacokinetic Properties**). 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. Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).[41]

The magnitude of CYP3A- and OATP1B1/1B3-mediated drug interactions on co-administered drugs may be different when letermovir is co-administered with cyclosporine. Use of atorvastatin is not recommended in patients taking letermovir co-administered with cyclosporine.[41]

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. Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).

Inducers of Cytochrome P450 3A4

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations (see **section 5.2. Pharmacokinetic Properties**).

Antacids

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides decreased atorvastatin plasma concentrations (ratio of AUC: 0.66); however, LDL-C reduction was not altered.

Antipyrine

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

Colestipol

Plasma concentrations of atorvastatin were lower (ratio of concentration: 0.74) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

Digoxin

When multiple doses of digoxin and 10 mg of atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased (ratio of AUC: 1.15) following administration of digoxin with 80 mg of atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Azithromycin

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

Oral Contraceptives

Co-administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyl estradiol increased the area under the concentration versus time curve (AUC) values for norethindrone (ratio of AUC: 1.28) and ethinyl estradiol (ratio of AUC: 1.19), respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin

An atorvastatin interaction study with warfarin was conducted, and no clinically significant interactions were observed.

***Fusidic Acid*[12,30]**

Although interaction studies with atorvastatin and fusidic acid have not been conducted, there is an increased risk of rhabdomyolysis in patients receiving a combination of statins, including atorvastatin, and fusidic acid. The mechanism of this interaction is not known. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

***Colchicine*[24]**

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.

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 specific agents have not been conducted.

4.6. FERTILITY, PREGNANCY AND LACTATION

Amlodipine/atorvastatin is contraindicated in pregnancy due to the atorvastatin component.[2] Women of childbearing potential should use adequate contraceptive measures.[2]

Amlodipine/atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.[2]

Amlodipine/atorvastatin is contraindicated while breast-feeding due to the atorvastatin component.[2] It is not known whether atorvastatin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking amlodipine/atorvastatin should not breast-feed.[1,2]

Safety of amlodipine in human pregnancy or lactation has not been established.[1] Amlodipine did not demonstrate toxicity in animal reproductive studies other than to delay parturition and prolong labor in rats at a dose level 50 times the maximum recommended dose in humans.[1] There was no effect on the fertility of rats treated with amlodipine (see **section** – **5.3. Preclinical Safety Data**).

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.[33]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on the available information on amlodipine and atorvastatin, this medication is unlikely to impair a patient's ability to drive or use machinery.

4.8. UNDESIRABLE EFFECTS

Combination therapy with amlodipine and atorvastatin has been evaluated for safety in 1092 patients in double-blind, placebo-controlled studies treated for concomitant hypertension and dyslipidemia. In clinical trials, no adverse events peculiar to combination therapy with amlodipine and atorvastatin have been observed. Adverse events have been limited to those that were reported previously with amlodipine and/or atorvastatin (please see respective adverse event experiences below).[5,6]

In general, combination therapy with amlodipine and atorvastatin was well tolerated. For the most part, adverse events have been mild or moderate in severity. In controlled clinical trials, discontinuation of therapy due to adverse events or laboratory abnormalities was required in 5.1% of patients treated with both amlodipine and atorvastatin compared to 4.0% of patients given placebo.[7]

The following information is based on clinical trials and post-marketing experience with amlodipine and atorvastatin.[1,2]

Amlodipine Experience[1]

Amlodipine is well tolerated. In placebo-controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were:

MedDRA System Organ Class	**Undesirable Effects**
Nervous System Disorders	Headache, dizziness, somnolence
Cardiac Disorders	Palpitations
Vascular Disorders	Flushing
Gastrointestinal Disorders	Abdominal pain, nausea
General Disorders and Administration Site Conditions	Oedema, fatigue

In these clinical trials, no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed.

Less commonly observed side effects in marketing experience with amlodipine include:

MedDRA System Organ Class	**Undesirable Effects**
Blood and Lymphatic System Disorders	Leucopenia, thrombocytopenia
Metabolism and Nutrition Disorders	Hyperglycaemia
Psychiatric Disorders	Insomnia, mood altered
Nervous System Disorders	Hypertonia, hypoaesthesia/paraesthesia, neuropathy peripheral, syncope, dysgeusia, tremor, extrapyramidal disorder[28]
Eye Disorders	Visual impairment
Ear and Labyrinth Disorders	Tinnitus
Vascular Disorders	Hypotension, vasculitis
Respiratory, Thoracic, and Mediastinal Disorders	Cough, dyspnoea, rhinitis
Gastrointestinal Disorders	Change in bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
Skin and Subcutaneous Tissue Disorders	Alopecia, hyperhidrosis, purpura, skin discolouration, urticaria
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle spasms, myalgia
Renal and Urinary Disorders	Pollakiuria, micturition disorder, nocturia

Reproductive System and Breast Disorders	Gynaecomastia, erectile dysfunction
General Disorders and Administration Site Conditions	Asthenia, malaise, pain
Investigations	Weight increased/decreased

Rarely reported events were allergic reactions including pruritus, rash, angioedema, and erythema multiforme.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

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: MI, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

Pediatric Patients (Aged 6-17 years)

Amlodipine is well tolerated in children. Adverse events were similar to those seen in adults. In a study of 268 children, the most frequently reported adverse events were:

MedDRA System Organ Class	**Undesirable Effects**
Nervous System Disorders	Headache, dizziness
Vascular Disorders	Vasodilatation
Respiratory, Thoracic, and Mediastinal Disorders	Epistaxis
Gastrointestinal Disorders	Abdominal pain
General Disorders and Administration Site Conditions	Asthenia

The majority of adverse events were mild or moderate. Severe adverse events (predominantly headache) were experienced by 7.2% with amlodipine 2.5 mg, 4.5% with amlodipine 5 mg, and 4.6% with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant change in heart rate.

Atorvastatin Experience[2]

Atorvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.[20]

The most frequent (≥1%) adverse effects that may be associated with atorvastatin therapy, reported in patients participating in placebo-controlled clinical studies include:

Infections and infestations: nasopharyngitis

Metabolism and nutrition disorders: hyperglycaemia

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis

Gastrointestinal disorders: diarrhoea, dyspepsia, nausea, flatulence

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

Investigations: liver function test abnormal, blood creatine phosphokinase increased

Additional adverse effects reported in atorvastatin placebo-controlled clinical trials include:

Psychiatric disorders: nightmare

Eye disorders: vision blurred

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: abdominal discomfort, eructation

Hepatobiliary disorders: hepatitis, cholestasis

Skin and subcutaneous tissue disorders: urticaria

Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain

General disorders and administration site conditions: malaise, pyrexia

Investigations: white blood cells urine positive

Not all effects listed above have been causally associated with atorvastatin therapy.

Pediatric Patients

Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections.[13]

No clinically significant effect on growth and sexual maturation was observed in a 3-year study in children ages 6 and above based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in pediatric patients was similar to the known safety profile of atorvastatin in adult patients.

Post-marketing Experience

In post-marketing experience, the following additional undesirable effects have been reported with atorvastatin:

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: allergic reactions (including anaphylaxis)

Injury, poisoning and procedural complications: tendon rupture

Metabolism and nutrition disorders: weight gain

Nervous system disorders: hypoesthesia, amnesia, dizziness, dysgeusia

Gastrointestinal disorders: pancreatitis[24]

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema,[29] erythema multiforme, bullous rashes

Musculoskeletal and connective tissue disorders: rhabdomyolysis, immune-mediated necrotising myopathy,[26] myositis,[29] back pain

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

4.9. OVERDOSE

There is no information on overdosage with amlodipine/atorvastatin in humans.

Due to amlodipine's and atorvastatin's extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance amlodipine/atorvastatin clearance[1,2] (see also **section 5.2. Pharmacokinetic Properties – Renal Insufficiency**).

Additional data on amlodipine ingestion[1] suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. 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. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and BP, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

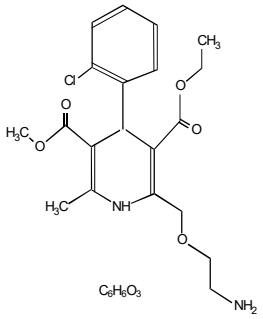
Additional data on atorvastatin ingestion[2] suggest that there is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required.

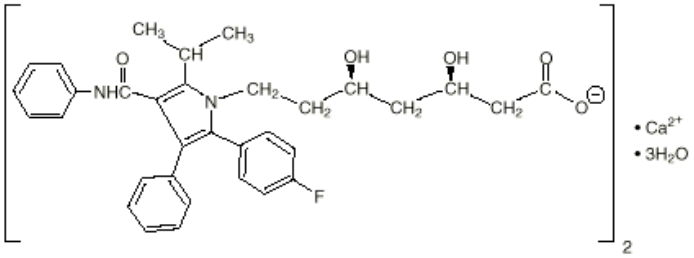
5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Amlodipine/Atorvastatin Pharmacodynamics[1,2]

The amlodipine besilate component of amlodipine/atorvastatin is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedi-carboxylate benzenesulfonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$. The atorvastatin calcium component of amlodipine/atorvastatin is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$. The structural formulae are shown below:





Amlodipine besilate Atorvastatin calcium

<u>Mechanism of Amlodipine/Atorvastatin</u>[1,2]

Amlodipine/atorvastatin combines two mechanisms of action: the dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) action of amlodipine and the HMG-CoA reductase inhibition of atorvastatin. The amlodipine component of amlodipine/atorvastatin inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of amlodipine/atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol.

<u>Clinical Studies of Combined Amlodipine and Atorvastatin in Patients with Hypertension and Dyslipidemia</u>[5,6]

In a double-blind, placebo-controlled study of 1660 patients with comorbid hypertension and dyslipidemia, once-daily treatment with eight-dose combinations of amlodipine and atorvastatin (5/10 mg, 10/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg, 5/80 mg, or 10/80 mg) was compared vs. amlodipine alone (5 mg or 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, or 80 mg), and placebo. In addition to concomitant hypertension and dyslipidemia, 15% of the patients had diabetes mellitus, 22% were smokers and 14% had a positive family history of CVD. At 8 weeks, all eight combination-treatment groups demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP and LDL-C (see table below).

Efficacy in Terms of Reduction in Blood Pressure and LDL-C

Efficacy of the Combined Treatments in Reducing Systolic BP[a]						
Parameter/Analysis		**ATO[b] 0 mg**	**ATO 10 mg**	**ATO 20 mg**	**ATO 40 mg**	**ATO 80 mg**
AML[c] 0 mg	**Mean change (mmHg)**	-3.0	-4.5	-6.2	-6.2	-6.4
	Difference vs. placebo (mmHg)	-	-1.5	-3.2	-3.2	-3.4
AML 5 mg	**Mean change (mmHg)**	-12.8	-13.7	-15.3	-12.7	-12.2
	Difference vs. placebo (mmHg)	-9.8	-10.7	-12.3	-9.7	-9.2
AML 10 mg	**Mean change (mmHg)**	-16.2	-15.9	-16.1	-16.3	-17.6

	Difference vs. placebo (mmHg)	-13.2	-12.9	-13.1	-13.3	-14.6

[a] Blood pressure.
[b] Atorvastatin.
[c] Amlodipine.

Efficacy of the Combined Treatments in Reducing Diastolic BP[a]

Parameter/Analysis		**ATO[b] 0 mg**	**ATO 10 mg**	**ATO 20 mg**	**ATO 40 mg**	**ATO 80 mg**
AML[c] 0 mg	**Mean change (mmHg)**	-3.3	-4.1	-3.9	-5.1	-4.1
	Difference vs. placebo (mmHg)	-	-0.8	-0.6	-1.8	-0.8
AML 5 mg	**Mean change (mmHg)**	-7.6	-8.2	-9.4	-7.3	-8.4
	Difference vs. placebo (mmHg)	-4.3	-4.9	-6.1	-4.0	-5.1
AML 10 mg	**Mean change (mmHg)**	-10.4	-9.1	-10.6	-9.8	-11.1
	Difference vs. placebo (mmHg)	-7.1	-5.8	-7.3	-6.5	-7.8

[a] Blood pressure.
[b] Atorvastatin.
[c] Amlodipine

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

Parameter/Analysis		**ATO[b] 0 mg**	**ATO 10 mg**	**ATO 20 mg**	**ATO 40 mg**	**ATO 80 mg**
AML[c] 0 mg						
	Mean % change	-1.1	-33.4	-39.5	-43.1	-47.2
AML 5 mg						
	Mean % change	-0.1	-38.7	-42.3	-44.9	-48.4
AML 10 mg						
	Mean % change	-2.5	-36.6	-38.6	-43.2	-49.1

[a] Low density lipoprotein cholesterol.
[b] Atorvastatin.
[c] Amlodipine

In an open-label trial, 1220 patients with comorbid hypertension and dyslipidemia received elective dose titration with amlodipine/atorvastatin over a 14-week period. Patients were required to have uncontrolled BP to enter the trial (whether or not they were using antihypertensive medications at enrollment; patients were allowed to continue on previous antihypertensives, other than calcium channel blockers, during the 14 week dose titration period) but could enter with either controlled or uncontrolled LDL-C. As a result, no patient entered the trial with both BP and LDL-C controlled, and neither was controlled in 62% of patients. Treatment with amlodipine/atorvastatin reduced mean BP –17.1 mmHg systolic and -9.6 mmHg diastolic, and reduced mean LDL-C by –32.7%, resulting in control of both BP and LDL-C for 58% of these patients (controlled BP and LDL-C were defined, respectively, as <140/90 mmHg and <160 mg/dL for patients with comorbid hypertension and dyslipidemia only; <140/90 mmHg and <130 mg/dL for patients with comorbid hypertension and dyslipidemia plus 1 additional cardiovascular risk factor, excluding known CHD or diabetes mellitus; and <130/85 mmHg and <100 mg/dL for patients with comorbid hypertension and dyslipidemia plus known CHD, diabetes mellitus, or other atherosclerotic disease). Only 13% of the patients in this trial used amlodipine/atorvastatin as initial therapy for comorbid hypertension and dyslipidemia, whereas the amlodipine component of amlodipine/atorvastatin comprised add-on therapy for hypertension in 56% of patients, including patients for whom the atorvastatin component of amlodipine/atorvastatin comprised initial therapy for dyslipidemia (20%), a substitution for atorvastatin taken previously (18%), or a switch from another statin (18%). When evaluated according to the use of antihypertensive and lipid-lowering medications at enrollment, results showed that both BP and LDL-C were brought under control for 65% of patients who used amlodipine/atorvastatin as initial therapy for comorbid hypertension and dyslipidemia and for 55% to 64% of patients for whom the amlodipine component of amlodipine/atorvastatin constituted add-on therapy for hypertension (55% for such patients who had previously used lipid-lowering medications other than atorvastatin, 58% for such patients who had previously used atorvastatin, and 64% for such patients who had not previously used lipid-lowering medications).[8]

Anglo-Scandinavian Cardiac Outcomes Trial[15,16,17]

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a randomized 2×2 factorial design study comparing two antihypertensive regimens in a total of 19,342 patients (Blood Pressure Lowering arm – ASCOT-BPLA), as well as the effect of addition of 10 mg of atorvastatin compared to placebo in 10,305 patients (Lipid-Lowering arm - ASCOT-LLA) on fatal and non-fatal coronary events. There are 19,257 and 10,240 efficacy evaluable patients in ASCOT-BPLA and ASCOT-LLA, respectively.

In Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm[15]

The effect of treatment regimens based on amlodipine (5-10 mg) (n=9681) or atenolol (50-100 mg) (n=9661) was compared in a prospective randomized open blinded endpoint (PROBE) design in 19,342 hypertensive patients, ≥40 to <80 years of age with no previous MI or treatment for angina, at least three of the following predefined cardiovascular risk factors: male gender, age ≥55 years, smoking, Type 2 diabetes, history of CAD event occurring in a first-degree relative before the age of 55 years (males) or 60 years (females), total C:HDL ≥6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific electrocardiogram (ECG) abnormalities, proteinuria/albuminuria.

To attain further BP goals (<140/90 mmHg for non-diabetic patients, <130/80 mmHg for diabetic patients), perindopril (4-8 mg) could be added to the amlodipine group and bendroflumethiazide potassium (1.25-2.5 mg) to the atenolol group. Third line therapy was doxazosin gastrointestinal therapeutic system (GITS) (4 8 mg) in both arms.

The ASCOT-BPLA study was stopped prematurely after 903 primary events (non-fatal MI and fatal CHD) with median follow-up of 5.5 years due to significant benefit of the amlodipine-based regimen on the

following secondary endpoints: all-cause mortality, cardiovascular (CV) mortality and stroke. The study had planned to need at least 1150 primary endpoints.

The primary endpoint of non-fatal MI + fatal CHD did not reach statistical significance when comparing the amlodipine-based group to the atenolol-based group. The secondary endpoints of total coronary events, all-cause mortality, fatal and non-fatal stroke were statistically significantly reduced when comparing amlodipine-based group to the atenolol-based group.

The incidence of the primary and secondary endpoints in the 19,257 efficacy evaluable patients:

Event	**Amlodipine-based Therapy N=9639 n (%)**	**Atenolol-based Therapy N=9618 n (%)**	**Risk Decrease (%)**	**Log Rank p-value**
Non-fatal MI[a] + Fatal CHD (Primary Endpoint)	429 (4.5)	474 (4.9)	10	0.105
Total CV Events and Procedures[b]	1362 (14.1)	1602 (16.7)	16	<0.001
Total Coronary Events[c]	753 (7.8)	852 (8.9)	13	0.007
Non-fatal MI (excluding silent MI) + Fatal CHD	390 (4.0)	444 (4.6)	13	0.046
All Cause Mortality	738 (7.7)	820 (8.5)	11	0.025
Cardiovascular Mortality[d]	263 (2.7)	342 (3.6)	24	<0.001
Fatal and Non-fatal Stroke	327 (3.4)	422 (4.4)	23	<0.001
Fatal and Non-fatal Heart Failure	134 (1.4)	159 (1.7)	16	0.126

[a] Myocardial infarction
[b] Cardiovascular mortality, non-fatal MI (symptomatic and silent), unstable angina, chronic stable angina, life-threatening arrhythmias, non-fatal heart failure, non-fatal stroke, transient ischemic attack (TIA), reversible ischemic neurological deficit (RIND), retinal vascular thromboses, peripheral arterial disease and revascularization procedures.
[c] Fatal CHD, non-fatal MI (symptomatic and silent), chronic stable angina, unstable angina, fatal and non-fatal heart failure.
[d] Includes RIND.

Blood pressure (SBP/DBP) decreased significantly on both treatment regimens when compared to baseline (p-values <0.001). The SBP/DBP decreases from baseline were significantly more with the amlodipine-based regimen than with the atenolol-based regimen (-27.5/-17.7 mmHg vs. -25.7/-15.6 mmHg, respectively), and the p-values on differences between the two groups were both <0.001 for SBP and DBP.

In Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm

In the ASCOT-LLA, the effect of atorvastatin on fatal and non-fatal CHD was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), without a previous MI and with TC levels <6.5 mmol/L (251 mg/dL). Additionally, all patients had at least three of the following cardiovascular risk factors: male gender, age >55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. In this 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 allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137). As the effect of atorvastatin treatment compared to placebo exceeded the significance threshold during an interim analysis, the ASCOT-LLA was terminated early at 3.3 years instead of 5 years. Additionally, BP was well

controlled and similar in patients assigned to atorvastatin and placebo. These changes persisted throughout the treatment period.

Atorvastatin reduced the rate of the following events:

Event	**Risk Decrease (%)**	**No. of Events (Atorvastatin vs. Placebo)**	**p-value**
Coronary events (fatal CHD[a] plus non-fatal MI[b])	36%	100 vs. 154	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	0.0008
Total coronary events	29%	178 vs. 247	0.0006
Fatal and non-fatal stroke*	26%	89 vs. 119	0.0332
[a] Coronary Heart Disease. [b] Myocardial infarction *Although the reduction of fatal and non-fatal strokes did not reach a predefined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction.			

The total mortality and cardiovascular mortality have not been significantly reduced, although a favorable trend was observed.

In Anglo-Scandinavian Cardiac Outcomes Trial 2×2[18]:

The pre-specified ASCOT 2×2 factorial analysis investigated the potential differential effect (interaction) of adding atorvastatin to the amlodipine vs. the atenolol group in ASCOT-LLA.

For the 10,305 patients enrolled in ASCOT-LLA, there were 5168 patients in the atorvastatin group (2584 patients received amlodipine and 2584 patients received atenolol) and 5137 in the placebo group (2554 patients received amlodipine and 2583 patients received atenolol).

The risk reductions on the composite endpoint of non-fatal MI and fatal CHD were based on the 10,240 efficacy evaluable patients.

The combination of amlodipine with atorvastatin resulted in a significant risk reduction in the composite primary endpoint of fatal CHD and non fatal MI by:

• 53% (95% CI 31%-68%, p<0.0001) compared to amlodipine + placebo,

• 39% (95% CI 8%-59%, p<0.016) compared to atenolol + atorvastatin.

The p-value for the interaction was 0.027, which was not statistically significant at the pre-specified 0.01 level.

Blood pressure (SBP/DBP) decreased significantly on all four treatment regimens when compared to baseline (p-values <0.001). The SBP/DBP decreases from baseline were significantly more with the amlodipine-based regimens than with the atenolol-based regimens (-26.5/-15.6 mmHg vs. -24.7/-13.6 mmHg for amlodipine/atorvastatin vs. atenolol/atorvastatin, and -27.1/-15.8 mmHg vs. -24.1/-13.6 mmHg for amlodipine/placebo vs. atenolol/placebo, respectively). The p-values on differences between the two groups were all <0.01 for SBP and DBP.

Amlodipine Pharmacodynamics[1]

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.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic 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. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking-induced coronary vasoconstriction.

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

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

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in Patients with CAD

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

The effectiveness of amlodipine in preventing clinical events in patients with CAD has been evaluated in an independent, multicenter, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these, 663 were treated with amlodipine 5 mg to 10 mg and 655 patients were treated with placebo, in addition to standard care of statins, beta blockers, diuretics and aspirin, for 2 years. The key efficacy results are

presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of Significant Clinical Outcomes for CAMELOT

	CAMELOT[a]		
Clinical Outcomes N (%)	**Amlodipine (N=663)**	**Placebo (N=655)**	**Risk Reduction (p-value)**
Composite CV[b] Endpoint*	110 (16.6)	151 (23.1)	31% (0.003)
Hospitalization for Angina	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization	78 (11.8)	103 (15.7)	27% (0.033)

*1). Defined in CAMELOT as cardiovascular death, non-fatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or non-fatal stroke or TIA, any diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD.
2). The composite CV endpoint was the primary efficacy endpoint in CAMELOT.
[a] Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis.
[b] Cardiovascular.

Treatment to Prevent Heart Attack Trial

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5 mg to 10 mg/day (calcium channel blocker) or lisinopril 10 mg to 40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5 to 25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including MI or stroke >6 months or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C <35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal MI. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98; 95% CI 0.90-1.07 p=0.65. In addition, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.96;95% CI 0.89-1.02; p=0.20.

Use in Patients with Heart Failure

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

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

In a follow-up, long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III -IV heart failure without clinical symptoms or objective findings suggestive of underlying ischemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Use in Pediatric Patients (Aged 6 to 17 years)

The efficacy of amlodipine in hypertensive pediatric patients 6 to 17 years of age was demonstrated in one 8-week, double-blind, placebo-controlled, randomized withdrawal trial in 268 patients with hypertension. All patients were randomized to the 2.5 mg or 5 mg treatment arms and followed for 4 weeks after which they were randomized to continue 2.5 mg or 5 mg amlodipine or placebo for an additional 4 weeks. Compared to baseline, once-daily treatment with amlodipine 5 mg resulted in statistically significant reductions in SBP and DBP. Placebo-adjusted mean reduction in seated SBP was estimated to be 5.0 mmHg for the 5 mg dose of amlodipine and 3.3 mmHg for the 2.5 mg dose of amlodipine. Subgroup analyses indicated that younger pediatric patients aged 6 to 13 years had efficacy results comparable to those of the older pediatric patients aged 14 to 17 years.

Atorvastatin Pharmacodynamics[2]

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

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

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

Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration. Individualization of drug dosage should be based on therapeutic response (see **section 4.2. Posology and Method of Administration**).

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

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

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median percent increases from baseline in HDL-C for atorvastatin (10-80 mg) were 5.1% to 8.7% in a non-dose-related manner. Additionally, analysis of this pooled data demonstrated significant dose-related decreases in total-C/HDL-C and LDL-C/HDL-C ratios, ranging from -29% to -44% and -37% to -55%, respectively.

The effects of atorvastatin on ischemic events and total mortality were studied in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study (MIRACL). This multicenter, randomized, double-blind, placebo-controlled study followed 3086 patients with acute coronary syndromes; unstable angina or non-Q wave MI. Patients were treated with standard care, including diet, and either atorvastatin 80 mg daily or placebo for a median duration of 16 weeks. The final LDL-C, total-C, HDL-C and TG levels were 72 mg/dL, 147 mg/dL, 48 mg/dL, and 139 mg/dL in the atorvastatin group, respectively, and 135 mg/dL, 217 mg/dL, 46 mg/dL, and 187 mg/dL, respectively, in the placebo group. Atorvastatin significantly reduced the risk of ischemic events and death by 16%. The risk of experiencing re-hospitalization for angina pectoris with documented evidence of myocardial ischemia was significantly reduced by 26%. Atorvastatin reduced the risk of ischemic events and death to a similar extent across the range of baseline LDL-C. In addition, atorvastatin reduced the risk of ischemic events and death to similar extents in patients with non-Q wave MI and unstable angina, as well as in males and females and in patients ≤65 years of age and >65 years of age.

Prevention of Cardiovascular Complications

The effect of atorvastatin on fatal and non-fatal CHD is discussed in this section under *Clinical Studies of Combined Amlodipine and Atorvastatin in Patients with Hypertension and Dyslipidemia, Anglo-Scandinavian Cardiac Outcomes Trial.*

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and non-fatal CVD was assessed in 2838 patients with Type 2 diabetes 40 to 75 years of age, without prior history of CVD and with LDL ≤4.14 mmol/L (160 mg/dL) and TG ≤6.78 mmol/L (600 mg/dL). Additionally, all patients had at least one of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomized, double-blind, multicenter, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years. As the effect of atorvastatin treatment on the primary endpoint reached the predefined stopping rules for efficacy, CARDS was terminated 2 years earlier than anticipated.

The absolute and relative risk reduction effect of atorvastatin is as follows:

Event	Relative Risk Reduction (%)	No. of Events (atorvastatin vs. placebo)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs. 64	0.0070

Stroke (fatal and non-fatal)	48%	21 vs. 39	0.0163

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level.

A relative risk reduction in death of 27% (82 deaths in the placebo group compared to 61 deaths in the treatment arm) has been observed with a borderline statistical significance (p=0.0592).

The overall incidence of adverse events or serious adverse events was similar between the treatment groups.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with CHD. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), the median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin, the effects of atorvastatin were statistically significant (p=0.02).

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L ± 0.8 (78.9 mg/dL ± 30) from baseline 3.89 mmol/L ± 0.7 (150 mg/dL ± 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L ± 0.7 (110 mg/dL ± 26) from baseline 3.89 mmol/L ± 0.7 (150 mg/dL ± 26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apo B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: +5.6%, p=*NS*). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

The safety and tolerability profiles of the two treatment groups were comparable.

Recurrent Stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or TIA within the preceding 6 months and no history of CHD. Patients were 60% male, 21 to 92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (hazard ratio [HR] 0.85; 95% CI 0.72-1.00; p=0.05 or HR 0.84; 95% CI 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. Atorvastatin 80 mg significantly reduced the risk of major coronary events (HR 0.67; 95% CI 0.51-0.89; p=0.006), any CHD event (HR 0.60; 95% CI 0.48-0.74; p<0.001), and revascularization procedures (HR 0.57; 95% CI 0.44-0.74; p<0.001).

In a post-hoc analysis, atorvastatin 80 mg, reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366,

1.4%, p=0.02) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between the groups (17 atorvastatin vs. 18 placebo). Reduction in the risk of cardiovascular events with atorvastatin 80 mg was demonstrated in all patient groups except in patients who entered the study with a hemorrhagic stroke and had a recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo), where the number of events was too small to discern risk or benefit.

In patients treated with atorvastatin 80 mg, there were fewer strokes of any type (265 atorvastatin vs. 311 placebo) and fewer CHD events (123 atorvastatin vs. 204 placebo). Overall mortality was similar across treatment groups (216 atorvastatin vs. 211 placebo). The overall incidence of adverse events and serious adverse events was similar between the treatment groups.

Secondary Prevention of Cardiovascular Events

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident CHD who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The mean LDL-C, TC, TG, non-HDL and HDL cholesterol levels at 12 weeks were 73 mg/dL, 145 mg/dL, 128 mg/dL, 98 mg/dL and 47 mg/dL, respectively, during treatment with 80 mg of atorvastatin and 99 mg/dL, 177 mg/dL, 152 mg/dL, 129 mg/dL and 48 mg/dL, respectively, during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%.

Atorvastatin 80 mg significantly reduced the risk of the following:

Significant Endpoint	**Atorvastatin 10 mg (N=5006)**		**Atorvastatin 80 mg (N=4995)**		**HR[a] (95% CI)**
Primary Endpoint*	n	%	N	%	
First major cardiovascular endpoint	548	10.9	434	8.7	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
Non-fatal, non-procedure related MI	308	6.2	243	4.9	0.78 (0.66, 0.93)
Stroke (fatal and non-fatal)	155	3.1	117	2.3	0.75 (0.59, 0.96)
Secondary Endpoints**					
First CHF with hospitalization	164	3.3	122	2.4	0.74 (0.59, 0.94)
First CABG or other coronary revascularization procedure[b]	904	18.1	667	13.4	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	12.3	545	10.9	0.88 (0.79, 0.99)

[a] Atorvastatin 80 mg: atorvastatin 10 mg.
[b] Component of other secondary endpoints.
* MCVE = death due to CHD, non-fatal MI, resuscitated cardiac arrest, and fatal and non-fatal stroke.

** secondary endpoints not included in primary endpoint.
HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; CHF = congestive heart failure; CABG = coronary artery bypass graft.
Confidence intervals for the secondary endpoints were not adjusted for multiple comparisons.

There was no significant difference between the treatment groups for all-cause mortality: 282 (5.6%) in the atorvastatin 10 mg/day group vs. 284 (5.7%) in the atorvastatin 80 mg/day group. The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke were numerically smaller in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with simvastatin 20 mg/day to 40 mg/day in 8888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL and non-HDL cholesterol levels at Week 12 were 78 mg/dL, 145 mg/dL, 115 mg/dL, 45 mg/dL and 100 mg/dL, respectively, during treatment with 80 mg of atorvastatin and 105 mg/dL, 179 mg/dL, 142 mg/dL, 47 mg/dL and 132 mg/dL, respectively, during treatment with 20 mg to 40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin 80 mg/day group vs. 463 (10.4%) in the simvastatin 20 mg to 40 mg/day group, HR 0.89; 95% CI 0.78,1.01; p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin 80 mg/day group vs. 374 (8.4%) in the simvastatin 20 mg to 40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin 80 mg group and the simvastatin 20 mg to 40 mg group.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients[14,31]

The following pediatric-exclusive studies have been completed with atorvastatin.

In an-open label, single-arm study, 271 male and female Heterozygous Familial Hypercholesterolemia (HeFH) children 6-15 years of age were enrolled and treated with atorvastatin for up to 3 years. Inclusion in the study required confirmed HeFH and a baseline LDL-C level ≥4 mmol/L (approximately 152 mg/dL). The study included 139 children at Tanner 1 development stage (generally ranging from 6-10 years of age). The dosage of atorvastatin (once daily) was initiated at 5 mg (chewable tablet) in children less than 10 years of age. Children age 10 and above were initiated at 10 mg atorvastatin (once daily). All children could titrate to higher doses to achieve a target of <3.35 mmol/L LDL-C. The mean weighted dose for children aged 6 to 9 years was 19.6 mg and the mean weighted dose for children aged 10 years and above was 23.9 mg.[31]

The mean (+/- SD) baseline LDL-C value was 6.12 (1.26) mmol/L which was approximately 233 (48) mg/dL. See table 2 below for final results.[31]

The data were consistent with no drug effect on any of the parameters of growth and development (i.e., height, weight, BMI, Tanner stage, Investigator assessment of Overall Maturation and Development) in

pediatric and adolescent subjects with HeFH receiving atorvastatin treatment over the 3 year study. There was no Investigator-assessed drug effect noted in height, weight, BMI by age or by gender by visit.[31]

TABLE 2 Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia (mmol/L)[31]

Timepoint	N	TC (S.D.)	LDL-C (S.D.)	HDL-C (S.D.)	TG (S.D.)	Apo B (S.D.)#
Baseline	271	7.86 (1.30)	6.12 (1.26)	1.314 (0.2663)	0.93 (0.47)	1.42 (0.28)**
Month 30	206	4.95 (0.77)*	3.25 (0.67)	1.327 (0.2796)	0.79 (0.38)*	0.90 (0.17)*
Month 36/ET	240	5.12 (0.86)	3.45 (0.81)	1.308 (0.2739)	0.78 (0.41)	0.93 (0.20)***

TC = total cholesterol; LDL-C = low density lipoprotein cholesterol-C; HDL-C = high density lipoprotein cholesterol-C; TG = triglycerides; Apo B = apolipoprotein B; "Month 36/ET" included final visit data for subjects who ended participation prior to the scheduled 36 month timepoint as well as full 36 month data for subjects completing the 36 month participation; "*" = Month 30 N for this parameter was 207; "**" = Baseline N for this parameter was 270; "***" = Month 36/ET N for this parameter was 243; "#" =g/L for Apo B.

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10 to 17 years of age (mean age 14.1 years) with heterozygous FH or severe hypercholesterolemia were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥190 mg/dL or 2) a baseline LDL-C ≥160 mg/dL and positive family history of FH or documented premature CVD in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >130 mg/dL. The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, TG, and apo B during the 26-week double-blind phase (see Table 3).

TABLE 3 Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia

(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

Dosage	N	Total-C[a]	LDL-C[b]	HDL-C[c]	TG[d]	Apo B[e]
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

[a]Total cholesterol
[b] Low density lipoprotein cholesterol
[c] High density lipoprotein cholesterol
[d] Total glycerides
[e] Apolipoprotein-B

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26-week

double-blind phase. In this 1-year study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls.[31]

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in 39 patients, 6 to 17 years of age with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/L. Cohort A included 15 patients, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 patients, 10 to 17 years of age and at Tanner Stage ≥2.[31]

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a patient had not attained target LDL-C of <3.35 mmol/L at Week 4 and if atorvastatin was well tolerated.[31]

Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all patients. For patients whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether patients remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.[31]

The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2. PHARMACOKINETIC PROPERTIES

Pharmacokinetics and Metabolism

Absorption

In studies with amlodipine/atorvastatin[9,10]

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

The bioavailability of the amlodipine component of amlodipine/atorvastatin was not affected under the fed state as assessed by C_{max}: 105% (90% CI: 99, 111) and AUC: 101% (90% CI: 97, 105) relative to the fasted state.[11] Although food decreases the rate and extent of absorption of atorvastatin from amlodipine/atorvastatin by approximately 32% and 11%, respectively, as assessed by C_{max}: 68% (90% CI 60, 79) and AUC: 89% (90% CI 83, 95) relative to the fasted state,[11] similar reductions in plasma concentrations in the fed state have been seen with atorvastatin taken as monotherapy without reduction in LDL-C effect (see below).

In studies with amlodipine[1]

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 to 12 hours post-dose. Absolute bioavailability has been estimated to be between 64% and 80%. The

volume of distribution is approximately 21 L/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Absorption of amlodipine is unaffected by consumption of food.

In studies with atorvastatin[2]

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.[34,35,36,37] The absolute bioavailability of atorvastatin is approximately 14%, and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for 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. Posology and Method of Administration**).

Distribution

In studies with atorvastatin[2]

Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥98% bound to plasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism and Excretion

In studies with amlodipine[1]

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

In studies with atorvastatin[2]

Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. *In vitro* studies also indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Atorvastatin co-administration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by cytochrome P450 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other cytochrome P450 3A4 substrates (see **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Atorvastatin and its metabolites are 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.[2]

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.[40]

Special Populations

Hepatic Insufficiency

In studies with atorvastatin[2]

Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B) (see **section 4.3. Contraindications**).

Renal Insufficiency (see **section 4.2. Posology and Method of Administration**)

In studies with amlodipine[1]

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

In studies with atorvastatin[2]

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.

Gender

In studies with atorvastatin[2]

Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. However, there were no clinically significant differences in lipid effects between men and women.

Elderly

In studies with amlodipine[1]

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

In studies with atorvastatin[2]

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (aged ≥65 years) than in young adults. The ACCESS study specifically evaluated elderly patients with respect to reaching their NCEP treatment goals. The study included 1087 patients under 65 years of age, 815 patients over 65 years of age, and 185 patients over 75 years of age. No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Pediatrics

In studies with amlodipine[1]

In one clinical chronic exposure study, 73 hypertensive pediatric patients, aged 12 months to less than or equal to 17 years, amlodipine was dosed at an average daily dose of 0.17 mg/kg. Clearance for subjects with the median weight of 45 kg was 23.7 L/h and 17.6 L/h for males and females, respectively. This is in a similar range to the published estimates of 24.8 L/h in a 70 kg adult. The average estimate for volume of distribution for a 45 kg patient was 1130 L (25.11 L/kg). Maintenance of the BP effect over the 24-hour dosing interval was observed with little difference in peak and trough variation effect. When compared to historical adult pharmacokinetics, the parameters observed in this study indicate that once daily dosing is appropriate.

In studies with atorvastatin[31]

In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥2 (N=24) pediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Drug Interactions

In studies with atorvastatin

The effect of co-administered drugs on the pharmacokinetics of atorvastatin as well as the effect of atorvastatin on the pharmacokinetics of co-administered drugs are summarized below (see **section 4.4. Special Warnings and Precautions for Use** and **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**).

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin			
Co-administered Drug and Dosing Regimen	**Atorvastatin**		
	Dose (mg)	**Ratio of AUC[&]**	**Ratio of C_{max}[&]**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD[a] for 28 days	8.7	10.7
[#]Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	10 mg SD[c]	9.4	8.6

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin			
Co-administered Drug and Dosing Regimen	**Atorvastatin**		
#Glecaprevir 400 mg QD[a]/Pibrentasvir 120 mg QD[a], 7 days[40]	10 mg QD[a] for 7 days	8.3	22.0
#Telaprevir 750 mg q8h[f], 10 days	20 mg SD[c]	7.9	10.6
#Elbasvir 50 mg QD[a]/grazoprevir 200 mg QD[a]. 13 days[40]	10 mg SD[c]	1.95	4.3
#Boceprevir 800 mg TID[d], 7 days[26]	40 mg SD[c]	2.3	2.7
#Simeprevir 150 mg QD[a], 10 days[40]	40 mg SD[c]	2.12	1.70
#Lopinavir 400 mg BID[b]/ ritonavir 100 mg BID[b], 14 days	20 mg QD[a] for 4 days	5.9	4.7
#, ‡ Saquinavir 400 mg BID[b]/ ritonavir 400 mg BID[b], 15 days	40 mg QD[a] for 4 days	3.9	4.3
#Clarithromycin 500 mg BID[b], 9 days	80 mg QD[a] for 8 days	4.5	5.4
#Darunavir 300 mg BID[b]/ritonavir 100 mg BID[b], 9 days	10 mg QD[a] for 4 days	3.4	2.2
#Itraconazole 200 mg QD[a], 4 days	40 mg SD[c]	3.3	1.20
#Letermovir 480 mg QD, 10 days[a, 41]	20 mg SD[c]	3.29	2.17
#Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.5	2.8
#Fosamprenavir 1400 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.3	4.0
#Nelfinavir 1250 mg BID[b], 14 days	10 mg QD[a] for 28 days	1.74	2.2
#Grapefruit Juice, 240 mL QD[a] *	40 mg SD[c]	1.37	1.16
Diltiazem 240 mg QD[a] for 28 days	40 mg SD[c]	1.51	1.00
Erythromycin 500 mg QID[e] for 7 days	10 mg SD[c]	1.33	1.38
Amlodipine 10 mg, single dose	80 mg SD[c]	1.18	0.91
Cimetidine 300 mg QID[e], 2 weeks	10 mg QD[a] for 2 weeks	1.00	0.89
Colestipol 10 g BID[b], 24[39] weeks	40 mg QD[a] for 8 weeks	NA	0.74**
Maalox TC® 30 mL QID[e], 17 days	10 mg QD[a] for 15 days	0.66	0.67
Efavirenz 600 mg QD[a], 14 days	10 mg for 3 days	0.59	1.01
#Rifampin 600 mg QD[a], 7 days (co-administered) †	40 mg SD[c]	1.12	2.9

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin			
Co-administered Drug and Dosing Regimen	**Atorvastatin**		
#Rifampin 600 mg QD[a], 5 days (doses separated) †	40 mg SD[c]	0.20	0.60
#Gemfibrozil 600 mg BID[b], 7 days	40 mg SD[c]	1.35	1.00
#Fenofibrate 160 mg QD[a] for 7 days	40 mg SD[c]	1.03	1.02

& Represents ratio treatments (co-administered drug plus atorvastatin versus atorvastatin alone).
# See **section 4.4. Special Warnings and Precautions for Use** and **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction** for clinical significance.
***** Greater increases in AUC (ratio of AUC up to 2.5) and/or C_{max} (ratio of C_{max} up to 1.71) have been reported with excessive grapefruit consumption (≥750 mL-1.2 L/day).
****** Ratio based on a single sample taken 8-16 hours post dose.
† Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.
‡ The dose of saquinavir/ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be exercised and the lowest dose necessary should be used.
[a] Once daily
[b] Twice daily
[c] Single dose
[d] Three times daily
[e] Four times daily
[f] Every 8 hours

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs			
Atorvastatin	**Co-administered Drug and Dosing Regimen**		
	Drug/Dose (mg)	**Ratio of AUC[&]**	**Ratio of C_{max}[&]**
80 mg QD[a] for 15 days	Antipyrine 600 mg SD[c]	1.03	0.89
80 mg QD[a] for 10 days	Digoxin 0.25 mg QD[a] for 20 days[#]	1.15	1.20
40 mg QD[a] for 22 days	Oral contraceptive QD[a], 2 months		
	- Norethindrone 1 mg	1.28	1.23
	- Ethinyl estradiol 35 µg	1.19	1.30
10 mg SD[c]	Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b] for 7 days	1.08	0.96
10 mg QD[a] for 4 days	Fosamprenavir 1400 mg BID[b], 14 days	0.73	0.82
10 mg QD[a] for 4 days	Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	0.99	0.94

& Represents ratio treatments (co-administered drug plus atorvastatin versus atorvastatin alone).
# See **section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction** for clinical significance.

[a] Once daily
[b] Twice daily
[c] Single dose

5.3. PRECLINICAL SAFETY DATA

Carcinogenesis

In studies with amlodipine[1]

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

In studies with atorvastatin[2]

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on $AUC_{(0-24)}$ values. In a 2-year study in mice, incidences of hepatocellular adenomas in males and hepatocellular carcinomas in females were increased at the maximum dose used, which was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on $AUC_{(0-24)}$.

All other chemically similar drugs in this class have induced tumors in both mice and rats at multiples of 12 to 125 times their highest recommended clinical doses, on a mg/kg body weight basis.

*Based on patient weight of 50 kg.

Mutagenesis

In studies with amlodipine[1]

Mutagenicity studies revealed no drug-related effects at either the gene or chromosome level.

In studies with atorvastatin[2]

Atorvastatin did not demonstrate mutagenic or clastogenic potential in four *in vitro* tests with and without metabolic activation or in one *in vivo* assay. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* hypoxanthine-guanine phosphoribosyl transferase (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.

Impairment of Fertility

In studies with amlodipine[1]

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis).

*Based on patient weight of 50 kg.

In studies with atorvastatin[2]

No adverse effects on fertility or reproduction were observed in male rats given doses of atorvastatin up to 175 mg/kg/day or in female rats given doses up to 225 mg/kg/day. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg basis. Atorvastatin caused no adverse effects on sperm or semen parameters or on reproductive organ histopathology in dogs given doses of 10 mg/kg, 40 mg/kg, or 120 mg/kg for 2 years.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

CADUET contains the following excipients:

Calcium Carbonate, Croscarmellose Sodium, Microcrystalline Cellulose, Pregelatinized Starch, Polysorbate 80, Hydroxypropyl Cellulose, Purified Water, Colloidal Silicon Dioxide (anhydrous).

The film-coated tablet contains Magnesium Stearate, Opadry II White 85F28751 or Opadry II Blue 85F10919.

6.2. INCOMPATIBILITIES

Not applicable

6.3. SHELF LIFE

24 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

CADUET tablets are available in aluminum PVC blister packs as follows:

- CADUET (amlodipine besilate 5 mg/atorvastatin calcium 10 mg): 7s blister strip.
- CADUET (amlodipine besilate 5 mg/atorvastatin calcium 20 mg): 7s blister strip.

6.6. INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL

No special requirement.

Caduet/LPD/PK-13
According to CDS V 26 Dated: December 15, 2020 Supersedes CDS V 25 Dated: January 24, 2020

Marketed by:
Pfizer Pakistan Limited

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

7. REFERENCES

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7. Amlodipine/Atorvastatin Study Discontinuation Tables

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    b. Amlodipine/Atorvastatin Protocol A3841001DB Table 4.1.1; Discontinuations from Study: Double-Blind Phase.

    c. Amlodipine/Atorvastatin Protocol A3841012 Table 4.1; Discontinuations from Study.

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