DUALPRESS FILM-COATED TABLET 5MG/10MG

1. TRADE NAME OF THE MEDICINAL PRODUCT

DUALPRESS FILM-COATED TABLET 5MG/10MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: amlodipine besylate, atorvastatin calcium.

The tablets for oral administration contain amlodipine besylate and atorvastatin calcium equivalent to 5 mg/10 mg amlodipine/atorvastatin respectively.

3. PHARMACEUTICAL FORM

Film-coated Tablets.

Dualpress tablets 5 mg/10 mg are white, oval and film-coated tablets; engraved with "975" on one side and "SCP" on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The amlodipine/atorvastatin combination product (henceforth in this document termed “amlodipine/atorvastatin”) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate:

Amlodipine

Hypertension
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.

Coronary Artery Disease

Chronic Stable Angina
Amlodipine is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal drugs.

Vasospastic Angina (Prinzmetal's or Variant Angina)
Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina.

Amlodipine may be used as monotherapy, or in combination with other antianginal drugs.

Angiographically Documented Coronary Artery Disease
In patients with recently documented coronary artery disease (CAD) by angiography and without heart failure or an ejection fraction <40%, amlodipine is indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure.

Atorvastatin

Dyslipidemia
The atorvastatin component is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) in patients with primary hypercholesterolemia, heterozygous familial hypercholesterolemia (FH) or combined (mixed) hyperlipidemia (*Fredrickson* Types IIa and IIb), elevated serum TG levels (*Fredrickson* Type IV), and in patients with dysbetalipoproteinemia (*Fredrickson* Type III) when response to diet and other non-pharmacological measures is inadequate.

The atorvastatin component also raises high-density lipoprotein cholesterol (HDL-C) and lowers the LDL-HDL and total-C/HDL ratios.

The atorvastatin component is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total-C, LDL-C and apo B in patients with homozygous FH.

Prevention of Cardiovascular Disease
Atorvastatin is indicated to reduce the risk of myocardial infarction (MI) in adult hypertensive patients without clinically evident coronary heart disease (CHD), but with at least three additional risk factors for CHD, such as age ≥55 years, male sex, smoking, left ventricular hypertrophy, other specified abnormalities on electrocardiogram (ECG), microalbuminuria or proteinuria, ratio of plasma total cholesterol to HDL-cholesterol ≥6, or premature family history of CHD.

In patients with Type 2 diabetes and without clinically evident CHD, but with multiple risk factors for CHD, such as retinopathy, albuminuria, smoking or hypertension, atorvastatin is indicated to:

- Reduce the risk of MI
- Reduce the risk of stroke

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

4.2. Posology and method of administration

General Considerations

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.

Initial Therapy

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

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. Amlodipine/atorvastatin has also been safely administered with the aforementioned medicines.

The atorvastatin component of amlodipine/atorvastatin may be used in combination with a bile acid-binding resin for additive effect on lipid lowering. The combination of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrates should generally be avoided (see **sections 4.4. Special warnings and precautions for use** and **4.5. Interaction with other medicinal products and other forms of interaction**).

Amlodipine (Hypertension or Angina)

For both hypertension and angina, the usual initial dose is 5 mg amlodipine once daily which

may be increased to a maximum of 10 mg depending on the individual patient's response.

In general, titration should proceed over 7-14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Coronary Artery Disease (Amlodipine Studies)

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 CAD).

Atorvastatin (Hyperlipidemia)

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin. The recommended starting dose of atorvastatin is 10 mg or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range is 10 mg to 80 mg once daily. After initiation and/or upon titration of atorvastatin, lipid levels should be analysed within 2 to 4 weeks, and dosage adjusted accordingly.

Prevention of Cardiovascular Disease

For primary prevention, the recommended dose is 10 mg once daily. For secondary prevention, optimal dosing may range from 10 mg to 80 mg atorvastatin once daily, to be given at the discretion of the prescriber, taking into account the expected benefit and safety considerations relevant to the patient to be treated (see **section 5.1. Pharmacodynamic properties - Secondary Prevention of Cardiovascular Events**).

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia (Atorvastatin Studies)

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)

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

Amlodipine/atorvastatin should not be used in patients with hepatic impairment (see **sections 4.3. Contraindications** and **4.4. Special warnings and precautions for use**).

Use in Patients with Impaired Renal Function

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

Safety and effectiveness in children have not been established for amlodipine/atorvastatin.

Use in Combination with Other Medicinal Compounds

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

Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir (see **sections 4.4. Special warnings and precautions for use - Skeletal Muscle Effects** and **4.5. Interaction with other medicinal products and other forms of interaction**).

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

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, elbasvir/grazoprevir, simeprevir), clarithromycin, itraconazole and letermovir. 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 (see **sections 4.4. Special warnings and precautions for use - Skeletal Muscle Effects** and **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 x 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.
4. Are concomitantly treated with glecaprevir/pibrentasvir.

*Amlodipine is a dihydropyridine calcium channel blocker.

4.4. Special warnings and precautions for use

General

Since the vasodilation induced by amlodipine component of Dualpress is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering Dualpress as with any other peripheral vasodilator
particularly in patients with severe aortic stenosis.

Before instituting therapy with Dualpress, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat other underlying medical problems.

Beta-blocker Withdrawal
The amlodipine component of Dualpress is not a beta-blocker and therefore, gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Endocrine Function
HMG-CoA reductase inhibitors, such as the atorvastatin component of Dualpress interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Caution should be exercised if a HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone and cimetidine.

Use in Patients with Heart Failure
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 non-ischemic 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
As with other lipid-lowering agents of the HMG-CoA reductase inhibitor class, moderate (>3 x 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 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10 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 x 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
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 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. 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 **sections 4.5. Interaction with other medicinal products and other forms of interaction** and **5.2 Pharmacokinetic properties**). 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 non-structural protein 5A (NS5A)/non-structural protein 5B (NS5B) inhibitors, letermovir, 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**).

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. 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 pre-disposing 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.

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.

Hemorrhagic Stroke

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) (see **section 5.1. Pharmacodynamic properties - Recurrent Stroke**). The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1 to 6 months) stroke or TIA.

Endocrine Function

Increases in glycated hemoglobin (HbA1c) and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins. Periodic monitoring of these patients is recommended.

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

Information for the Patient
Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Adolescent females and women of childbearing potential should be counseled on appropriate contraceptive methods while on amlodipine/atorvastatin therapy (see **section 4.6. Fertility, pregnancy and lactation**).

For NOD
Increases in HbA1c and fasting serum glucose levels have been reported with statins

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.

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:

Interaction Studies with Amlodipine

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. Erythromycin co-administration in healthy volunteers (18-43 years of age) did not significantly change amlodipine systemic exposure (22% increase in AUC). Although the clinical relevance of these findings is uncertain, the pharmacokinetic variations may be more pronounced in the elderly.

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

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

CYP3A4 inducers: There are no data available regarding the effect of CYP3A4 inducers on amlodipine. 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: Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs, such as calcium channel blockers. Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased BP lowering effects.

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).

Special Studies: Effect of Other Agents on Amlodipine

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

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

Sildenafil: A single 100 mg dose of sildenafil in 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.

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

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

Drug/Laboratory Test Interactions: None known.

Interaction Studies with Atorvastatin

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 (e.g., erythromycin and azole antifungals) (see below and also **sections 4.2. Posology and method of administration - Use in Combination with Other Medicinal Compounds** and **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.

Clarithromycin: Concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) resulted in a 4.4-fold increase in atorvastatin AUC (see **sections 4.4. Special warnings and precautions for use - Skeletal Muscle Effects** and **4.2. Posology and method of administration - Use in Combination with Other Medicinal Compounds**).

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with co-administration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see **sections 4.4. Special warnings and precautions for use - Skeletal Muscle Effects** and **5.2. Pharmacokinetic properties**).

Protease Inhibitors: Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC (see **sections 4.2. Posology and method of administration - Use in Combination with Other Medicinal Compounds** and **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 a 2.5- to 3.3-fold 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: 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 and concomitant use with atorvastatin is contraindicated.

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, multidrug resistance- associated protein 2 (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**).

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.

Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary. Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir (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 aluminium 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.

Terfenadine: Co-administration of atorvastatin and terfenadine did not produce a clinically significant effect on the pharmacokinetics of terfenadine.

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: 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: 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.

Drug/Laboratory Test Interactions: None known.

4.6. Fertility, pregnancy and lactation

Amlodipine/atorvastatin is contraindicated in pregnancy due to the atorvastatin component. Women of childbearing potential should use 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/atorvastatin is contraindicated while breast-feeding due to the atorvastatin component. 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.

Safety of amlodipine in human pregnancy or lactation has not been established. 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. 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.

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).

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.

The following information is based on clinical trials and post-marketing experience with amlodipine and atorvastatin.

Amlodipine Experience

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

Vascular Disorders: Flushing

General Disorders and Administration Site Conditions: Edema, fatigue

Nervous System Disorders: Dizziness, headaches, somnolence

Gastrointestinal Disorders: Abdominal pain, nausea

Cardiac Disorders: Palpitations

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

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

General Disorders and Administration Site Conditions: Asthenia, malaise, pain

Vascular Disorders: Hypotension, vasculitis

Nervous System Disorders: Hypertonia, hypoesthesia/paraesthesia, neuropathy peripheral, syncope, dysgeusia, tremor, extrapyramidal disorder

Reproductive System and Breast Disorders: Gynaecomastia, erectile dysfunction

Gastrointestinal Disorders: Change in bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting

Metabolism and Nutrition Disorders: Hyperglycemia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, muscle spasms, myalgia

Blood and Lymphatic System Disorders: Leukopenia, thrombocytopenia

Psychiatric Disorders: Insomnia, mood altered

Respiratory, Thoracic and Mediastinal Disorders: Cough, dyspnoea, rhinitis

Skin and Subcutaneous Tissue Disorders: Alopecia, hyperhidrosis, purpura, skin discolouration, urticaria

Ear and Labyrinth Disorders: Tinnitus

Renal and Urinary Disorders: Pollakiuria, micturition disorder, nocturia

Eye Disorders: Visual impairment

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.

Atorvastatin Experience

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.

Adverse events occurring at a frequency ≥1% and assessed as being associated with atorvastatin treatment are listed below:

Infections and infestations: Nasopharyngitis

Metabolism and nutrition disorders: Hyperglycemia

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 events occurring at a frequency <1% that have been reported in the atorvastatin clinical trials are listed below:

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.

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

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, erythema multiforme, bullous rashes

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis, immune-mediated necrotizing myopathy, myositis, back pain

General Disorders and Administration Site Conditions: Chest pain, peripheral edema, fatigue

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These

cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

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 (see also **section 5.2. Pharmacokinetic properties - Renal Insufficiency**).

Additional data on amlodipine ingestion 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.

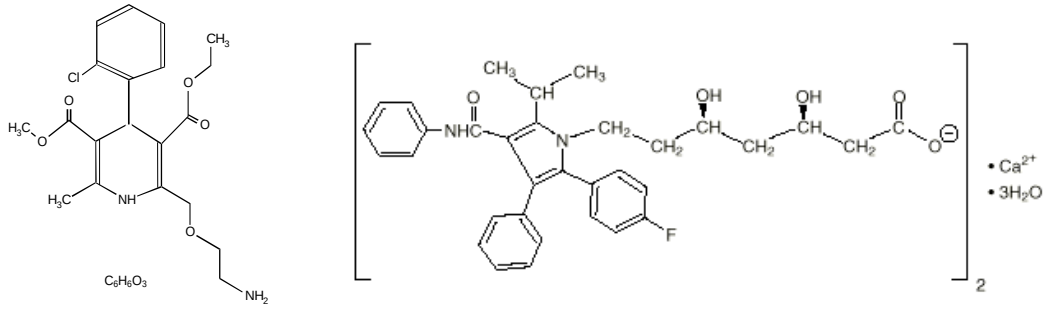
Additional data on atorvastatin ingestion suggest that there is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Amlodipine/Atorvastatin Pharmacodynamics

The amlodipine besylate 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-pyridinedicarboxylate 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)-ß, 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 $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$. The structural formulae are shown below:



Amlodipine besylate Atorvastatin calcium

Mechanism of Amlodipine/Atorvastatin

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.

Clinical Studies of Combined Amlodipine and Atorvastatin in Patients with Hypertension and Dyslipidemia

In a double-blind, placebo-controlled study of 1660 patients with co-morbid 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 cardiovascular disease (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 BP 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 co-morbid hypertension and dyslipidemia only; <140/90 mmHg and <130 mg/dL for patients with co-morbid 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 co-morbid 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).

Anglo-Scandinavian Cardiac Outcomes Trial

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a randomized 2x2 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

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, and had untreated hypertension or sub-optimally hypertension treatment with at least one drug, with no previous MI or treatment for angina, at least three of the following pre-defined 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 ECG abnormalities, or proteinuria by dipstick/microalbuminuria.

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 with 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 endpoints (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 cardiovascular events and procedures, total coronary events, non-fatal MI (excluding silent MI) plus fatal CHD, all-cause mortality, cardiovascular mortality, as well as 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) and not taking a statin or a fibrate. 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 by dip stick/microalbuminuria. In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive 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 procedure	20%	389 vs. 483	0.0008
Non-fatal MI (excludes silent MI) plus fatal CHD	38%	686 vs. 137	0.0005
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 pre-defined 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 2x2

The pre-specified ASCOT 2x2 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

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.

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

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

Use in Patients with 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.

CAMELOT enrolled 1997 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine besylate tablets (5 mg to 10 mg once-daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerine (50%), anti-coagulants (40%), and diuretics (32%), but excluded other calcium channel blockers, for 2 years. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease.

The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures (see Table 1). The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, MI, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease (PVD) did not demonstrate a significant difference between amlodipine besylate and placebo.

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 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 years 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 ECG 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. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38; 95% Cl 1.25-1.52; p<0.001). However, 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.

Atorvastatin Pharmacodynamics

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, non-familial 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.

Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD.

Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL in patients with homozygous 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, non-familial 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.

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 pre-defined 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**
MCVE (fatal and non-fatal AMI, silent MI, acute CHD death, stroke, CABG, PTCA, revascularization procedure, unstable angina)	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
CABG, PTCA or other coronary revascularization procedure	31%	24 vs. 34	0.1557
Unstable angina	22%	8 vs. 10	0.5991
Acute CHD death (excluding confirmed acute MI)	-	10 vs. 5	0.2211
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.

There were 61 deaths in the Lipitor group vs. 82 deaths in the placebo group (Hazard ratio [HR] 0.73, p=0.0592).

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

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% (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. All-cause mortality was 9.1% (216/2365) for atorvastatin vs. 8.9% (211/2366) for placebo. 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 non-fatal hemorrhagic stroke was significantly greater in the atorvastatin group (38 atorvastatin vs. 16 placebo) while the incidence of fatal hemorrhagic stroke was similar between the groups (17 atorvastatin vs. 18 placebo). The risk of hemorrhagic stroke was increased in patients who entered the study with a hemorrhagic stroke (7 atorvastatin vs. 2 placebo).

All-cause mortality was 15.6% (7/45) for atorvastatin vs. 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke.

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 primary endpoint was the time-to-first occurrence of any of the following MCVE: death due to CHD, non-fatal MI, resuscitated cardiac arrest, and fatal and non-fatal stroke. 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%.

Overview of Efficacy Results in TNT

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					
CHD death	127	2.5	101	2.0	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	6.2	243	4.9	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	0.5	25	0.5	0.96 (0.56, 1.67)
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 PVD endpoint	282	5.6	275	5.5	0.97 (0.83, 1.15)
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)
All-cause mortality	282	5.6	284	5.7	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	3.1	126	2.5	0.81 (0.64, 1.03)

Non-cardiovascular death	127	2.5	158	3.2	1.25 (0.99, 1.57)
Cancer death	75	1.5	85	1.7	1.13 (0.83, 1.55)
Other non-CV death	43	0.9	58	1.2	1.35 (0.91, 2.00)
Suicide, homicide and other traumatic non-CV death	9	0.2	15	0.3	1.67 (0.73, 3.82)

[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; CHD = coronary heart disease; CI = confidence interval; MI = myocardial infarction; CHF = congestive heart failure; CV = cardiovascular; PVD = peripheral vascular disease; 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.

There were more serious adverse events and discontinuations due to adverse events in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively). Persistent transaminase elevations (≥3 x ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CPK (≥10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

5.2. Pharmacokinetic properties

Pharmacokinetics and Metabolism

Absorption

In studies with amlodipine/atorvastatin: 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. 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, 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: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 and 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: 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. 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 pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared to morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see **section 4.2. Posology and method of administration**).

Distribution

In studies with atorvastatin: 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: 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: 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.

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

Special Populations

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

In studies with amlodipine: As with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should be administered with caution in these patients.

Renal Insufficiency (see **section 4.2. Posology and method of administration**)
In studies with amlodipine: Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

In studies with atorvastatin: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary.

Hemodialysis
While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin and/or amlodipine since both drugs are extensively bound to plasma proteins.

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

Elderly
In studies with amlodipine: 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: 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
Pharmacokinetic data in the pediatric population are not available.

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 **sections 4.4. Special warnings and precautions for use** and **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
[#]Glecaprevir 400 mg QD[a]/Pibrentasvir 120 mg QD[a], 7 days	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	10 mg SD[c]	1.95	4.3
[#]Boceprevir 800 mg TID[d], 7 days	40 mg SD[c]	2.3	2.7
[#]Simeprevir 150 mg QD[a], 10 days	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]	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

Co-administered Drug and Dosing Regimen	Atorvastatin		
[#]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 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
[#]Rifampin 600 mg QD[a] for 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 vs. atorvastatin alone).
[#] See **sections 4.4. Special warnings and precautions for use** and **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 [&]**
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 - Ethinyl estradiol 35 µg	 1.28 1.19	 1.23 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 vs. 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: 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.

*Based on patient weight of 50 kg.

In studies with atorvastatin: 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.

Mutagenesis

In studies with amlodipine: Mutagenicity studies revealed no drug related effects at either the gene or chromosome level.

In studies with atorvastatin: Atorvastatin did not demonstrate mutagenic or clastogenic potential in four *in vitro* tests with and without metabolic activation or in one *in vivo* assay. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* 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: 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: 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

Microcrystalline cellulose, Pre-gelatinized starch, Calcium carbonate, Poloxamer, Hydroxypropyl cellulose, Crospovidone, Croscarmellose Sodium, Magnesium stearate, Alcohol 95%, Hypromellose, Macrogol 6000, Titanium dioxide, Purified water

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

Refer to outer carton.

6.4. Special precautions for storage

Refer to outer carton.

6.5. Nature and content of container

PTP blister (10's/Alu-Alu blister X 3 blister/box).

6.6. Special precautions for disposal and other handling

None.

7. Marketing Authorization Holder

Novem Healthcare Pte Ltd

23 New Industrial Road #03-08

Solstice Business Center

Singapore 536209

8. Marketing Authorization Number(s)

SINXXXXXP

9. Date of First Authorization/Renewal of The Authorization

DD/MM/YYYY

10. Date of Revision of The Text

7 January 2022