CADUET® Tablets
(amlodipine besilate/atorvastatin calcium)

1. TRADE NAME(S) OF THE MEDICINAL PRODUCT

CADUET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients: amlodipine besilate, atorvastatin calcium (crystalline powder).

Excipient: calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, silica colloidal anhydrous, magnesium stearate, opradry II white (5 mg/10 mg and 5 mg/20 mg), opradry II blue (10 mg/10 mg) and purified water

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

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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.

Reduction of cardiovascular events in patients at high risk of CHD
In adult hypertensive patients without clinically evident coronary heart disease but with at least three other risk factors including type 2 diabetes, age greater than or equal to 55, microalbuminuria/proteinuria, smoking, history of coronary artery disease (CAD) event occurring in a first degree relative before the age of 55 (males) or 60 years (women), Caduet is indicated to:
- Reduce the risk of myocardial infarction (MI)
- Reduce the risk of stroke
- Reduce the risk of revascularization procedures and angina

4.2. Posology and method of administration

General Considerations

CADUET is not suggested as initial treatment in patients with hyperlipidemia and either hypertension or angina.

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

The dosage range for CADUET is 5 mg/10 mg to a maximum dose of 10 mg/80 mg once daily. The starting dose and maintenance dose should be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and dyslipidemia. Current treatment guidelines should be consulted to establish treatment goals for patients based on their baseline characteristics. Therapy may be started by using medication of individual parent component, then switch to CADUET after titration to optimal dosage according to patient’s individual medical needs. Doses may be taken at any time of day with or without food.

As a component of multiple-risk factor intervention, CADUET 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 CADUET, lipid levels should be analyzed and blood pressure (BP) measured within 2 to 4 weeks, and dosage of amlodipine and atorvastatin components should be adjusted accordingly. Titration for BP response may proceed more rapidly if clinically warranted.

Initial Therapy

CADUET is not suggested as initial treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of CADUET should be based on the appropriate combination of recommendations for the amlodipine and atorvastatin components considered separately. The maximum dose of the amlodipine
component of CADUET is 10 mg once daily. The maximum dose of the atorvastatin component of CADUET is 80 mg once daily.

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

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

**Concomitant Medication (See also section 4.5. Interaction with other medicinal products and other forms of interaction)**

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

The atorvastatin component of CADUET may be used in combination with a bile acid binding resin for additive effect on lipid lowering. The combination of 3 hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrates should generally be avoided (see 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**

**Use in Patients with Impaired Hepatic Function**
CADUET 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 CADUET (combination product) in pediatric populations.

Use in Combination with Other Medicinal Compounds
Studies with atorvastatin:
In patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided.

In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg.

In case where co-administration of itraconazole and atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 40 mg daily (see section 4.4. Special warnings and precautions for use and section 4.5. Interaction with other medicinal products and other forms of interaction).

In case where co-administration of clarithromycin or other HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir) is necessary, the dose of atorvastatin should not exceed 20 mg daily.

Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have been noted with HIV protease inhibitors (lopinavir plus ritonavir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir and nelfinavir), hepatitis C protease inhibitor (boceprevir), clarithromycin and itraconazole. 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/atorvastatin is contraindicated in patients who:

1. Have known hypersensitivity to dihydropyridines,* amlodipine, atorvastatin, or any component of this medication.
2. Have active liver disease or unexplained persistent elevations of serum transaminases >3 x the upper limit of normal [ULN].
3. Are pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. Amlodipine/atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.

* Amlodipine is a dihydropyridine calcium channel blocker.

4.4. Special warnings and precautions for use

**Use in Patients with Heart Failure**

In general, calcium channel blockers should be used with caution in patients with heart failure.

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

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

**Hepatic Effects**

Atorvastatin may cause elevations in serum transaminases. It is recommended liver function tests be obtained for all patients prior to initiating therapy and inform patients that attention should be paid if symptoms of liver injury occurs during treatment, including fatigue, anorexia, right-upper abdominal discomfort, dark urine and jaundice.

As with other lipid-lowering agents of the HMG-CoA reductase inhibitor class, moderate (>3 x ULN) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin given at doses of 10 mg, 20 mg, 40 mg and 80 mg.
Persistent increases in serum transaminases (>3 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10 mg, 20 mg, 40 mg and 80 mg, respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve(s). Should an increase in alanine transaminase (ALT) or aspartate transaminase (AST) >3 x ULN persist, reduction of dose or withdrawal of amlodipine/atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases (see section 4.8. Undesirable effects).

Amlodipine/atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of amlodipine/atorvastatin (see section 4.3. Contraindications).

**Skeletal Muscle Effects**
Myalgia has been reported in atorvastatin-treated patients (see section 4.8. Undesirable effects). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Amlodipine/atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, azole antifungals, colchicine, telaprevir, boceprevir or the combination of tipranavir/ritonavir. Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. CYP 3A4 is the primary hepatic 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, or lipid modifying doses of niacin should carefully weigh the potential
benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of the atorvastatin component should also be considered when taken concomitantly with the aforementioned drugs. The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin is advised during fusidic acid therapy (see section 4.5. Interaction with other medicinal products and other forms of interaction). Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Atorvastatin/amlodipine may cause an elevation of CPK due to the atorvastatin component (see section 4.8. Undesirable effects).

As with other drugs in the class of HMG-CoA reductase inhibitors, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. Amlodipine/atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection; hypotension; major surgery; trauma; severe metabolic, endocrine and electrolyte disorders; and uncontrolled seizures). Control of hypertension may be continued with the appropriate dose of amlodipine.

**Haemorrhagic Stroke**

In a post-hoc analysis of stroke subtypes in patients without CHD who had a recent stroke or transient ischemic attack (TIA), there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment.

**Endocrine Function**

HbA1c elevation: Increases in glycated haemoglobin (HbA1c) and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.
4.5. Interaction with other medicinal products and other forms of interaction

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

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

**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, antibiotics, and oral hypoglycemic drugs.

**CYP3A4 Inhibitors**

Co-administration of a 180 mg daily dose of diltiazem with 5 mg of amlodipine in elderly hypertensive patients (69 - 87 years of age) resulted in a 57% increase in amlodipine system exposure. Erythromycin co-administration in healthy volunteers (18-43 years of age) did not significantly change amlodipine systemic exposure (22% increase in AUC). The clinical relevance of these findings is uncertain. Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

**Clarithromycin**

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

**CYP3A4 Inducers**

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

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

*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**

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

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

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

**Special Studies: Effect of Amlodipine on Other Agents**

**Digoxin**
Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
**Ethanol (alcohol)**
Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

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

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

**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.

**Drug/Laboratory Test Interactions**
None known

**Atorvastatin Interactions**
The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g., erythromycin and azole antifungals) (see below and also section 4.2. Posology and method of administration – Use in Combination with Other Medicinal Compounds and section 4.4. Special warnings and precautions for use – Skeletal Muscle Effects).

**Inhibitors of Cytochrome P450 3A4**
Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on cytochrome P450 3A4.
**Transporter Inhibitors**
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7-fold increase in exposure to atorvastatin (see also section 4.2. Posology and method of administration – Use in Combination with Other Medicinal Compounds). In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg.

**Erythromycin/Clarithromycin**
Erythromycin and clarithromycin are known inhibitors of cytochrome P450 3A4. Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) was associated with higher plasma concentrations of atorvastatin (see section 4.4 Special warnings and precautions for use – Skeletal Muscle Effects and 5.2 Pharmacokinetic properties – Drug Interactions). In cases where co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20 mg daily. Patients who normally require 40 mg or 80 mg of atorvastatin should either reduce their dosage during concomitant clarithromycin treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.

**Protease Inhibitors**
Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin (see section 5.2. Pharmacokinetic properties). In patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg.

Concomitant use of HIV protease inhibitors, boceprevir, telaprevir or nefazodone reduces the elimination of LIPITOR and increases the risk of myopathy.

**Diltiazem Hydrochloride**
Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin. After initiation of diltiazem or following dosage adjustment, lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.
**Cimetidine**

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

**Itraconazole**

Concomitant administration of atorvastatin (20-40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC. In cases where co-administration of itraconazole with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 40 mg daily. Patients who normally require 80 mg of atorvastatin should either reduce their dosage during concomitant itraconazole treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered (see section 4.4 Special warnings and precautions for use: Skeletal Muscle Effects and 5.2 Pharmacokinetic properties: Drug Interactions).

**Grapefruit Juice:** Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L/day).

**Inducers of Cytochrome P450 3A4**

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

**Gemfibrozil/fibrates:** The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates. Should avoid concomitant administration of atorvastatin with gemfibrozil or other fibrate (see section 4.4. Special warnings and precautions for use: Skeletal Muscle Effects).

**Antacids**

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides, decreased atorvastatin plasma concentrations by approximately 35%; however, LDL-C reduction was not altered.
**Antipyrine**  
Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

**Colestipol**  
Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

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

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

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

**Warfarin**  
An atorvastatin interaction study with warfarin was conducted, and no clinically significant interactions were observed. Nevertheless, patients receiving warfarin should be closely monitored when Lipitor is added to their therapy.

**Fusidic Acid**  
Although interaction studies with atorvastatin and fusidic acid have not been conducted, there is an increased risk of rhabdomyolysis in patients receiving a combination of statins, including atorvastatin, and fusidic acid. The mechanism of this interaction is not known. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. Statin therapy may be re-introduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

**Colchicine**

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

4.6. Fertility, pregnancy and lactation

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

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

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

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

4.7. Effects on ability to drive and use machines

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

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

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

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

Amlodipine Experience

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

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

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

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

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
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<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Leucopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Hyperglycaemia</td>
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<tr>
<td>Psychiatric Disorders</td>
<td>Insomnia, mood altered</td>
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<tr>
<td>Nervous System Disorders</td>
<td>Hypertonia, hypoaesthesia/paraesthesia, neuropathy</td>
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<td></td>
<td>peripheral, syncope, dysgeusia, tremor, extrapyramidal</td>
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<td></td>
<td>disorder</td>
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<tr>
<td>Eye Disorders</td>
<td>Visual impairment</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>Tinnitus</td>
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<tr>
<td>Vascular Disorders</td>
<td>Hypotension, vasculitis</td>
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</tbody>
</table>
### Respiratory, Thoracic, and Mediastinal Disorders
Cough, dyspnoea, rhinitis

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

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

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

### Renal and Urinary Disorders
Pollakiuria, micturition disorder, nocturia

### Reproductive System and Breast Disorders
Gynaecomastia, erectile dysfunction

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

### Investigations
Weight increased/decreased

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

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

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

### Atorvastatin Experience

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

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

**Infections and Infestations:** nasopharyngitis.

**Metabolism and nutrition disorders:** hyperglycaemia.

**Respiratory, thoracic and mediastinal disorders:** pharyngolaryngeal pain, epistaxis.
Gastrointestinal disorders: diarrhoea, dyspepsia, nausea, flatulence.

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

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

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

Psychiatric disorders: nightmare

Eye disorders: vision blurred

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: abdominal discomfort, eructation

Hepatobiliary disorders: hepatitis, cholestasis

Skin and subcutaneous tissue disorders: urticaria

Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain

General disorders and administration site conditions: malaise, pyrexia

Investigations: white blood cells urine positive

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

Pediatric Patients
Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections.
In post-marketing experience, the following additional undesirable effects have been reported with atorvastatin:

**Blood and lymphatic system disorders:** thrombocytopenia

**Immune system disorders:** allergic reactions (including anaphylaxis)

**Injury, poisoning and procedural complications:** tendon rupture

**Metabolism and nutrition disorders:** weight gain

**Nervous system disorders:** hypoesthesia, amnesia, dizziness, dysgeusia

**Gastrointestinal disorders:** pancreatitis

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

**Musculoskeletal and connective tissue disorders:** rhabdomyolysis, immune-mediated necrotising myopathy, myositis, back pain

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

Reversible cognitive impairment: There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

4.9. Overdose

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

Due to amlodipine’s and atorvastatin’s extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance amlodipine/atorvastatin clearance (see also section 5.2. Pharmacokinetic properties – Renal Insufficiency).

Additional data on amlodipine ingestion suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine
output. A vasoconstrictor may be helpful in restoring vascular tone and BP, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

**Amlodipine/Atorvastatin Pharmacodynamics**

The amlodipine besilate component of amlodipine/atorvastatin is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxyethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate. Its empirical formula is C_{20}H_{25}ClN_{2}O_{6}•C_{6}H_{6}O_{3}S. The atorvastatin calcium component of amlodipine/atorvastatin is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C_{33}H_{34}F_{2}N_{2}O_{5})_{2}Ca•3H_{2}O. The structural formulae are shown below:
**Mechanism of Amlodipine/Atorvastatin**

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

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

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

#### Efficacy of the Combined Treatments in Reducing Systolic BP<sup>a</sup>

<table>
<thead>
<tr>
<th>Parameter/Analysis</th>
<th>ATO&lt;sup&gt;b&lt;/sup&gt; 0 mg</th>
<th>ATO 10 mg</th>
<th>ATO 20 mg</th>
<th>ATO 40 mg</th>
<th>ATO 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML&lt;sup&gt;c&lt;/sup&gt; 0 mg</td>
<td>Mean change (mmHg)</td>
<td>-3.0</td>
<td>-4.5</td>
<td>-6.2</td>
<td>-6.2</td>
</tr>
<tr>
<td>Difference vs. placebo (mmHg)</td>
<td>-</td>
<td>-1.5</td>
<td>-3.2</td>
<td>-3.2</td>
<td>-3.4</td>
</tr>
<tr>
<td>AML 5 mg</td>
<td>Mean change (mmHg)</td>
<td>-12.8</td>
<td>-13.7</td>
<td>-15.3</td>
<td>-12.7</td>
</tr>
<tr>
<td>Difference vs. placebo (mmHg)</td>
<td>-9.8</td>
<td>-10.7</td>
<td>-12.3</td>
<td>-9.7</td>
<td>-9.2</td>
</tr>
<tr>
<td>AML 10 mg</td>
<td>Mean change (mmHg)</td>
<td>-16.2</td>
<td>-15.9</td>
<td>-16.1</td>
<td>-16.3</td>
</tr>
<tr>
<td>Difference vs. placebo (mmHg)</td>
<td>-13.2</td>
<td>-12.9</td>
<td>-13.1</td>
<td>-13.3</td>
<td>-14.6</td>
</tr>
</tbody>
</table>

<sup>a</sup>Blood pressure.

<sup>b</sup>Atorvastatin.

<sup>c</sup>Amlodipine.

#### Efficacy of the Combined Treatments in Reducing Diastolic BP<sup>a</sup>

<table>
<thead>
<tr>
<th>Parameter/Analysis</th>
<th>ATO&lt;sup&gt;b&lt;/sup&gt; 0 mg</th>
<th>ATO 10 mg</th>
<th>ATO 20 mg</th>
<th>ATO 40 mg</th>
<th>ATO 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML&lt;sup&gt;c&lt;/sup&gt; 0 mg</td>
<td>Mean change (mmHg)</td>
<td>-3.3</td>
<td>-4.1</td>
<td>-3.9</td>
<td>-5.1</td>
</tr>
<tr>
<td>Difference vs. placebo (mmHg)</td>
<td>-</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-1.8</td>
<td>-0.8</td>
</tr>
<tr>
<td>AML 5 mg</td>
<td>Mean change (mmHg)</td>
<td>-7.6</td>
<td>-8.2</td>
<td>-9.4</td>
<td>-7.3</td>
</tr>
<tr>
<td>Difference vs. placebo (mmHg)</td>
<td>-4.3</td>
<td>-4.9</td>
<td>-6.1</td>
<td>-4.0</td>
<td>-5.1</td>
</tr>
<tr>
<td>AML 10 mg</td>
<td>Mean change (mmHg)</td>
<td>-10.4</td>
<td>-9.1</td>
<td>-10.6</td>
<td>-9.8</td>
</tr>
<tr>
<td>Difference vs. placebo (mmHg)</td>
<td>-7.1</td>
<td>-5.8</td>
<td>-7.3</td>
<td>-6.5</td>
<td>-7.8</td>
</tr>
</tbody>
</table>

<sup>a</sup>Blood pressure.

<sup>b</sup>Atorvastatin.

<sup>c</sup>Amlodipine.
### Efficacy of the Combined Treatments in Reducing LDL-C (% change)

<table>
<thead>
<tr>
<th>Parameter/Analysis</th>
<th>ATO&lt;sup&gt;a&lt;/sup&gt; 0 mg</th>
<th>ATO&lt;sup&gt;a&lt;/sup&gt; 10 mg</th>
<th>ATO&lt;sup&gt;a&lt;/sup&gt; 20 mg</th>
<th>ATO&lt;sup&gt;a&lt;/sup&gt; 40 mg</th>
<th>ATO&lt;sup&gt;a&lt;/sup&gt; 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML&lt;sup&gt;c&lt;/sup&gt; 0 mg</td>
<td>Mean % change</td>
<td>-1.1</td>
<td>-33.4</td>
<td>-39.5</td>
<td>-43.1</td>
</tr>
<tr>
<td>AML&lt;sup&gt;c&lt;/sup&gt; 5 mg</td>
<td>Mean % change</td>
<td>-0.1</td>
<td>-38.7</td>
<td>-42.3</td>
<td>-44.9</td>
</tr>
<tr>
<td>AML&lt;sup&gt;c&lt;/sup&gt; 10 mg</td>
<td>Mean % change</td>
<td>-2.5</td>
<td>-36.6</td>
<td>-38.6</td>
<td>-43.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Low-density lipoprotein cholesterol.

<sup>b</sup> Atorvastatin.

<sup>c</sup> Amlodipine.

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

**Amlodipine Pharmacodynamics**

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions.

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal’s or variant angina) and blunts smoking-induced coronary vasoconstriction.

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

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

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 Heart Failure

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

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

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

Atorvastatin Pharmacodynamics

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

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

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

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

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

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

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

In the Anglo-Scandinavian Cardiac Outcomes Trial, the effect of LIPITOR (atorvastatin calcium) on fatal and non-fatal CHD was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous MI and with TC levels ≤251 mg/dL(6.5 mmol/L). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mmHg for non-diabetic patients, <130/80 mmHg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the LIPITOR group) or non-fatal MI (108 events in the placebo group vs. 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.
LIPITOR also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or non-cardiovascular causes (p=0.17).

**Heterozygous Familial Hypercholesterolemia in Pediatric Patients**

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and post-menarchal 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 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.
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)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>N</th>
<th>Total-C&lt;sup&gt;a&lt;/sup&gt;</th>
<th>LDL-C&lt;sup&gt;b&lt;/sup&gt;</th>
<th>HDL-C&lt;sup&gt;c&lt;/sup&gt;</th>
<th>TG&lt;sup&gt;d&lt;/sup&gt;</th>
<th>apoB&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>47</td>
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<td>-0.4</td>
<td>-1.9</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>140</td>
<td>-31.4</td>
<td>-39.6</td>
<td>2.8</td>
<td>-12.0</td>
<td>-34.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Total cholesterol.

<sup>b</sup>Low-density lipoprotein cholesterol.

<sup>c</sup>High-density lipoprotein cholesterol.

<sup>d</sup>Total glycerides.

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

5.2. Pharmacokinetic properties

Pharmacokinetics and Metabolism

Absorption

In studies with amlodipine/atorvastatin: Following oral administration of amlodipine/atorvastatin two distinct peak plasma concentrations were observed. The first, within 1 to 2 hours of administration, is attributable to atorvastatin; the second, between 6 and 12 hours after dosing, is attributable to amlodipine. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from amlodipine/atorvastatin are not significantly different from the bioavailability of amlodipine and atorvastatin from co-administration of amlodipine and atorvastatin tablets as assessed by C<sub>max</sub>: 101% (90% CI: 98, 104) and AUC: 100% (90% CI: 97, 103) for the amlodipine component and C<sub>max</sub>: 94% (90% CI: 85, 104) and AUC: 105% (90% CI: 99, 111) for the atorvastatin component, respectively.
The bioavailability of the amlodipine component of amlodipine/atorvastatin was not affected under the fed state as assessed by $C_{\text{max}}$: 105% (90% CI: 99, 111) and AUC: 101% (90% CI: 97, 105) relative to the fasted state. Although food decreases the rate and extent of absorption of atorvastatin from amlodipine/atorvastatin by approximately 32% and 11%, respectively, as assessed by $C_{\text{max}}$: 68% (90% CI 60, 79) and AUC: 89% (90% CI 83, 95) relative to the fasted state, similar reductions in plasma concentrations in the fed state have been seen with atorvastatin taken as monotherapy without reduction in LDL-C effect (see below).

In studies with amlodipine: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 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% bioavailable compared to solutions. The absolute bioavailability of atorvastatin is approximately 14%, and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by $C_{\text{max}}$ and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for $C_{\text{max}}$ and AUC) following evening drug administration compared to morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see section 4.2. Posology and method of administration).

Distribution

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

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

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

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

Special Populations

Hepatic Insufficiency
In studies with atorvastatin: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in \( C_{\text{max}} \) and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B) (see section 4.3. Contraindications).
Renal Insufficiency
See section 4.2. Posology and method of administration.

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

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

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

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

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

Pediatrics
In studies with amlodipine
Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to the values in adults.
In studies with atorvastatin
Pharmacokinetic data in the pediatric population are not available.

**Drug Interactions**

In studies with atorvastatin
The effect of co-administered drugs on the pharmacokinetics of atorvastatin as well as the effect of atorvastatin on the pharmacokinetics of co-administered drugs are summarized below (see 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**

<table>
<thead>
<tr>
<th>Co-administered Drug and Dosing Regimen</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg)</td>
</tr>
<tr>
<td>* Cyclosporine 5.2 mg/kg/day, stable dose</td>
<td>10 mg QD&lt;sup&gt;d&lt;/sup&gt; for 28 days</td>
</tr>
<tr>
<td>*Tipranavir 500 mg BID/ritonavir 200 mg BID for 7 days</td>
<td>10 mg SD&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>*Telaprevir 750 mg q8h for 10 days</td>
<td>20 mg SD</td>
</tr>
<tr>
<td>*Boceprevir 800 mg TID&lt;sup&gt;f&lt;/sup&gt; for 7 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>*Lopinavir 400 mg BID/ritonavir 100 mg BID for 14 days</td>
<td>20 mg QD for 4 days</td>
</tr>
<tr>
<td>**Saquinavir 400 mg BID/ritonavir 400 mg BID for 15 days</td>
<td>40 mg QD for 4 days</td>
</tr>
<tr>
<td>*Clarithromycin 500 mg BID for 9 days</td>
<td>80 mg QD for 8 days</td>
</tr>
<tr>
<td>*Darunavir 300 mg BID/ritonavir 100 mg BID for 9 days</td>
<td>10 mg QD for 4 days</td>
</tr>
<tr>
<td>*Itraconazole 200 mg QD for 4 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>*Fosamprenavir 700 mg BID/ritonavir 100 mg BID for 14 days</td>
<td>10 mg QD for 4 days</td>
</tr>
<tr>
<td>*Fosamprenavir 1400 mg BID for 14 days</td>
<td>10 mg QD for 4 days</td>
</tr>
<tr>
<td>*Nelfinavir 1250 mg BID for 14 days</td>
<td>10 mg QD for 28 days</td>
</tr>
<tr>
<td><em>Grapefruit Juice, 240 mL QD&lt;sup&gt;</em>&lt;/sup&gt;</td>
<td>40 mg, SD</td>
</tr>
<tr>
<td>Diltiazem 240 mg QD for 28 days</td>
<td>40 mg, SD</td>
</tr>
<tr>
<td>Erythromycin 500 mg QID&lt;sup&gt;*&lt;/sup&gt; for 7 days</td>
<td>10 mg, SD</td>
</tr>
<tr>
<td>Amlodipine 10 mg, single dose</td>
<td>80 mg, SD</td>
</tr>
<tr>
<td>Cimetidine 300 mg QID for 2 weeks</td>
<td>10 mg QD for 2 weeks</td>
</tr>
<tr>
<td>Colestipol 10 mg BID for 28 weeks</td>
<td>40 mg QD for 28 weeks</td>
</tr>
<tr>
<td>Maalox TC&lt;sup&gt;®&lt;/sup&gt; 30 mL QD for 17 days</td>
<td>10 mg QD for 15 days</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD for 14 days</td>
<td>10 mg for 3 days</td>
</tr>
<tr>
<td>*Rifampin 600 mg QD for 7 days (co-administered)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>*Rifampin 600 mg QD for 5 days (doses separated)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID for 7 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>Fenofibrate 160 mg QD for 7 days</td>
<td>40 mg SD</td>
</tr>
</tbody>
</table>

* "Fold" change = change ratio [(I-B)/B], where I = pharmacokinetic value during the Interaction phase, and B = pharmacokinetic value during the Baseline phase.
See section 4.4. Special warnings and precautions for use and section 4.5. Interaction with other medicinal products and other forms of interaction for clinical significance.

* Greater increases in AUC (up to 1.5-fold) and/or Cmax (up to 0.71-fold) have been reported with excessive grapefruit consumption (≥750 mL - 1.2 L/day).

** Single sample taken 8 to 16 hours post-dose.

† Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

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

a once daily
b twice daily
c single dose
d three times daily
e four times daily

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

<table>
<thead>
<tr>
<th>Atorvastatin</th>
<th>Co-administered Drug and Dosing Regimen</th>
<th>Change in AUC*</th>
<th>Change in Cmax*</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg QD* for 15 days</td>
<td>Antipyrine, 600 mg SD*</td>
<td>↑ 0.03 fold</td>
<td>↓ 0.11 fold</td>
</tr>
<tr>
<td>80 mg QD for 14 days</td>
<td>Digoxin 0.25 mg QD for 20 days</td>
<td>↑ 0.15 fold</td>
<td>↑ 0.20 fold</td>
</tr>
<tr>
<td>40 mg QD for 22 days</td>
<td>Oral contraceptive QD for 2 months - norethindrone 1 mg - ethinyl estradiol 35 µg</td>
<td>↑ 0.28 fold</td>
<td>↑ 0.23 fold</td>
</tr>
<tr>
<td>10 mg SD</td>
<td>Tipranavir 500 mg BID/ritonavir 200 mg BID for 7 days</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>10 mg QD for 4 days</td>
<td>Fosamprenavir 1400 mg BID for 14 days</td>
<td>↓ 0.27 fold</td>
<td>↓ 0.18 fold</td>
</tr>
<tr>
<td>10 mg QD for 4 days</td>
<td>Fosamprenavir 700 mg BID/ritonavir 100 mg BID for 14 days</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

* "Fold" change = change ratio [(I-B)/B], where I = pharmacokinetic value during the Interactions phase, and B = pharmacokinetic value during the Baseline phase.

See section 4.5. Interaction with other medicinal products and other forms of interaction for clinical significance.

a once daily
b single dose
c twice daily
5.3. Preclinical safety data

Carcinogenesis

In studies with amlodipine
Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.
*Based on patient weight of 50 kg.

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

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

Mutagenesis

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

In studies with atorvastatin
Atorvastatin did not demonstrate mutagenic or clastogenic potential in four in vitro tests with and without metabolic activation or in one in vivo assay. It was negative in the Ames test with Salmonella typhimurium and Escherichia coli, and in the in vitro hypoxanthine-guanine phosphoribosyl transferase (HGPRT) forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the in vitro Chinese hamster lung cell assay and was negative in the in vivo mouse micronucleus test.
Impairment of Fertility

In studies with amlodipine
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis).

*Based on patient weight of 50 kg.

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

6. PHARMACEUTICAL PARTICULARS

6.1. Storage
15-30°C

6.2. Nature and content of container
2-1000 tablets, blister/box

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

Distributed by:
Pfizer Limited
177 Chung Cheng East Road, Sec.2, Tamsui District, New Taipei City, 251, Taiwan, R.O.C.

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