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Grapefruit Juice

besilate component of amlodipine/atorvastatin is chemically (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)amlodipine described 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 $C_{\infty}H_{\infty}ClN_{\nu}Q_{\nu}$ -Ca, $H_{\nu}Q_{\nu}Q_{\nu}$. The atorvastatin calcium component of amlodipine/atorvastatin is chemically described as [R-(R^*, R^*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-([phenylamihocyatonyl-1-hypyrole-1-heptanoic acid, calcium sat (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{\infty}H_{34}$ FN $_{\nu}Q_{\nu}Ca^{\bullet}3H_{\nu}Q$. The structural formula is shown below:

• Ca²⁺ • 3H₂O

Amlodipine besilate Atorvastatin calcium

3.0 FORMULATION/COMPOSITION

Amiodipine besilate/Atorvastatin calcium (Norvasc Protect[®]) 5 mg/10 mg Tablets: Each tablet contains amiodipine besilate equivalent to 5 mg amiodipine and atorvastatin calcium, equivalent to 10 mg

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) 10 mg/10 mg Tablets: Each tabletอาการของสนาก หลวยสนาก เลยเนนาก เพชาหลระ Frotect") 10 mg/10 mg lablets: Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine and atorvastatin calcium, equivalent to 10 mg atorvastatin.

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) 5 mg/20 mg Tablets; Each tablet contains amlodinine besilate equivalent to 5 mg amlodinine and atorvastatin calcium, equivalent to 20 mg Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) 10 mg/20 mg Tablets: Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine and atorvastatin calcium, equivalent

4.0 CLINICAL PARTICULARS 4.1 Therapeutic Indications

Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) Tablet is indicated for the following patient

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

Patients at increased cardiovascular risk due to the presence of symptomatic Coronary Heart Disease (CHD) expressed as angina with the additional modifiable risk factor of dyslipidemia; 3. Prevention of cardiovascular complications in hypertensive patients (see below - Prevention of

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

Hypertension 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 amiodipine) may benefit from the addition of the amiodipine component of Amiodipine besilate/Altovastatin calcium (Norvasc Protect®), in the same manner as they would benefit from the addition of amiodipine alone. Amlodinine is also indicated to reduce the risk of fatal CHD and non-fatal myocardial infarction (MI).

and to reduce the risk of stroke Coronary Artery Disease he amlodipine component is indicated to reduce the risk of coronary revascularization procedures and the need for hospitalization due to angina in patients with coronary artery disease (CAD).

Chronic Stable Angina The amlodipine component is indicated for the first-line treatment of myocardial ischemia, whether due The aminoiphile component is microacer for the inits-line freatment of injudication is crienia, whether due to fixed obstruction (stable anglina) and/or vasospasmivasconstriction (Prizmetal's or variant anglina) of coronary vasculature. Amilodipine besilate/Atorvastatin calcium (Norvasc Protect®) may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasmivasoconstriction has not been confirmed. Amilodipine besilate/Atorvastatin calcium (Norvasc Protect®) may be used alone or in combination with other antianginal drugs in patients with section better to extract the abstract part of the control of the protection of the control of the control

with angina that is refractory to nitrates and/or adequate doses of beta-blockers. The atoryastatin component is indicated as an adjunct to diet for the treatment of patients with elevated The advastant on pippinent is mindated as an adjunct to dier to the retardinant placents with elevative total cholesterol (total-O), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) and to increase high-density lipoprotein -cholesterol (HDL-C) in patients with primary hypercholesterolemia, cheterozygous familial and nonfamilial hypercholesterolemia, combined (mixed) hyperlipidemia (Fredrickson Types IIa and IIb), elevated serum TG levels (Fredrickson Type IV), and in patients with dyspetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

The atorvastatin component is also indicated for the reduction of total C and LDL-C in patients with homozygous familial hypercholesterolemia (FH). Prevention of Cardiovascular Complications In patients without clinically evident cardiovascular disease (CVD), and with or without dyslipidemia, but with multiple risk factors for CHD such as smoking, hypertension, diabetes, low HDL-C, or a family history of early CHD, atorvastatin is indicated to: Reduce the risk of fatal CHD and non-fatal MI

Reduce the risk of stroke Reduce the risk of revascularization procedures and angina pectoris In patients with clinically evident CHD, atorvastatin is indicated to:

Reduce the risk of non-fatal MI Reduce the risk of fatal and non-fatal stroke

Reduce the risk for revascularization procedures Reduce the risk of hospitalization for congestive heart failure (CHF) Reduce the risk of angina

Pediatric Patients (10-17 years of age)

Initial Therapy

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

nary tie colorwing includings are present.

LDL-C remains ≥190 mg/dL or

LDL-C remains ≥160 mg/dL and

• There is a positive family history of premature CVD or

• Two or more other CVD risk factors are present in the pediatric patient.

4.2 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 5 mg/10 mg to a maximum dose of 10 mg/20 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/atoryastatin should be used in addition to non-pharmacological measures, including an appropriate diet, exercise and weight reduction in obese patients, smoking cessation, and to treat underlying medical problems, when the response to these measures have been inadequate. Following initiation and/or titration of amlodipine/atorvastatin, lipid levels should be analyzed and BP

measured within 2 to 4 weeks, and dosage of amiddipine and atorvastatin components should be adjusted accordingly. Titration for BP response may proceed more rapidly if clinically warranted.

Initial Inerapy
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 amilodipine adorvastatin components considered separately. The maximum dose of the amlodipine component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) is 10 mg once daily. The maximum dose of the atorvastatin component of Amlodipine besilate/Atorvastatin calcium (Norvasc Protect) is 20 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 and Atorvastatin calcium or a dose of Amlodipine besilate and Atorvastatin calcium (Norvasc Protect®) with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, BP lowering, or lipid

lowering effect. Ambidipine 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 Ambidipine 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. <u>Concomitant Medication</u> (see also section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction)

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

The atorvastatin 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 3-hydroxy-3-methylgilutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrates should generally be avoided (see section 4.4 Special Warnings and Precautions for Use and section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction).

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

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 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 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 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 in pediatric populations with amlodipine alone and atorvastatin

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

upper limit of normal [ULN]

Skeletal Muscle Effects

alone (see below)

The effect of amlodipine on BP in patients less than 6 years of age is not known. Studies with atorvastatin Use in Pediatric Patients with Severe Dyslipidemias The regidure ration with Severe Dysiphoenias.

For patients aged 10 years and above, the recommended starting dose is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy (see section 4.1 Therapeutic

Indications, and section 5.1 Pharmacodynamic Properties). Adjustments should be made at intervals of 4 weeks or more. Experience in pediatric patients younger than 10 years of age is derived from open-label studies (see section 4.8 Undesirable Effects, section 5.1 Pharmacodynamic Properties, and section 5.2 Pharmacokinetic Properties - Special Populations).

Use in Combination with Other Medicinal Compounds Studies with atorvastatin In cases where co-administration of atorvastatin with cyclosporine, telaprevir, the combination tipranavir/ritonavir, or glecaprevir/pibrentasvir is necessary, the dose of atorvastatin should not exceed 10 mg.

Use of atorvastatin is not recommended in patients taking letermovir co-administered with cyclosporine Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have also been noted with other human immunodeficiency virus (HIV) protease inhibitors (loginavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir, fosamprenavir/ritonavir and nelfinavir), hepatitis C (HCV) protease inhibitors (boceprevir, elbasvir/grazoprevir, simeprevir), clarithomycin, 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 section 4.4 Special Warnings and Precautions for Use - Skeletal Muscle Effects and section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction 4.3 Contraindications Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) is contraindicated in patients who: Have known hypersensitivity to dihydropyridines,* amlodipine, atorvastatin, or any component of this medication including: calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, magnesium stearate, silicon dioxide and hydroxypropylcellulose,

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.

2. Have active liver disease or unexplained persistent elevations of serum transaminases >3 x the

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

Use in Patients with Impaired Hepatic Function (see also section 4.3 Contraindications)

As with other input-overing agents of the nivid-coar reductase inhibition class, intolerate (>3 × 0Liv) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin given at doses of 10 mg, 20 mg, 40 mg and 80 mg. Persistent increases in serum transaminases (>3 × ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10 mg, 20 mg, 40 mg and 80 mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels

returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin

Liver function tests should be performed before the initiation of treatment and periodically thereafter.

As with other lipid-lowering agents of the HMG-CoA reductase inhibitor class, moderate (>3 \times ULN)

performed. Patients who develop increased transaminase levels should be monitored until the annormality(es) resolve(s). Should an increase in alanine transaminase (ALT) or aspartate transaminase (AST) > 3 x ULN persist, reduction of dose or withdrawal of Amlodipine besilate/Abovastatin 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)

Myalgia has been reported in atorvastatin-treated patients (see section 4.8 Undesirable Effects). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 × ULN, should be considered in any patient with diffuse myalgias.

muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to

nuscle 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 is increased with concurrent administration of drugs that increase the systemic concentration of atorvastatin (see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction and section 5.2 Pharmacokinetic Properties). Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. CYP3A4 is the primary hepatic isozyme known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, HIV/HCV protease inhibitors, HCV NS5A/NSSB inhibitors, letermovir, or lipid-modifying doses of niacin should carefully weight he potential benefits and risks and should carefully moritor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the 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 Initial motions of treatpy and curry gary periods or upward ocsage turduor to retirier drug. Interetore, lower starting and maintenance doses of the atorvastatin component should also be considered when taken concomitantly with the aforementioned drugs (see section 4.2 Dosage 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 (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 besilate/Atorvastatin calcium (Norvasc Protect®) may cause an elevation of CPK due to the atorvastatin component (see section **4.8 Undesirable Effects**) There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after

treatment with some statins (see section 4.8 Undesirable Effects). IMNM is clinically characterized

by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, positive anti-HMG CoA reductase antibody and improvement with immunosuppressive agents. 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 that damyopality of uniting a list accomplished by the properties of the properties Hemorrhagic Stroke A post-hoc analysis of a clinical study in 4,731 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 ischemic attack (1IA) 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 atorvastatia 180 mg there were fewer strokes of any type (265 atorvastatin vs. 311 placebo) and fewer CHD events (123 atorvastatin vs. 204 placebo) (see section 5.1 Pharmacodynamic Properties

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_{min} 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 besilate/Atorvastatin calcium (Norvasc Protect®) and other drugs, although studies have been conducted using the individual amlodipine and atorvastatin components, as described below: Amlodipine Interactions Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs,

Increases in glycated hemoglobin (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.

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, irtonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors.

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. 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 CYPSA4, the primary enzyme responsible for metabolism of amlodipine with therefore, administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in

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.

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) In the following studies, there were no significant changes in the pharmacokinetics of either amlodipine or another drug within the study, when co-administered. Special Studies: Effect of Other Agents on Amlodipine

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

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

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

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 section 4.2 Dosage and Method of Administration - Use in Combination with Other Medicinal Compounds and section 4.4 Special Warnings and Precautions for Use - Skeletal Muscle Effects).

with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin The extent of interaction and potentiation of effects depend on the variability of effect on cytochrome P450 3A4. Erythromycin/Clarithromycin

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin. (see section 5.2 Pharmacokinetic Properties). Diltiazem Hvdrochloride

with an increase in atoryastatin ALIC (see section 5.2 Pharmacokinetic Properties)

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

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

Atoryastatin 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 an inclease in exposure to advissant (radio of ADC: 8.7; see section 9.2.2 Pharmacownieus Properties). Cyclosporine is an inhibitor of organic anion-transporting polypeptide 1811 (OATP181), OATP183, 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 Dosage and Method of Administration - Use in Combination with Other Medicinal Compounds).

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

Concomitant administration of atorvastatin 20 mg and letermovir 480 mg daily resulted in an increase in exposure to atorvastatin (ratio of AUC: 3.29; see section **5.2 Pharmacokinetic Properties**). Letermovir inhibits efflux transporters P-gp, BCRP, MRP2, OAT2 and hepatic transporter OATP1B1/1B3, thus it increases exposure to atorvastatin. Do not exceed 20 mg atorvastatin daily (see section 4.2 Dosage 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 (see section 4.2 Dosage 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 atoryastatin with rifampin is recommended. as delayed administration of atoryastatin after administration of rifamnin has been associated with significant reduction in atorvastatin plasma concentrations (see section 5.2 Pharmacokinetic Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides decreased atorvastatin plasma concentrations (ratio of AUC: 0.66); however,

LDI-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 atoryastatin, However, lipid effects were greater when atoryastatin 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 $Co-administration of at or vastatin (10 \ mg \ once \ daily) \ and \ az ith romycin (500 \ mg \ once \ daily) \ did \ not \ alter the \ plasma \ concentrations \ of \ atorvastatin.$

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

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

were observed. 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

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

of fusidic acid treatment. Statin therapy may be re-introduced seven days after the last dose of

Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine. Other Concomitant Therapy In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

4.6 Fertility, Pregnancy and Lactation Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) is contraindicated in pregnancy due to the atorvastatin component. Women of childbearing potential should use adequate contraceptive 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 bazards to the fetus. . Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) is contraindicated while breast-feeding due to the atoryastatin component. It is not known whether atoryastatin 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 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). Evening of rats feated with announce (see section 1.5. Trectimina State) takes. Experience in humans indicates that annotdipine 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

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 1,092 patients in double blind, placebo-controlled studies treated for concomitant hypertension and dyslipidemia In clinical trials, no adverse events peculiar to combination therapy with amiodipine and atorvastatin have been observed. Adverse events have been limited to those that were reported previously with amiodipine and/or atorvastatin (please see respective adverse event experiences below).

was 4.17 mcg/kg

MedDRA System Organ Class

Nervous System Disorders

4.7 Effects on Ability to Drive and Use Machines

in general, combination ribriapy with annothing and advives when the latest. 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 postmarketing experience with amlodipine Amlodipine Experience Amlodipine is well tolerated. In placebo-controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects wer

In general, combination therapy with amlodipine and atorvastatin was well tolerated. For the most part,

Cardiac Disorders Palpitations

Undesirable Effects

Headache, dizziness, somnolence

vasculai Distribers		Fluaring
Gastrointestinal Disorders		Abdominal pain, nausea
General Disorders and Administration Sit	te Conditions	Edema, fatigue
In these clinical trials no pattern of clinical amlodipine has been observed. Less commonly observed side effects in management of the common of the clinical strains of the	, ,	ant laboratory test abnormalities related rience with amlodipine include:
MedDRA System Organ Class	Undesirable	Effects
Blood and Lymphatic System Disorders	Leukopenia, 1	thrombocytopenia
Metabolism and Nutrition Disorders	Hyperglycemi	ia

Psychiatric Disorders Insomnia, mood altered

Nervous System Disorders	Hypertonia, hypoesthesia/paresthesia, neuropathy peripheral, syncope, dysgeusia, tremor, extrapyramidal disorder
Eye Disorders	Visual impairment
Ear and Labyrinth Disorders	Tinnitus
Vascular Disorders	Hypotension, vasculitis
Respiratory, Thoracic, and Mediastinal Disorders	Cough, dyspnea, rhinitis
Gastrointestinal Disorders	Change in bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
Skin and Subcutaneous Tissue Disorders	Alopecia, hyperhidrosis, purpura, skin discoloration, urticaria
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle spasms, myalgia
Renal and Urinary Disorders	Pollakiuria, micturition disorder, nocturia
Reproductive System and Breast Disorders	Gynecomastia, erectile dysfunction
General Disorders and Administration Site Conditions	Asthenia, malaise, pain
Investigations	Weight increased/decreased
multiforme. Hepatitis, jaundice and hepatic enzyme econsistent with cholestasis). Some cases in association with use of amlodipine. In As with other calcium channel blockers, cannot be distinguished from the natural bradycardia, ventricular tachycardia and a	ctions including pruritus, rash, angioedema, and erythema elevations have also been reported very infrequently (mostly severe enough to require hospitalization have been reported many instances, causal association is uncertain. the following adverse events have been rarely reported and history of the underlying disease: MI, arrhythmia (including atrial fibrillation) and chest pain.
Pediatric Patients (Aged 6-17 years) Amlodipine is well tolerated in children. A	dverse events were similar to those seen in adults. In a study

Vascular Disorders Vasodilatation Respiratory, Thoracic, and Mediastinal Disorders Epistaxis Gastrointestinal Disorders Abdominal pain General Disorders and Administration Site Conditions | Asthenia The majority of adverse events were mild or moderate. Severe adverse events (predominantly headache) were experienced by 7.2% with amlodipine 2.5 mg, 4.5% with amlodipine 5 mg, and 4.6% with placebo. The most common cause of discontinuation from the study was uncontrolled

hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In the

Undesirable Effects

Headache, dizzine

of 268 children, the most frequently reported adverse events were

MedDRA System Organ Class

Nervous System Disorder

change in heart rate. Atorvastatin Experience

Post-marketing Experience

with atorvastatin:

Autovastatin placebo-controlled clinical trial database of 16,066 (8,755 atorvastatin vs. 7,311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo. The most frequent (≥1%) adverse effects that may be associated with atorvastatin therapy, reported in patients participating in placebo-controlled clinical studies include Infections and infestations: Nasopharyngitis Metabolism and nutrition disorders: Hyperglycemia

 $\textbf{Respiratory, thoracic and mediastinal disorders:} \ \textbf{Pharyngolaryngeal pain, epistaxis}$ 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 placebo-controlled clinical trials include: Psychiatric disorders: Nightmare Eve disorders: Blurred vision 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 positive in urine.

Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. No clinically significant effect on growth and sexual maturation was observed in a 3-year study in children ages 6 and above based on the assessment of overall maturation and development assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in pediatric patients was similar to the known safety profile of atorvastatin in adult patients.

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

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, dysqeusia Gastrointestinal disorders: Pancreatitis
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis,

post-marketing experience, the following additional undesirable effects have been reported

angioedema, erythema multiforme, bullous rashes Musculoskeletal and connective tissue disorders: Rhabdomyolysis, immune-mediated necrotizing General disorders and administration site conditions: Chest pain, peripheral edema, fatigue 4.9 Overdose and Treatment There is no information on overdosage with Amlodipine besilate/Atorvastatin calcium (Norvasc

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 rippotentision by 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. 5.0 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 a precursor of sterols, including cholesterol. Clinical Studies of Combined Amlodipine and Atorvastatin in Patients with Hypertension and

eter/Analysis Mean change ATOb 0 mg ATO 10 mg ATO 20 mg ATO 40 mg ATO 80 mg (mmHg) Difference vs AML° 0 mg placebo (mmHg) -12.8 Mean change

-16.2

Efficacy in Terms of Reduction in Blood Pressure and LDL-C Efficacy of the Combined Treatments in Reducing Systolic B

(mmHq)

Difference vs

Mean change

(mmHg)
Difference vs.
placebo (mmHg)

AML 5 mg

AML 10 mg

Blood pres Atorvastatin

a Blood pressi

^c Amlodipine

c Amlodipine

Efficacy of the Combined Treatments in Reducing Diastolic BPa Parameter/Analysis ATO 0 mg ATO 10 mg ATO 20 mg ATO 40 mg ATO 80 mg Mean change -3.3 (mmHg) AML° 0 mg Difference vs. placebo (mmHg) -0.8 1.8 -8.4 -9.4 Mean change -7.6 -8.2 (mmHg)
Difference vs AML 5 mg 4.3 4.9 -6.1 4.0 olacebo (mmHg) Mean change -10.4 -9.1 -9.8

12.9

In an open-label trial, 1,220 patients with comorbid hypertension and dyslipidemia received elective dose titration with Amlodipine besilate/Altorvastatin calcium 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 besilate/Altorvastatin calcium 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 55% of these patients
(controlled BP and LDL-C were defined, respectively, as <140/90 mmHg and <160 mg/dL for patients
with comorbid hypertension and dyslipidemia only; <140/90 mmHg and <130 mg/dL for patients
with comorbid hypertension and dyslipidemia plus 1 additional cardiovascular risk factor, excluding
known CHD or diabetes mellitus; and <130/85 mmHg and <100 mg/dL for patients with comorbid
hypertension and dyslipidemia plus known CHD, diabetes mellitus, or other atherosclerotic disease).
Only 13% of the patients in this trial used Amlodipine besilate/Atorvastatin calcium as initial therapy
for comorbid hypertension and dyslipidemia, whereas the amlodipine component of Amlodipine
besilate/Atorvastatin calcium comprised add-on therapy for hypertension in 56% of patients, including
patients for whom the atorvastatin calcium component of Amlodipine besilate/Atorvastatin calcium
comprised initial therapy for dyslipidemia (20%), a substitution for atorvastatin taken previously (18%).

to a switch from another statin (-or), when evaluated according to the use of antihyper lensive 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 besilate/Atorvastatin calcium as initial therapy for comorbid hypertension and dyslipidemia and for 55% to 64% of patients for whom the amlodipine component of Amlodipine besilate/Atorvastatin calcium constituted add-on therapy for hypertension 55% for such patients who had previously used lipid-lowering medications other than atorvastatin, Component of Aminophile Desilater-Andreasam calcular Constitute activity in energy for hypereniston (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 2×2 factorial design Study comparing two antihypertensive regimens in a total of 19,342 patients (Blood Pres Lowering arm – ASCOT-BPLA), as well as the effect of addition of 10 mg atorvastatin comp 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 In Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm The effect of treatment regimens based on amlodipine (5 mg-10 mg) (n = 9681) or atenolol (50 mg-100 mg) (n = 9661) was compared in a prospective randomized open blinded endpoint

The primary endpoint of non-fatal ML+ fatal CHD did not reach statistical significance when comparing The primary endpoint of non-tatal with Hadat Christopher and the anicologine-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.

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VIATRIS NORVASC_PROTECT_5mg_10mg_10mg_10mg_5mg_20mg_10mg_20mg_30 PP NORVASC PROTECT 5,10/10, 5,10/20mg PH Date: 07 Aug 23 Description Component Type Leaflet 2768 No. of colours 400564226;400564231 **Affiliate Item Code** 3221597 Viatris SAP No. Colours 400564232:400564233 perseded Affiliate Item Code Vendor Job No. 109047930/0020 N/A Non-Print 3221597 TrackWise/GLAMS Job No-Artwork Proof No. Colours DRP - 2791, DRP - 3146, DR - XY30121, DR - XY3012 MA No. **Client Market Philippines Equate CMYK** Supplier SAP No. N/A Barcode Info N/A with 3D Render ID **New Supplier Code** PAA212318 N/A Main Font Dimensions PAA191655 Superseded Supplier Code Packing Site/Printer

(PROBE) design in 19,342 hypertensive patients, ≥40 to <80 years of age with no previous MI or treatment for angina, at least three of the following predefined cardiovascular risk factors: male gender, age ≥55 years, smoking, Type 2 diabetes, history of CAD event occurring in a first-degree relative before the age of 55 years (males) or 60 years (females), total-C: HDL ≥6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific electrocardiogram (ECG) abnormalities, proteinuria/albuminuria. To attain further BP goals (<140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients), perindopril (4 mg-8 mg) could be added to the amlodipine group and bendroffumethiazide potassium (1.25 mg-2.5 mg) to the atenolol group. Third line therapy was doxazosin gastrointestinal therapeutic system (GITS) (4 mg-8 mg) in both arms The ASCOT-BPLA study was stopped prematurely after 903 primary events (non-fatal MI and fatal CHD) with median follow-up of 5.5 years due to significant benefit of the amlodipine based regimen on the following secondary endpoints: all-cause mortality, cardiovascular (CV) mortality and stroke. The study had planned to need at least 1,150 primary endpoints. Time: 18:00 Page Count 1 of 2 Black **Helvetica Neue LT W1G** Body Text Size 6 pt 1000 x 180 mm Min Text Size used 6 pt 003000009427_3_1000x180mm_v1_FVID1387845

antibiotics, and oral hypoglycemic drugs.

Recurrent Stroke)

CYP3A4 Inducers

Cimetidine

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

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

Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine Aluminum/Magnesium (Antacid) Special Studies: Effect of Amlodipine on Other Agents

of ethanol.

Inhibitors of Cytochrome P450 3A4 Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin

Diaoxin

None known Atorvastatin Interactions

Pfizer Manufacturing Freiburg (Freiburg - DE) Keyline/Drawing No Sign-offs

V3 MAY 2023

-3.4

-12.2

-9.2

14.6

-12.7

-9.7

-16.3

-16.1

-13.1

-6.5 -7.8 -7.3 -44.9

In a double-blind, placebo-controlled study of 1,660 patients with comorbid hypertension and dyslipidemia, once-daily treatment with eight dose combinations of amiodipine 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. amiodipine alone (5 mg or 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, or 80 mg), and placebo. In addition to concomitant hypertension and dyslipidemia, 15% of the patients had diabetes mellitus, 22% were smokers and 14% had a positive family history of CVD. At 8 weeks all eight combination-treatment groups demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP and LDL-C (see table below).

(mmHg)
Difference vs. -5.8 placebo (mmHg) Efficacy of the Combined Treatments in Reducing LDL-C* (% change)

Parameter/Analysis ATO* 0 mg ATO 10 mg ATO 20 mg ATO 40 mg ATO 80 mg AML 5 mg Mean% change AML 10 mg | Mean% change

or a switch from another statin (18%). When evaluated according to the use of antihypertensive and

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Dosage

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 Mortalityd	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
Myocardial infarction cardiovascular mortality, non-fatal	, , , ,	, , , ,		

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
catal CHD, non-fatal MI (symptomatic and silent), chronic stable angina, unstable angina, fatal an non-fatal heart failure dt 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. -25.77-15.6 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 the ASCOT-LLA, the effect of atorvastatin on fatal and non-fatal CHD was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), without a previous MI and with TC levels <6.5 mmol/L (251 mg/dL). Additionally all patients had at least three of the following cardiovascular risk factors: male gender, age >55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. In this double-blind, placebo-controlled study patients were treated with antihypertensive therapy (goal BP <140/90 mmHg for non-diabetic patients, <130/80 mmHg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n = 5168) or placebo (n = 5137). As the effect of atorvastatin treatment compared to placebo exceeded the significance threshold during an interim analysis, the ASCOT-LLA was terminated early at 3.3 years instead of 5 years. Additionally, BP was well controlled and similar in patients assioned to atorvastatin and placebo. These changes persisted throughout the and similar in patients assigned to atorvastatin and placebo. These changes persisted throughout the treatment period.

Atorvastatin reduced the rate of the following events:

No. of Events p-value Decrease (%) (Atorvastatin vs. Placebo Coronary events (fatal CHDa plus 100 vs. 154

non-fatal MIb)					
Total cardiovascular events and	20%	389 vs. 483	0.0008		
revascularization procedures					
Total coronary events	29%	178 vs. 247	0.0006		
Fatal and non-fatal stroke*	26%	89 vs. 119	0.0332		
^a Coronary Heart Disease					
^b Myocardial Infarction					
*Although the reduction of fatal and non-fatal strokes did not reach a predefined significance level					
(p = 0.01), a favorable trend was observed with a 26% relative risk reduction.					
The total mortality and cardiovascular	mortality have no	nt heen significantly r	reduced although		

ough a favorable trend was observed. In Anglo-Scandinavian Cardiac Outcomes Trial 2×2

In Augustian and a Colonia Control Property of the pre-specified ASCOT 2×2 factorial analysis investigated the potential differential effect (interaction) of adding atomastatin to the amflodipine vs. the atenolol group in ASCOT-LLA.

For the 10,305 patients enrolled in ASCOT-LLA, there were 5,168 patients in the atomastatin group (2.584 patients received amlodipine and 2.584 patients received atendol) and 5.137 in the placebo

(2,304 patients received annoughing and 2,363 patients received atendor) and 3,137 in the placebo group (2,554 patients received annologing and 2,583 patients received atendor). 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 amilodipine with atorvastatin resulted in a significant risk reduction in the composite primary endpoint of fatal CHD and non-fatal MI by: 65% (65% CI 31%-68%, p <0.0001) compared to amilodipine + 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

blood pressure (2010). 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/lacebo 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 amilodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking-induced coronary vasoconstriction. In patients with hypertension, once daily dosing provides clinically significant reductions of BP in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption. Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids

and is suitable for use in patients with asthma, diabetes, and gout Use in Patients with CAD The effects of amlodipine on cardiovascular morbidity and mortality, the progression of coronary atherosclerosis, and carotid atherosclerosis were studied in the Prospective Randomized Evaluation of the Vascular Effects of NORVASC Trial (PREVENT), This multicenter, randomized, double blind,

placebo-controlled study followed 825 patients with angiographically defined CAD for 3 years. The population included patients with previous MI (45%), percutaneous transluminal coronary angioplasty (PTCA) at baseline (42%), or history of angina (69%). Severity of CAD ranged from 1-vessel disease (45% of patients) to 3+ vessel disease (21% of patients). Patients with uncontrolled hypertension (DBP > 95 mm Hg) 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 endopint of cardiovascular death. ML stroke, PTCA company aftery bypass graft (CABG), hospitalization for unstable angina, and worsening CHF. A significant reduction (-42%) in revascularization procedures (PTCA and CABG) was also seen in the amlodipine-treated patients. Fewer hospitalizations (-33%) were seen for unstable angina in amlodipine-treated patients than in the placebo group. The effectiveness of amlodipine in preventing clinical events in patients with CAD has been evaluated

in an independent, multicenter, randomized, double-blind, placebo-controlled study of 1,997 patients; in an independent, mulicentier, failubilities of the comparison of Amoldipine vs. Enalagni to Limit Occurrences of Thrombosis (CAMELOT). Of these, 663 were treated with amlodipine 5 mg to 10 mg and 655 patients were treated with placebo, in

addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amiodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD. Table 1. Incidence of Significant Clinical Outcomes for CAMELOT CAMELOT Clinical Outcomes Risk Reduction Placebo N (%) (N = 663)(p-value) Composite CV^b Endpoint

Hospitalization for Angina	51	84	42%				
	(7.7)	(12.8)	(0.002)				
Coronary Revascularization	78	103	27%				
	(11.8)	(15.7)	(0.033)				
*1). Defined in CAMELOT as cardiov							
coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or							
non-fatal stroke or TIA, any diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD							
2). The composite CV endpoint was							
^a Comparison of Amlodipine vs. Ena	lapril to Limit Occurre	nces of Thrombosis.					
^b Cardiovascular.							
Treatment to Prevent Heart Attack Tr	rial						
A randomized double-blind me	orbidity-mortality str	udy called the A	intihypertensive and				
Lipid-Lowering Treatment to Prevent	Heart Attack Trial (ALL	HAT) was performed to	o compare newer drug				

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including MI or stroke >6 months or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C <35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%). The primary endpoint was a composite of fatal CHD or non-fatal MI. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98; 95% Cl 0.90-1.07; p=0.65. In addition, there was no significant difference in all-cause

Expire-Lowering freedings of resembles to resemble a fundamental execution was performed to compare never originate the respired and produced and the respirate and office and the respirate and

in mild to moderate hypertension.

and Method of Administration).

Prevention of Cardiovascular Complications

Anglo-Scandinavian Cardiac Outcomes Trial.

MI (fatal and non-fatal AMI, silent MI)

Stroke (fatal and non-fatal)

efficacy, CARDS was terminated 2 years earlier than anticipated. The absolute and relative risk reduction effect of atorvastatin is as follows:

mortality between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.96; 95% CI 0.89-1.02; p = 0.20. Use in Patients with Heart Failure Hemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise

tolerance, left ventricular ejection fraction and clinical symptomatology. A placebo-controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure. In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III - IV heart failure without clinical symptoms or objective findings suggestive of underlying ischemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total

or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo Use in Pediatric Patients (Aged 6 to 17 years) The efficacy of amiodipine in hypertensive pediatric patients 6 to 17 years of age was demonstrated in one 8-week double-blind, placebo-controlled randomized withdrawal trial in 268 patients

with hypertension. All patients were randomized to the 2.5 mg or 5 mg treatment arms and followed for 4 weeks after which they were randomized to continue 2.5 mg or 5 mg amlodipine or placebo for an additional 4 weeks. Compared to baseline, once daily treatment with amlodipine 5 mg resulted in statistically significant reductions in SBP and DBP. Placebo-adjusted, mean reduction in seated SBP

was estimated to be 5.0 mmHg for the 5 mg dose of amlodipine and 3.3 mmHg for the 2.5 mg dose of amlodipine. Subgroup analyses indicated that younger pediatric patients aged 6 to efficacy results comparable to those of the older pediatric patients aged 14 to 17 years 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, nonfamilial forms of hypercholesterolemia, and mixed dyslighdemia, atorvastatin reduces total-C, LDL-C, and apo B. Atorvastatin also reduces very-low-density lipoprotein cholesterol (VLDI-C) and TG and produces variable increases in HDI-C. Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL in patients with homozygous FH, a population that has not normally responded to lipid-lowering medication. Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration. Individualization of drug dosage should be based on therapeutic response (see section 4.2 Dosage

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

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

The effects of atorvastatin on ischemic events and total mortality were studied in the Myocardial

ischemia Reduction with Aggressive Cholesterol Lowering study (MiRACL). This multicenter, randomized, double-blind, placebo-controlled study followed 3,086 patients with acute coronary syndromes; unstable angina or non-Q wave MI. Patients were treated with standard care, including diet, and either atorvastatin 80 mg daily or placebo for a median duration of 16 weeks. The final LDL-C, total-C, HDL-C and TG levels were 72 mg/dL, 147 mg/dL, 48 mg/dL, and 139 mg/dL in the atorvastatin group, respectively, and 135 mg/dL, 217 mg/dL, 46 mg/dL, and 187 mg/dL, respectively, in the placebo group. Atorvastatin significantly reduced the risk of ischemic events and death by 16% The risk of experiencing re-hospitalization for angina pectoris with documented evidence of myocardial ischemia was significantly reduced by 26%. Atorvastatin reduced the risk of ischemic events and death to a similar extent across the range of baseline LDL-C. In addition, atorvastatin reduced the risk

of ischemic events and death to similar extents in patients with non-Q wave MI and unstable angina, as well as in males and females and in patients ≤65 years of age and >65 years of age

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,

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 \leq 4.14 mmol/L (160 mg/dL) and TG \leq 6.78 mmol/L (600 mg/dL). Additionally, all patients had at least one of the following risk factors: hypertension, current smoking retinopathy, microalbuminuria or macroalbuminuria. In this randomized, double-blind, multicenter, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n = 1428) or placebo (n = 1410) for a median follow-up of 3.9 years. As the effect of atorvastatin treatment on the primary endpoint reached the predefined stopping rules for

No. of Events p-value Reduction (%) (atorvastatir vs. placebo) 83 vs. 127 Major cardiovascular events (fatal and non-fatal AMI silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)

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.

38 vs. 64 21 vs. 39

Once daily 7 Twice daily Single dose Three times daily Four times daily

f Every 8 hours

80 mg QDa for 10 days

40 mg QDa for 22 days

10 mg QDa for 4 days

10 mg, SD^c

based on AUC.

A relative risk reduction in death of 27% (82 deaths in the placebo group compared to 61 deaths in the treatment arm) has been observed with a borderline statistical significance ($p=0.0592$).
The overall incidence of adverse events or serious adverse events was similar between the treatment
groups.
Atherosclerosis
In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with CHD. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n = 253), the median percent change, from baseline, in total atheroma

volume (the primary study criteria) was -0.4% (p = 0.98) in the atorvastatin group and +2.7% (p = 0.001) in the pravastatin group (n = 249). When compared to pravastatin, the effects of atorvastatin were statistically significant (p = 0.02). atorvastatin vere statistically significant by = 0.02 a mean of 2.04 mmol/L \pm 0.8 (78.9 mg/dL \pm 30) from baseline 3.89 mmol/L \pm 0.7 (150 mg/dL \pm 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L \pm 0.7 (150 mg/dL \pm 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L \pm 0.7 (150 mg/dL \pm 26) (pc-0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apo B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: -5.6%, p = NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

The safety and tolerability profiles of the two treatment groups were comparable. Recurrent Stroke In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of

atorvastatin 80 mg daily or placebo on stroke was evaluated in 4,731 patients who had a stroke or TIA within the preceding 6 months and no history of CHD. Patients were 60% male, 21 to 92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years. Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (hazard ratio [HR] 0.85; 95% Cl 0.72-1.00; p = 0.05 or HR 0.84; 95% Cl 0.71-0.99; p = 0.03 after adjustment for baseline factors) compared to placebo. Atorvastatin 80 mg significantly reduced the risk of major coronary events (HR 0.67; 95% Cl 0.51-0.89; p = 0.006), any CHD event (HR 0.60; 95% Cl 0.51-0.89; p = 0.006). Cl 0.48-0.74; p<0.001), and revascularization procedures (HR 0.57; 95% Cl 0.44-0.74; p<0.001). In a post-hoc analysis, atoryastatin 80 mg, reduced the incidence of ischemic stroke (218/2365, 9.2%) in a post-rior analysis, activastatin or light reduced the incidence of inscrientic active (276/2366, 2.3% vs. 33/2366, 1.4%, p = 0.02) compared to placebo. The incidence of fatal hemorrhagic stroke was

similar between the groups (17 atorvastatin vs. 18 placebo). Reduction in the risk of cardiovascular similar between the groups (17 addivioustatin vs. 16 placebo), reduction in the risk of cardioviouscular events with atorvastatin 80 mg was demonstrated in all patient groups except in patients who entered the study with a hemorrhagic stroke and had a recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo), where the number of events was too small to discern risk or benefit. In patients treated with atorvastatin 80 mg, there were fewer strokes of any type (265 atorvastatin vs. 311 placebo) and fewer CHD events (123 atorvastatin vs. 204 placebo). Overall mortality was similar across treatment groups (216 atorvastatin vs. 211 placebo). The overall incidence of adverse events and serious adverse events was similar between the treatment groups. Secondary Prevention of Cardiovascular Events In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident CHD who had achieved a target LDL-C level <130 mg/dL after

completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly

completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The mean LDL-C, TC, TC, non-HDL and HDL cholesterol levels at 12 weeks were 73 mg/dL, 145 mg/dL, 128 mg/dL, 98 mg/dL and 47 mg/dL, respectively, during treatment with 80 mg of atorvastatin and 99 mg/dL, 177 mg/dL, 152 mg/dL, 129 mg/dL and 48 mg/dL, respectively, during treatment with 10 mg of atorvastatin. Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%. Atorvastatin 80 mg significantly reduced the risk of the following Significant Endpoint Atorvastatir Atorvastatin HRa (95% CI) 80 mg (N = 4995) (N = 5006)Primary Endpoint*

Components of the Primary Endpoint Non-fatal, non-procedure related MI 308 243 4.9 0.78 (0.66, 0.93) 6.2 Stroke (fatal and non-fatal) 117 0.75 (0.59, 0.96) Secondary Endpoints** First CHF with hospitalization 164 3.3 122 0.74 (0.59, 0.94) 2.4 First CABG or other coronary 904 18.1 667 13.4 0.72 (0.65, 0.80)

> 12.3 545

MCVE = death due to CHD, non-fatal MI, resuscitated cardiac arrest, and fatal and non-fatal stroke

615

10.9

434

10.9

0.78 (0.69, 0.89)

0.88 (0.79, 0.99)

First major cardiovascular endpoin

evascularization procedure

First documented angina endpoint^b Atorvastatin 80 mg: atorvastatin 10 mg.

Component of other secondary endpoints

secondary endpoints not included in primary endpoint

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; CHF = congestive heart failure; CABG = coronary artery bypass graft Confidence intervals for the secondary endpoints were not adjusted for multiple comparisons.
There was no significant difference between the treatment groups for all-cause mortality: 282 (5.6%) in the atorvastatin 10 mg/day group vs. 284 (5.7%) in the atorvastatin 80 mg/day group. The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke were numerically smaller in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.
In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with sinwastatin 20 mg/day to 40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risks 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, bilinded 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, 140 mg/dL, 47 mg/dL and 130 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 $0.78,1.01;p=0.07.$

in the atorvastatin 80 mg/day group vs. 374 (8.4%) in the sinvastatin 20 mg to 40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin 80 mg group and the simvastatin 20 mg to 40 mg group Heterozygous Familial Hypercholesterolemia in Pediatric Patients The following pediatric-exclusive studies have been completed with atorvastatin. In an open-label, single-arm study, 271 male and female Heterozygous Familial Hypercholesterolemia (HeFH) children 6-15 years of age were enrolled and treated with atorvastatin for up to 3 years. Inclusion in the study required confirmed HeFH and a baseline LDL-C level \geq 4 mmol/L (approximately 152 mg/dL).

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%)

The study included 139 children at Tanner 1 development stage (generally ranging from 6-10 years of age). The dosage of atomostatin (once daily) was initiated at 5 mg (chewable tablet) in children less than 10 years of age. Children age 10 and above were initiated at 10 mg atomastatin (once daily). All children could titrate to higher doses to achieve a target of <3.35 mmol/L LDL-C. The mean weighted dose for children aged 6 to 9 years was 19.6 mg and the mean weighted dose for children aged 10 years and above was 23.9 mg. The mean (± SD) baseline LDL-C value was 6.12 (1.26) mmol/L which was approximately 233 (48) mg/dL. See table 2 below for final results.

The data were consistent with no drug effect on any of the parameters of growth and development (i.e., height, weight, BMI, Tanner stage, Investigator assessment of Overall Maturation and Development) in pediatric and adolescent subjects with HeFH receiving atorvastatin treatment over the 3 year study. There was no Investigator-assessed drug effect noted in height, weight, BMI by age or by gender TABLE 2. Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia (mmol/L) Timepoint TC (S.D.) LDL-C (S.D.) HDL-C (S.D.) TG (S.D.) Apo B (S.D.)# 7.86 (1.30) 6.12 (1.26) 1.314 (0.2663) 0.93 (0.47) 1.42 (0.28)* 206 | 4.95 (0.77)* | 3.25 (0.67) | 1.327 (0.2796) | 0.79 (0.38)* | 0.90 (0.17)* Month 30

Month 36/ET | 240 | 5.12 (0.86) | 3.45 (0.81) | 1.308 (0.2739) | 0.78 (0.41) | 0.93 (0.20)** TC = total cholesterol; LDL-C = low density lipoprotein cholesterol-C; HDL-C = high density lipoprotein cholesterol-C; TG = triglycerides; Apo B = apolipoprotein B; "Month 36/ET" included

N for this parameter was 243; "#" = g/L for Apo B.	ion; "*" = Month 30 N; "**" = Month 36/ET

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

the 26 week double-blind phase (see Table 3). TABLE 3. Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous

Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

Total-Ca I DI -Ct

Placebo Atorvastatin 140 Total cholest Low density lipoprotein cholesterol High density lipoprotein cholesterol Total glycerides

HDL-C

Apolipoprotein-B The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase. In this 1-year study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls.

tolerability of atorvastatin was conducted in 39 patients, 6 to 17 years of age with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/L. Cohort A included 15 patients, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 patients,

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and

10 to 17 years of age and at Tanner Stage ≥2. The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a patient had not attained target LDL-C of <3.35 mmol/L at Week 4 and if atorvastatin was well tolerated. Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all patients. For patients whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first

assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether patients remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic Properties Pharmacokinetics and Metabolism Absorption

In studies with amlodipine/atorvastatin: Following oral administration of Ambdipine 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

is authorizate to account, persent of an artificial interest and a state of a sorption (bioavailability) of amilodipine and atomisation from Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) are not significantly different from the bioavailability of amlodipine and atorvastatin from co-administration of amlodipine and atorvastatin bloadradability of amidoliphile and adovastatin from co-administration of amidoliphile and adovastatin trablets as assessed by $C_{\rm max}$: 101% (90% Cl: 98, 104) and AUC: 100% (90% Cl: 97, 103) for the amidoliphile component and $C_{\rm max}$: 94% (90% Cl: 85, 104) and AUC: 105% (90% Cl: 99, 111) for the atorvastatin component, respectively. The bigavailability of the amlodinine component of Amlodinine besilate/Atorvastatin calcium (Norvasc Protect® was not affected under the fed state as assessed by C_{mix} 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 besilate/Atorvastatin calcium (Norvasc Protect®) by

approximately 32% and 11%, respectively, as assessed by C_{ass}: 68% (90% Cl 60, 79) and AUC: 89% (90% Cl 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 to 12 hours post-dose. Absolute bioavailability has been estimated to be between 64% and 80%. The volume of distribution is approximately 21 L/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. Absorption of amlodipine is unaffected by consumption of food. In studies with atorvastatin

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% bloavailable 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 attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9% respectively, as assessed by $C_{\rm max}$ and AUC, LDL-C reduction is similar whether attoractatin is given with or without food. Plasma attorvastatin concentrations are lower (approximately 30% for $C_{\rm max}$ 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 Dosage and Method of

Mean volume of distribution of atoryastatin is approximately 381 L. Atoryastatin 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 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 atoryastatin are substrates of OATP1B1. Atoryastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of Special Populations Hepatic Insufficiency

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

Renal Insufficiency See section 4.2 Dosage and Method of Administration

Gender

(0.003)

Distribution In studies with atorvastatin

In studies with amlodipine

In studies with amlodipine

Changes in amlodinine 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 atoryastatin. Thus,

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

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

Plasma concentrations of atorvastatin are higher (approximately 40% for C and 30% for AUC) in healthy, elderly subjects (aged \geq 65 years) than in young adults. The ACCESS study specifically

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

dose adjustment in patients with renal dysfunction is not necessary

evaluated elderly patients with respect to reaching their NCEP treatment goals. The study included 1,087 patients under 65 years of age, 815 patients over 65 years of age, and 185 patients over 75 years of age. No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population. Pediatrics In studies with amlodipine In one clinical chronic exposure study, 73 hypertensive pediatric patients, aged 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/h and 17.6 L/h for males and females, respectively. This is in a similar range to the published estimates of 24.8 L/h in a 70 kg adult. The average estimate for volume of distribution for a 45 kg patient was 1130 L (25.11 L/kg). Maintenance of the BP effect over the 24-hour dosing interval was observed with little difference in peak and trough variation effect. When compared to historical adult pharmacokinetics the parameters observed in this study indicate that once daily dosing is appropriate. In studies with atorvastatin In an open-label, 8-week study, Tanner Stage 1 (N = 15) and Tanner Stage ≥ 2 (N = 24) pediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline

DLL-C ≥4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population

PK model. Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to adults

when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures. Drug Interactions In studies with atorvastatin The effect of co-administered drugs on the pharmacokinetics of atorvastatin as well as the effect of atorvastatin on the pharmacokinetics of co-administered drugs are summarized below (see section 4.4 Special Warnings and Precautions for Use and section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction) Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin Co-administered drug and dosing regimen Atorvastatir Ratio of Dose (mg) Ratio of AUC

10 mg QDa for 28 days

10 mg QDa for 7 days

10 mg SD

10.7

8.6

22.0

"Cyclosporine 5.2 mg/kg/day, stable dose

*Tipranavir 500 mg BIDb/ritonavir 200 mg BIDb, 7 days

"Glecaprevir 400 mg QDa/Pibrentasvir 120 mg

*Telaprevir 750 mg q8hf, 10 days	20 mg SD°	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 TIDd, 7 days	40 mg SD°	2.3	2.7
"Simeprevir 150 mg QD", 10 days	40 mg SD ^c	2.12	1.70
"Lopinavir 400 mg BID ^b /ritonavir 100 mg BID ^b , 14 days	20 mg QDa for 4 days	5.9	4.7
^{#. ‡} Saquinavir 400 mg BID⁵/ritonavir 400 mg BID⁵, 15 days	40 mg QDa for 4 days	3.9	4.3
*Clarithromycin 500 mg BIDb, 9 days	80 mg QDa for 8 days	4.5	5.4
"Darunavir 300 mg BID ^b /ritonavir 100 mg BID ^b , 9 days	10 mg QDa for 4 days	3.4	2.2
"Itraconazole 200 mg QDa, 4 days	40 mg SD°	3.3	1.20
"Letermovir 480 mg QD, 10 daysa	20 mg SD°	3.29	2.17
"Fosamprenavir 700 mg BID ^b /ritonavir 100 mg BID ^b , 14 days	10 mg QDa for 4 days	2.5	2.8
"Fosamprenavir 1400 mg BIDb, 14 days	10 mg QDa for 4 days	2.3	4.0
"Nelfinavir 1250 mg BIDb, 14 days	10 mg QDa for 28 days	1.74	2.2
"Grapefruit Juice, 240 mL QDa *	40 mg SD°	1.37	1.16
Diltiazem 240 mg QDa for 28 days	40 mg, SD ^c	1.51	1.00
Erythromycin 500 mg QID° 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°, 2 weeks	10 mg QDa for 2 weeks	1.00	0.89
Colestipol 10 g BIDb, 24 weeks	40 mg QDa for 8 weeks	NA	0.74**
Maalox TC® 30 mL QIDo, 17 days	10 mg QDa for 15 days	0.66	0.67
Efavirenz 600 mg QDa, 14 days	10 mg for 3 days	0.59	1.01
#Rifampin 600 mg QDa, 7 days (co-administered)†	40 mg SD°	1.12	2.9
"Rifampin 600 mg QDa, 5 days (doses separated)†	40 mg SD°	0.20	0.60
#Gemfibrozil 600 mg BIDb, 7 days	40 mg SD°	1.35	1.00
"Fenofibrate 160 mg QDa for 7 days	40 mg SD°	1.03	1.02
§ Represents ratio treatments (co-administered dru "See section 4.4 Special Warnings and Precautic with Other Medicinal Products and Other Forms of "Greater increases in AUC (ratio of AUC up to 2.5) "Ratio based on a single sample taken 8-16 hour "Due to the dual interaction mechanism of rifampi with rifampin is recommended, as delayed adminis rifampin has been associated with a significant red "The dose of saquinavir/ritonavir in this study is no atorvastatin exposure when used clinically is likely study. Therefore caution should be exercised and the state of the cause of the ca	ns for Use and section 4. of Interaction for clinical stand/or C _{mass} (ratio of C _{mass} to 750 mL - 1.2 L/day). s post dose. n, simultaneous co-admirstration of atorvastatin afte fuction in atorvastatin plas to the clinically used dose, to be higher than what w	.5 Interacti significance up to 1.71) histration of er administrations are concer . The increases observed	on have been atorvastatir ration of atrations. ase in d in this

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs Co-administered drug and dosing regim Atorvastatin Drug/Dose (mg) 80 mg QDa for 15 days 1.03 Antipyrine, 600 mg SD° 0.89

Tipranavir 500 mg BIDb/ritonavir 200 mg

Fosamprenavir 1400 mg BIDb, 14 days

1.15

.28 .19

1.08

0.73

1.20

1.23

0.96

0.82

Digoxin 0.25 mg QDa for 20 days

Oral contraceptive QDa, 2 months

norethindrone 1 mg ethinyl estradiol 35 µg

10 mg QDa for 4 days	Fosamprenavir 700 mg BIDb/ritonavir 100 mg BIDb, 14 days	0.99	0.94				
A Represents ratio treatments (co-administered drug plus atorvastatin versus atorvastatin alone). See section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction for clinical significance. Once daily Tiwice daily Single dose							
5.3 Preclinical Safety Data							
<u>Carcinogenesis</u>							
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/m² basis) was close to the maximum tolerated dose for mice but not for rats.							
In studies with atorvastatin							
human dose (80 mg/day) values. In a 2-year study i carcinomas in females we	nogenic in rats. The maximum dose used was on a mg/kg body-weight basis and 8- to 16 n mice, incidences of hepatocellular adenon ere increased at the maximum dose used, w on a mg/kg body-weight basis. Systemic exp	6-fold higher bason has in males and which was 250-fo	ed on AUC ₍₀₋₂₄₎ hepatocellular ld higher than				

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

*Based on patient weight of 50 kg.

*Based on patient weight of 50 kg.

In studies with atorvastatin

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 amlodinine (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).

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 6.0 PHARMACEUTICAL PARTICULARS 6.1 Shelf-Life For expiry date, please see outer package 6.2 Storage Condition 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 Alu-alu blisterpacks of 10's in boxes of 30's.

Armilodipine 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 Alu-alu

Amiodipine besilate/Atorvastatin calcium (Norvasc Protect®) 5/20 mg Tablets are white, oval coated tablets debossed with "Pfizer" on one side and "CDT 052" on the other side. Available as Alu-alu blisterpacks of 10's in boxes of 30's. Amlodipine besilate/Atorvastatin calcium (Norvasc Protect®) 10/20 mg Tablets are blue, oval coated tablets debossed with "Pfizer" on one side and "CDT 102" on the other side. Available as Alu-alu blisternacks of 10's in boxes of 30's. 7.0 FDA REGISTRATION NUMBER

5 mg/20 mg Tablet

10 mg/20 mg Tablet

Menarco Tower

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32nd Street, Bonifacio Global City Taguig City, Metro Manila

Keep out of reach of children.

blisterpacks of 10's in boxes of 30's.

5 mg/10 mg Tablet : DRP - 2791 : DRP - 3146 10 mg/10 mg Tablet 5 mg/20 mg Tablet : DR - XY30121 10 mg/20 mg Tablet : DR - XY30122 8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION : 30 September 2004 5 mg/10 mg Tablet 10 mg/10 mg Tablet : 30 September 2004

: 30 September 2004

: 30 September 2004

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction. CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription Manufactured by:
Pfizer Manufacturing Deutschland-GmbH Betriebsstatte Freiburg Mooswaldallee 1, 79090 Freiburg, Germany Marketing Authorization Holder: VIATRIS. INC 22nd Floor Unit C & D

> Revision No.: 13 Revision Date: 23 August 2022

Reference: CDS version 26.0/MAH rebranding Reference Date: 15 Dec 2020

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Description	PP NORVASC PROTECT 5	5,10/10, 5,10/20mg PH	gg	Date: 07 Au	ug 23 II	me: 18:00	
Component Type	Leaflet	Site Barcode/ DataMatrix	2768	No. of colours	1	Page Count	2 of 2
Affiliate Item Code	3221597	Viatris SAP No.	400564226;400564231; 400564232;400564233	Colours	Black		
Superseded Affiliate Item Code	N/A	Vendor Job No.	109047930/0020				
TrackWise/GLAMS Job No-	3221597	Artwork Proof No.	1	Non-Print Colours	Keyline		
MA No.	DRP – 2791, DRP – 3146, DR – XY30121, DR – XY30122	Client Market	Philippines	Equate CMYK			
Supplier SAP No.	N/A	Barcode Info	N/A	with			
New Supplier Code	PAA212318	3D Render ID	N/A	Main Font	Helvetica Neue LT W1	G Body	Text Size 6 pt
Superseded Supplier Code	PAA191655			Dimensions	1000 x 180 mm	Min Tex	t Size used 6 pt
Packing Site/Printer	Pfizer Manufac	turing Freiburg	g (Freiburg - DE)	Keyline/Drawing No.	003000009427 3 100	00x180mm v1	FVID138784

