1. THERAPEUTIC CATEGORY

Calcium Channel Blocker
Lipid Regulating Agent

2. FORMULATION

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 5/10 mg Tablets: Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine and atorvastatin calcium, equivalent to 10 mg atorvastatin.

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 10/10 mg Tablets: Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine and atorvastatin calcium, equivalent to 10 mg atorvastatin.

3. DESCRIPTION

The amlodipine besilate component of amlodipine/atorvastatin is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is C_{20}H_{25}ClN_{2}O_{5}•C_{6}H_{6}O_{3}S. The atorvastatin calcium component of amlodipine/atorvastatin is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-8,8-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_{2}O_{5})_{2}Ca•3H_{2}O. The structural formula is shown below:

![Amlodipine besilate and Atorvastatin calcium structures](image)

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) Tablet is indicated for the following patient populations:

1. Patients at increased cardiovascular risk due to the presence of the two modifiable risk factors hypertension and dyslipidemia; and/or
2. Patients with increased cardiovascular risk due to the presence of symptomatic CHD (Coronary Heart Disease) expressed as angina with the additional modifiable risk factor of dyslipidemia; and/or
3. Prevention of cardiovascular complications in hypertensive patients (see below - Prevention of Cardiovascular Complications).

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

**Hypertension**

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

Amlodipine besilate is also indicated to reduce the risk of fatal coronary heart disease and non-fatal myocardial infarction, and to reduce the risk of stroke.

**Coronary Artery Disease**

The amlodipine besilate component is indicated to reduce the risk of coronary revascularization procedures and the need for hospitalization due to angina in patients with coronary artery disease.

**Chronic Stable Angina**

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

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

The atorvastatin calcium component is also indicated for the reduction of total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia.

**Prevention of Cardiovascular Complications**

In patients without clinically evident cardiovascular disease and with or without dyslipidemia, but with multiple risk factors for coronary heart disease such as smoking, hypertension, diabetes, low HDL-C, or family history of early coronary heart disease, atorvastatin calcium is indicated to:
- reduce the risk of fatal coronary heart disease and non-fatal myocardial infarction,
- reduce the risk of stroke,
- reduce the risk of revascularization procedures and angina pectoris.

**Pediatric Patients (10-17 years of age)**

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

a. LDL-C remains ≥ 190 mg/dL or 
b. LDL-C remains ≥ 160 mg/dL and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the pediatric patient

**4.2 Dosage and Method of Administration**

**General Considerations**

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) is a combination product targeting concomitant cardiovascular conditions, hypertension/angina and dyslipidemia.

The dosage range for Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) is 5mg/10mg to a maximum dose of 10mg/10mg 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 besilate /atorvastatin calcium should be used in addition to non-pharmacological measures, including an appropriate diet, exercise and weight reduction in obese patients, smoking cessation, and to treat underlying medical problems, when the response to these measures have been inadequate.
Following initiation and/or titration of amlodipine besilate /atorvastatin calcium, lipid levels should be analyzed and blood pressure measured within 2 to 4 weeks, and dosage of amlodipine besilate and atorvastatin calcium components should be adjusted accordingly. Titration for blood pressure response may proceed more rapidly if clinically warranted.

**Initial Therapy**

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

**Substitution Therapy**

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) may be substituted for its individually titrated components. Patients may be given the equivalent dose of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) or a dose of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) with increased amounts of amlodipine, atorvastatin or both for additional anti-anginal effects, blood pressure lowering, or lipid lowering effect.

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 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 besilate/Atorvastatin calcium (Norvasc Protect) 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 Drugs and Other Forms of Interaction)**

The amlodipine besilate component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) has been safely co-administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, and with sublingual nitroglycerine. Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) has also been safely administered with the aforementioned medicines.

The atorvastatin calcium component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) may be used in combination with a bile acid binding resin for additive effect on lipid lowering. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see section 4.4 Special Warnings and Special Precautions for Use, and section 4.5 Interaction with Other Drugs and Other Forms of Interaction).

**Special Populations and Special Considerations for Dosing**

**Coronary Artery Disease (CAD) (Amlodipine Studies)**
For patients with coronary artery disease the recommended dosage range is 5-10 mg amlodipine besilate once daily. In clinical studies the majority of patients required 10 mg once daily (see section 5.1 Amlodipine Pharmacodynamics - Use in Patients with Coronary Artery Disease (CAD))

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

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

**Use in Patients with Impaired Hepatic Function**

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) should not be used in patients with hepatic impairment. (see section 4.3 Contraindications and section 4.4 Special Warnings and Special Precautions for Use).

**Use in Patients with Impaired Renal Function**

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

**Use in the Elderly**

No adjustment of the dose is required in elderly patients.

**Use in Children**

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

*Studies with amlodipine besilate:*

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

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

*Studies with atorvastatin calcium:*

**Use in Combination with Other Medicinal Compounds**

*Studies with atorvastatin:*

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 (see section 4.4 Special warnings and precautions for use – Skeletal Muscle Effects and section 4.5
Interaction with other medicinal products and other forms of interaction - In Studies with Atorvastatin: Transporter Inhibitors).

4.3 Contraindications

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) is contraindicated in patients who have:

1. Known hypersensitivity to dihydropyridines*, amlodipine besilate, atorvastatin calcium, or any component of this medication: calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized, starch, polysorbate 80, magnesium state, silicon dioxide and hydroxypropylcellulose

2. Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal,

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

*Amlodipine is a dihydropyridine calcium channel blocker.

4.4 Special Warnings and Special Precautions for Use

Use in Patients with Heart Failure
In a long-term, placebo controlled study (PRAISE-2) of amlodipine besilate-treated patients with NYHA III and IV heart failure of non-ischemic etiology, amlodipine besilate 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 upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin calcium. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin calcium given at doses of 10, 20, 40 and 80 mg.

Persistent increases in serum transaminases (>3 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40 and 80 mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin calcium 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 ALT or AST of greater than three times the upper limit of normal persist, reduction of dose or withdrawal of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) is recommended. Atorvastatin can cause an elevation in transaminases (see section 4.8 Undesirable Effects).

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 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 besilate/Atorvastatin calcium (Norvasc Protect) (see section 4.3 Contraindications).

Skeletal Muscle Effects
Myalgia has been reported in atorvastatin calcium -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 besilate/Atorvastatin calcium (Norvasc Protect) therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, azole antifungals, colchicine, telaprevir, or the combination of tipranavir/ritonavir. Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. CYP 3A4 is the primary hepatic isozymes known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, 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. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy (See section 4.5 Interaction with other medicinal products and other forms of interaction). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) may cause an elevation of creatine phosphokinase due to the atorvastatin calcium 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 besilate/Atorvastatin calcium (Norvasc Protect) therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures). Control of hypertension may be continued with the appropriate dose of amlodipine besilate.
**Hemorrhagic Stroke** - A post-hoc analysis of a clinical study in 4,731 patients without CHD who had a stroke or TIA within the preceding 6 months and were initiated on atorvastatin 80 mg, revealed a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo (55 atorvastatin vs 33 placebo). Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke (7 atorvastatin vs 2 placebo). However, in patients treated with atorvastatin 80 mg there were fewer strokes of any type (265 vs 311) and fewer CHD events (123 vs 204). *(See section 5.1 Pharmacodynamic properties – Recurrent Stroke)*

**Endocrine Function** - Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

**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 besilate/Atorvastatin calcium (Norvasc Protect) therapy *(see section 4.6 Pregnancy and Lactation)*.

**4.5 Interaction with Other Drugs and Other Forms of Interaction**

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

No drug interaction studies have been conducted with Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) and other drugs, although studies have been conducted using the individual amlodipine besilate and atorvastatin calcium components, as described below:

**Amlodipine Interactions**

Amlodipine besilate has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme 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 amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers (18 to 43 years of age) did not significantly change amlodipine systemic exposure (22% increase in AUC). Although the clinical relevance of these finding 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.

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

**Grapefruit Juice:** Co-administration of 240 mL of grapefruit juice with a single oral dose 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 blood pressure 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).

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

**Special Studies: Effect of other agents on amlodipine besilate:**

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

**Aluminum/magnesium (antacid):** Co-administration of an aluminum/magnesium antacid with a single dose of amlodipine besilate 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 besilate and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

**Special Studies: Effect of amlodipine besilate on other agents.**

**Digoxin:** Co-administration of amlodipine besilate 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 besilate had no significant effect on the pharmacokinetics of ethanol.

**Warfarin:** Co-administration of amlodipine besilate with warfarin did not change the warfarin prothrombin response time.

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

**Drug/Laboratory Test Interactions:** None known.
**Atorvastatin Interactions**

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 inhibitors (eg erythromycin, and azole antifungals) (See below and also section 4.2 Dosage and method of administration: Use in Combination with Other Medicinal Compounds and section 4.4 Special Warnings and Special 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 depends on the variability of effect on cytochrome P450 3A4.

**Transporter Inhibitors:** Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin. (See also section 4.2 Dosage and method of administration - Use in Combination with Other Medicinal Compounds)

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

**Protease inhibitors:** Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin. (see section 5.2 Pharmacokinetic properties)

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

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

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

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

**Inducers of cytochrome P450 3A:** Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg 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.
Antacids: Co-administration of atorvastatin calcium with an oral antacid suspension containing magnesium and aluminum hydroxides, decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin calcium 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 (approximately 25%) when colestipol was administered with atorvastatin calcium. However, lipid effects were greater when atorvastatin calcium and colestipol were co-administered than when either drug was given alone.

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

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

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

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

Fucidic Acid: Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Colchicine: Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicines, and caution should be exercised when prescribing atorvastatin with colchicine.

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

4.6 Pregnancy and Lactation

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) is contraindicated in pregnancy due to the atorvastatin component. Women of childbearing potential should use adequate contraceptive measures.

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 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 besilate/Atorvastatin calcium (Norvasc Protect) is contraindicated while breast-feeding due to the atorvastatin calcium 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 besilate/Atorvastatin calcium (Norvasc Protect) should not breast-feed.

Safety of amlodipine besilate in human pregnancy or lactation has not been established. Amlodipine besilate does not demonstrate toxicity in animal reproductive studies other than to delay parturition and prolong labor in rates at a dose level fifty times the maximum recommended dose in humans (See section 5.2 – Preclinical safety data).

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

Combination therapy with amlodipine besilate and atorvastatin calcium 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 besilate and atorvastatin calcium 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 besilate and atorvastatin calcium 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 besilate and atorvastatin calcium compared to 4.0% of patients given placebo.

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

**Amlodipine Experience**

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

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
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<tbody>
<tr>
<td>Nervous System Disorders</td>
<td>headache, dizziness, somnolence</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Flushing</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>abdominal pain, nausea</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>oedema, fatigue</td>
</tr>
</tbody>
</table>

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

Less commonly observed side effects in marketing experience with amlodipine include:
<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>insomnia, mood alterations</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>hypertonia, hypoesthesia/paresthesia, neuropathy</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>visual impairment</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>hypotension, vasculitis</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>cough, dyspnoea, rhinitis</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>change in bowel habits, dry mouth, dyspepsia</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>alopecia, hyperhidrosis, purpura, skin</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>arthralgia, back pain, muscle spasms, myalgia</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>pollakiuria, micturition disorder, nocturia</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>gynecomastia, erectile dysfunction</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>asthenia, malaise, pain</td>
</tr>
<tr>
<td>Investigations</td>
<td>weight increased/decreased</td>
</tr>
</tbody>
</table>

Rarely reported events were allergic reaction 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 besilate. 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: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

**Pediatric Patients (ages 6-17 years)**

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

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System Disorders</td>
<td>headache, dizziness</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>abdominal pain</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Asthenia</td>
</tr>
</tbody>
</table>
The majority of adverse events were mild or moderate. Severe adverse events (predominantly headache) were experienced by 7.2% with amlodipine 2.5mg, 4.5% with amlodipine 5mg, and 4.6% with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant change in heart rate.

**Atorvastatin Calcium Experience**

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

**Infections and Infestations:** nasopharyngitis

**Metabolism and nutrition disorders:** hyperglycemia

**Respiratory, thoracic and mediastinal disorders:** pharyngolaryngeal pain-epistaxis

**Gastrointestinal disorders:** diarrhea, dyspepsia, nausea, flatulence

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

**Investigations:** liver function test abnormal, blood creatine phosphokinase increased

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

**Psychiatric disorders:** nightmare:

**Eye disorders:** vision blurred

**Ear and labyrinth disorders:** tinnitus

**Gastrointestinal Disorders:** abdominal discomfort, eructation

**Hepatobiliary Disorders:** hepatitis, cholestasis

**Skin and Subcutaneous Tissue Disorders:** urticaria

**Musculoskeletal and Connective Tissue Disorders:** muscle fatigue, neck pain

**General disorders and administration site conditions:** malaise, pyrexia

**Investigations:** white blood cells urine positive
Not all effects listed above have been causally associated with atorvastatin therapy.

**Pediatric Patients**

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

*In post-marketing experience, the following additional undesirable effects have been reported with atorvastatin calcium: 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: hypesthesia, amnesia, dizziness, dysgeusia, Gastrointestinal disorders: Pancreatitis, Skin and Subcutaneous Tissue Disorders: stevens-johnson syndrome, toxic epidermal necrolysis, erythema multiforme, bullous rashes. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, back pain, General Disorders and Administration Site Conditions: chest pain, peripheral edema, fatigue.*

**4.9 Overdosage**

There is no information on overdosage with Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) in humans.

Due to amlodipine’s and atorvastatin’s extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 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 two hours after ingestion of amlodipine besilate 10 mg has been shown to significantly decrease amlodipine besilate absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine besilate overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.*

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

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic Properties**

*Mechanism of Action*
Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 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 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

Clinical Studies of Combined Amlodipine Besilate and Atorvastatin Calcium 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 besilate and atorvastatin calcium (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, or 10/80 mg) was compared versus amlodipine besilate alone (5 mg or 10 mg), atorvastatin calcium 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. At eight weeks, all eight combination-treatment groups demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and LDL-cholesterol compared to placebo, with no overall modification of effect of either component on SBP, DBP and LDL-C (see table below).

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

<table>
<thead>
<tr>
<th>Parameter / Analysis</th>
<th>ATO 0 mg</th>
<th>ATO 10 mg</th>
<th>ATO 20 mg</th>
<th>ATO 40 mg</th>
<th>ATO 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change (mmHg)</td>
<td>-3.0</td>
<td>-4.5</td>
<td>-6.2</td>
<td>-6.2</td>
<td>-6.4</td>
</tr>
<tr>
<td>Difference versus placebo (mmHg)</td>
<td>-</td>
<td>-1.5</td>
<td>-3.2</td>
<td>-3.2</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter / Analysis</th>
<th>AML 0 mg</th>
<th>AML 5 mg</th>
<th>AML 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change (mmHg)</td>
<td>-12.8</td>
<td>-13.7</td>
<td>-15.3</td>
</tr>
<tr>
<td>Difference versus placebo (mmHg)</td>
<td>-9.8</td>
<td>-10.7</td>
<td>-12.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter / Analysis</th>
<th>AML 0 mg</th>
<th>AML 5 mg</th>
<th>AML 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change (mmHg)</td>
<td>-16.2</td>
<td>-15.9</td>
<td>-16.1</td>
</tr>
<tr>
<td>Difference versus placebo (mmHg)</td>
<td>-13.2</td>
<td>-12.9</td>
<td>-13.1</td>
</tr>
<tr>
<td>Parameter / Analysis</td>
<td>ATO 0 mg</td>
<td>ATO 10 mg</td>
<td>ATO 20 mg</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Mean change (mmHg)</td>
<td>-3.3</td>
<td>-4.1</td>
</tr>
<tr>
<td></td>
<td>Difference versus placebo (mmHg)</td>
<td>-</td>
<td>-0.8</td>
</tr>
<tr>
<td>AML 0 mg</td>
<td>Mean change (mmHg)</td>
<td>-7.6</td>
<td>-8.2</td>
</tr>
<tr>
<td></td>
<td>Difference versus placebo (mmHg)</td>
<td>-4.3</td>
<td>-4.9</td>
</tr>
<tr>
<td>AML 5 mg</td>
<td>Mean change (mmHg)</td>
<td>-10.4</td>
<td>-9.1</td>
</tr>
<tr>
<td></td>
<td>Difference versus placebo (mmHg)</td>
<td>-7.1</td>
<td>-5.8</td>
</tr>
</tbody>
</table>

### Efficacy of the Combined Treatments in Reducing LDL-C (% change)

<table>
<thead>
<tr>
<th>Parameter / Analysis</th>
<th>ATO 0 mg</th>
<th>ATO 10 mg</th>
<th>ATO 20 mg</th>
<th>ATO 40 mg</th>
<th>ATO 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML 0 mg</td>
<td>Mean % chg</td>
<td>-1.1</td>
<td>-33.4</td>
<td>-39.5</td>
<td>-43.1</td>
</tr>
<tr>
<td>AML 5 mg</td>
<td>Mean % chg</td>
<td>-0.1</td>
<td>-38.7</td>
<td>-42.3</td>
<td>-44.9</td>
</tr>
<tr>
<td>AML 10 mg</td>
<td>Mean % chg</td>
<td>-2.5</td>
<td>-36.6</td>
<td>-38.6</td>
<td>-43.2</td>
</tr>
</tbody>
</table>

In an open-label trial, 1220 patients with comorbid hypertension and dyslipidemia received elective dose-titration with Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) over a 14-week period. Patients were required to have uncontrolled blood pressure to enter the trial (whether or not they were using antihypertensive medications at 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 blood pressure and LDL-C controlled, and neither was controlled in 62% of patients. Treatment with Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) reduced mean blood pressure –17.1 mmHg systolic and -9.6 mmHg diastolic, and reduced mean LDL-C by –32.7%, resulting in control of both blood pressure and LDL-C for 58% of these patients (controlled blood pressure and LDL-C were defined, respectively, as <140/90 mmHg and <160 mg/dL for patients with comorbid hypertension and dyslipidemia only; <140/90 mmHg and <130 mg/dL for patients with comorbid hypertension and dyslipidemia plus 1 additional cardiovascular risk factor, excluding known coronary heart disease or diabetes mellitus; and <130/85 mm Hg and <100 mg/dL for patients with comorbid hypertension and dyslipidemia plus known coronary heart disease, diabetes mellitus, or other atherosclerotic disease). Only 13% of the patients in this trial used Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) as initial therapy for comorbid hypertension and dyslipidemia, whereas the amlodipine besilate component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) comprised add-on therapy for hypertension in 56% of patients, including patients for whom the atorvastatin calcium component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) comprised initial therapy for dyslipidemia (20%), a substitution for atorvastatin calcium taken previously (18%), or a switch from another statin (18%). When evaluated according to use of antihypertensive and lipid-lowering
medications at enrollment, results showed that both blood pressure and LDL-C were brought under control for 65% of patients who used Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) as initial therapy for comorbid hypertension and dyslipidemia and for 55% to 64% of patients for whom the amlodipine besilate component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) constituted add-on therapy for hypertension (55% for such patients who had previously used lipid-lowering medications other than atorvastatin calcium, 58% for such patients who had previously used atorvastatin calcium, and 64% for such patients who had not previously used lipid-lowering medications).

**Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)**

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 atorvastatin compared to placebo in 10,305 patients (Lipid-Lowering arm - ASCOT-LLA) on fatal and nonfatal coronary events. There are 19,257 and 10,240 efficacy evaluable patients in ASCOT-BPLA and ASCOT LLA, respectively.

**In ASCOT-BPLA:**

The effect of treatment regimens based on amlodipine (5-10 mg) (n=9,681) or atenolol (50-100 mg) (n=9,661) was compared in a prospective randomized open blinded endpoint design (PROBE) in 19,342 hypertensive patients, ≥40-<80 years of age with no previous myocardial infarction or treatment for angina, at least 3 of the following predefined cardiovascular risk factors: male gender, age ≥55 years), smoking, type 2 diabetes, history of coronary artery disease event occurring in a first-degree relative before the age of 55 (males) or 60 years (females), TC: HDL ≥6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormalities, proteinuria/albminuria.

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

The ASCOT-BPLA study was stopped prematurely after 903 primary events (non-fatal MI and fatal CHD) with median follow-up of 5.5 years due to significant benefit of the amlodipine based regimen on the following secondary endpoints: all cause mortality, CV mortality and stroke. The study had planned to need at least 1150 primary endpoints.

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

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Amlodipine Based Therapy N=9639</th>
<th>Atenolol Based Therapy N=9618</th>
<th>Risk Decrease (%)</th>
<th>Log Rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=9639</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18
Non-fatal MI + Fatal CHD (Primary Endpoint) | 429 (4.5) | 474 (4.9) | 10 | 0.105
---|---|---|---|---
Total CV Events and Procedures\textsuperscript{b} | 1362 (14.1) | 1602 (16.7) | 16 | <0.001
Total Coronary Events\textsuperscript{c} | 753 (7.8) | 852 (8.9) | 13 | 0.007
Non-fatal MI (excl 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\textsuperscript{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
\textsuperscript{b}: cardiovascular mortality, non-fatal MI (symptomatic and silent), unstable angina, chronic stable angina, life-threatening arrhythmias, non-fatal heart failure, non-fatal stroke, TIA, reversible ischemic neurological deficit (RIND), retinal vascular thromboses, peripheral arterial disease and revascularization procedures
\textsuperscript{c}: fatal CHD, non-fatal MI (symptomatic and silent), chronic stable angina, unstable angina, fatal and nonfatal heart failure
\textsuperscript{d}: includes RIND

Blood pressure (SBP/DBP) decreased significantly on both treatment regimens when compared with 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 two groups were both <0.001 for SBP and DBP.

**In ASCOT-LLA:**

In the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels <6.5 mmol/l (251 mg/dl). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender, age >55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg 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, blood pressure was well controlled and similar in patients assigned atorvastatin and placebo. These changes persisted throughout the treatment period.

**Atorvastatin reduced the rate of the following events:**

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk decrease (%)</th>
<th>No. of events (atorvastatin vs. placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary events (fatal CHD plus non-fatal MI)</td>
<td>36 %</td>
<td>100 vs. 154</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total cardiovascular events and revascularization procedures</td>
<td>20 %</td>
<td>389 vs. 483</td>
<td>0.0008</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>29 %</td>
<td>178 vs. 247</td>
<td>0.0006</td>
</tr>
<tr>
<td>Fatal and non-fatal stroke*</td>
<td>26 %</td>
<td>89 vs. 119</td>
<td>0.0332</td>
</tr>
</tbody>
</table>
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 ASCOT 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 5,168 patients in the atorvastatin group (2,584 patients received amlodipine and 2,584 patients received atenolol) and 5,137 in the placebo group (2,554 patients received amlodipine and 2,583 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% confidence interval 31% to 68%, p<0.0001) compared with amlodipine + placebo,
- 39% (95% confidence interval 8% to 59%, p<0.016) compared with 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 with 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 versus -24.7/-13.6 mmHg for amlodipine plus atorvastatin vs. atenolol plus atorvastatin, and -27.1/-15.8 mmHg vs. -24.1/-13.6 mmHg for amlodipine plus placebo vs. atenolol plus placebo, respectively). The p-values on differences between 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 blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

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

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

**Use in Patients with Coronary Artery Disease (CAD)**

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

The effectiveness of amlodipine besilate in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these 663 were treated with amlodipine 5-10 mg and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

<table>
<thead>
<tr>
<th>Table 1. Incidence of Significant Clinical Outcomes for CAMELOT</th>
</tr>
</thead>
</table>

21
## CAMELOT

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Amlodipine (N=663)</th>
<th>Placebo (N=655)</th>
<th>Risk Reduction (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite CV Endpoint*</td>
<td>110 (16.6)</td>
<td>151 (23.1)</td>
<td>31% (0.003)</td>
</tr>
<tr>
<td>Hospitalization for Angina</td>
<td>51 (7.7)</td>
<td>84 (12.8)</td>
<td>42% (0.002)</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>78 (11.8)</td>
<td>103 (15.7)</td>
<td>27% (0.033)</td>
</tr>
</tbody>
</table>

* 1). Defined in CAMELOT as cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal 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.

### Treatment to Prevent Heart Attack Trial (ALLHAT)

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 besilate 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

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

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

### Use in Patients with Heart Failure

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

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors has shown that amlodipine besilate did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure.
In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

**Use in Pediatric Patients (Ages 6 to 17 years)**

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

**Atorvastatin Pharmacodynamics**

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

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

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

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

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

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 5.1-8.7% 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 coronary heart disease is discussed in this section under Clinical Studies of Combined Amlodipine and Atorvastatin in Patients with Hypertension and Dyslipidemia, Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium on fatal and nonfatal cardiovascular disease was assessed in 2838 patients with type 2 diabetes 40-75 years of age, without prior history of cardiovascular disease 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 1 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 calcium 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years. As the effect of atorvastatin calcium treatment on the primary endpoint reached the predefined stopping rules for efficacy, CARDS was terminated 2 years earlier than anticipated.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>No of Events (atorvastatin vs. placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events [fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke]</td>
<td>37 %</td>
<td>83 vs. 127</td>
<td>0.0010</td>
</tr>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42 %</td>
<td>38 vs. 64</td>
<td>0.0070</td>
</tr>
<tr>
<td>Stroke (Fatal and non-fatal)</td>
<td>48 %</td>
<td>21 vs. 39</td>
<td>0.0163</td>
</tr>
</tbody>
</table>
AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

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

A relative risk reduction in death of 27% (82 deaths in the placebo group compared to 61 deaths in the treatment arm) has been observed with a borderline statistical significance (p=0.0592). The overall incidence of adverse events or serious adverse events was similar between the treatment groups.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to atorvastatin calcium (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the atorvastatin calcium group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in placebo group. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin calcium significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 5).

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>Apolipoprotein B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>47</td>
<td>-1.5</td>
<td>-0.4</td>
<td>-1.9</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>140</td>
<td>-31.4</td>
<td>-39.6</td>
<td>2.8</td>
<td>-12.0</td>
<td>-34.0</td>
</tr>
</tbody>
</table>

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

In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. Atorvastatin calcium has not been studied in controlled
clinical trials involving pre-pubertal patients or patients younger than 10 years of age. The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin calcium therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic Properties

Pharmacokinetics and Metabolism

Absorption

In studies with amlodipine/atorvastatin: Following oral administration of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 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 calcium and atorvastatin calcium from Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) are not significantly different from the bioavailability of amlodipine besilate and atorvastatin calcium from co-administration of amlodipine besilate and atorvastatin calcium tablets as assessed by Cmax: 101% (90% CI: 98, 104) and AUC: 100% (90% CI: 97, 103) for the amlodipine component and Cmax: 94% (90% CI: 85, 104) and AUC: 105% (90% CI: 99, 111) for the atorvastatin component, respectively.

The bioavailability of the amlodipine besilate component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) was not affected under the fed state as assessed by Cmax: 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 amlodipine calcium from Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) by approximately 32% and 11%, respectively, as assessed by Cmax: 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 amlodipine 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 6-12 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 one to two hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared with 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 presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9% respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless
of the time of day of drug administration (see section 4.2 Dosage and Method of Administration).

**Distribution**

In studies with atorvastatin: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is $\geq 98\%$ bound to plasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

**Metabolism and Excretion**

In studies with amlodipine: The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing. Amlodipine is extensively 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 Drugs and Other Forms of Interaction).

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.

**Special Populations**

**Hepatic Insufficiency**

In studies with atorvastatin: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B) (see section 4.3 Contraindications).

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

In studies with amlodipine: 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.

**Gender**
In studies with atorvastatin: Plasma concentrations of atorvastatin in women differ (approximately 20% higher for Cmax 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 congestive heart failure were as expected for the patient age group studied. Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated.

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

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

Drug Interactions
In studies with atorvastatin: The effect of co-administered drugs on the pharmacokinetics of atorvastatin as well as the effect of atorvastatin on the pharmacokinetics of co-administered drugs are summarized below (See section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicinal products and other forms of interaction).

<table>
<thead>
<tr>
<th>Co-administered drug and dosing regimen</th>
<th>Atorvastatin</th>
<th>Dose (mg)</th>
<th>Change in AUC</th>
<th>Change in Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Cyclosporine 5.2 mg/kg/day, stable dose</td>
<td>10 mg QD for 28 days</td>
<td>↑7.7 fold</td>
<td>↑9.7 fold</td>
<td></td>
</tr>
<tr>
<td>*Tipranavir 500 mg ID/ritonavir 200 mg BID, 7 days</td>
<td>10 mg, SD</td>
<td>↑8.4 fold</td>
<td>↑7.6 fold</td>
<td></td>
</tr>
<tr>
<td>Telaprevir 750 mg q8h, 10 days</td>
<td>20 mg, SD</td>
<td>↑6.9 fold</td>
<td>↑9.6 fold</td>
<td></td>
</tr>
<tr>
<td>*Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days</td>
<td>20 mg QD for 4 days</td>
<td>↑5.9 fold</td>
<td>↑4.7 fold</td>
<td></td>
</tr>
<tr>
<td>*Saquinavir 400 mg BID/ ritonavir400mg BID, 15 days</td>
<td>40 mg QD for 4 days</td>
<td>↑2.9 fold</td>
<td>↑3.3 fold</td>
<td></td>
</tr>
<tr>
<td>*Cralatromycin 500 mg BID, 9 days</td>
<td>80 mg QD for 8 days</td>
<td>↑3.4 fold</td>
<td>↑4.4 fold</td>
<td></td>
</tr>
<tr>
<td>*Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days</td>
<td>10 mg QD for 4 days</td>
<td>↑2.4 fold</td>
<td>↑1.3 fold</td>
<td></td>
</tr>
<tr>
<td>*Itraconazole 200 mg QD, 4 days</td>
<td>40 mg SD</td>
<td>↑2.3 fold</td>
<td>↑0.2 fold</td>
<td></td>
</tr>
<tr>
<td>*Posamprenavir 700 mg BID/ritonavir 100</td>
<td>10 mg QD for 4 days</td>
<td>↑1.5 fold</td>
<td>↑1.8 fold</td>
<td></td>
</tr>
</tbody>
</table>

28
### Co-administered drug and dosing regimen

<table>
<thead>
<tr>
<th>Drug/Dose (mg)</th>
<th>Change in AUC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Change in Cmax&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg QD for 15 days</td>
<td>Antipyrine, 600 mg SD</td>
<td>↑0.03 fold</td>
</tr>
<tr>
<td>80 mg QD for 14 days</td>
<td>Digoxin 0.25 mg QD, 20 days</td>
<td>↑0.15 fold</td>
</tr>
<tr>
<td>40 mg QD for 22 days</td>
<td>Oral contraceptive QD, 2 months - norethindrone 1 mg -ethinyl estradiol 35 μg</td>
<td>↑0.28 fold</td>
</tr>
<tr>
<td>10 mg, SD</td>
<td>Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days</td>
<td>No change</td>
</tr>
<tr>
<td>10 mg QD for 4 days</td>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>↓0.27 fold</td>
</tr>
<tr>
<td>10 mg QD for 4 days</td>
<td>Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days</td>
<td>No change</td>
</tr>
</tbody>
</table>

<sup>a</sup>“fold” change = % change ratio [(I-B)/B], where I = pharmacokinetic value during the Interactions phase, and B = pharmacokinetic value during the baseline phase.

<sup>b</sup>See Section 4.5 for clinical significance.

### Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

<table>
<thead>
<tr>
<th>Atorvastatin</th>
<th>Drug/Dose (mg)</th>
<th>Change in AUC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Change in Cmax&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg QD for 4 days</td>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>↓1.3 fold</td>
<td>↓1.2 fold</td>
</tr>
<tr>
<td>10 mg QD for 28 days</td>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>↑0.74 fold</td>
<td>↑0.16 fold</td>
</tr>
<tr>
<td>10 mg QD for 28 days</td>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>↑0.51 fold</td>
<td>0 fold</td>
</tr>
<tr>
<td>10 mg, SD</td>
<td>Atorvastatin 10 mg QD, 7 days</td>
<td>↑0.33 fold</td>
<td>↑0.38 fold</td>
</tr>
<tr>
<td>80 mg, SD</td>
<td>Amlodipine 10 mg, single dose</td>
<td>↑0.15 fold</td>
<td>↓0.12 fold</td>
</tr>
<tr>
<td>10 mg QD for 2 weeks</td>
<td>Cimetidine 500 mg QID, 2 weeks</td>
<td>↓0.001 fold</td>
<td>↓0.11 fold</td>
</tr>
<tr>
<td>40 mg QD for 28 weeks</td>
<td>Colestipol 10 mg BID, 2 weeks</td>
<td>Not determined</td>
<td>↓0.26 fold**</td>
</tr>
<tr>
<td>10 mg QD for 15 days</td>
<td>Maalox TC® 30 mL QD, 17 days</td>
<td>↓0.33 fold</td>
<td>↓0.34 fold</td>
</tr>
<tr>
<td>40 mg SD</td>
<td>Elavireze 600 mg QD, 14 days</td>
<td>↓0.41 fold</td>
<td>↓0.01 fold</td>
</tr>
<tr>
<td>40 mg SD</td>
<td>*Rifampin 600 mg QD, 7 days (co-administered)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>↑0.30 fold</td>
<td>↑1.72 fold</td>
</tr>
<tr>
<td>40 mg SD</td>
<td>*Rifampin 600 mg QD, 5 days (doses separated)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>↓0.80 fold</td>
<td>↓0.40 fold</td>
</tr>
<tr>
<td>40 mg SD</td>
<td>Gemfibrozil 600 mg BID, 7 days</td>
<td>↑0.35 fold</td>
<td>↓0.004 fold</td>
</tr>
<tr>
<td>40 mg SD</td>
<td>Fenofibrate 160 mg QD, 7 days</td>
<td>↑0.03 fold</td>
<td>↓0.02 fold</td>
</tr>
</tbody>
</table>

<sup>†</sup>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.

<sup‡</sup>The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used.

### 5.3 Preclinical Safety Data
Carcinogenesis

In studies with amlodipine: Rats and mice treated with amlodipine in the diet for two 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/m² basis) was close to the maximum tolerated dose for mice but not for rats.

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 levels.

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 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/m² 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, 40, or 120 mg/kg for two years.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf Life

For expiry date, please see outer package.
6.2 Special Precautions for Storage

*Store at temperatures not exceeding 30° C*

6.3 Availability

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 5/10 mg Tablets are white, oval coated tablets debossed with “Pfizer” on one side and “CDT 051” on the other side. Available as blisterpacks of 10’s in boxes of 30’s.

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) 10/10 mg Tablets are blue, oval coated tablets debossed with “Pfizer” on one side and CDT 101” on the other side. Available as blisterpacks of 10’s in boxes of 30’s.

6.4 Caution:

*Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. KEEP OUT OF REACH OF CHILDREN*

Manufactured by: Pfizer Manufacturing Deutschland
Mooswaldallee 1, 79090 Freiburg, Germany

Imported by: PFIZER, INC.
23/F Ayala Life – FGU Center
6811 Ayala Avenue, Makati City, Philippines
Under the authority of PFIZER INC., New York, N.Y., U.S.A.

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