SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 5 mg / 10 mg film-coated tablets
[Invented name] 10 mg / 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Invented name] 5 mg / 10 mg:	Each film-coated tablet contains 5 mg amlodipine (as amlodipine besilate) and 10 mg atorvastatin (as atorvastatin calcium).
[Invented name] 10 mg / 10 mg:	Each film-coated tablet contains 10 mg amlodipine (as amlodipine besilate) and 10 mg atorvastatin (as atorvastatin calcium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

[Invented name] 5 mg / 10 mg: Oval, biconvex, white or almost white film-coated tablets, with dimensions 4.6 mm × 9.2 mm.

[Invented name] 10 mg / 10 mg: Oval, biconvex, with score line on one side, light blue film-coated tablets, with dimensions 4.6 mm × 9.1 mm. The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Invented name] is indicated for prevention of cardiovascular events in hypertensive patients, with three concomitant cardiovascular risk factors normal to mildly elevated cholesterol levels, without clinically evident coronary heart disease where combined use of amlodipine and a low dose of atorvastatin is considered appropriate, in accordance with current treatment guidelines (see section 5.1).

[Invented name] should be used when response to diet and other nonpharmacological measures is inadequate.

4.2 Posology and method of administration

[Invented name] is for oral use.

Posology
The usual starting dose is 5 mg/10 mg once daily.

If a patient is identified as needing greater blood pressure control, 10 mg/10 mg once daily can be administered.

[Invented name] can be used either alone or in combination with anti-hypertensive drugs, but should not be taken in combination with another calcium channel blocker, or another statin.
The combination of [Invented name] and fibrates should be avoided (see sections 4.4 and 4.5).

Patients with renal insufficiency: No dose adjustment is required in patients with impaired renal function (see section 4.4 and section 5.2).

Patients with hepatic impairment: [Invented name] is contra-indicated in patients with active liver disease (see section 4.3).

Children/adolescents: Safety and efficacy of [Invented name] have not been established in children and adolescents. Therefore, the use of [Invented name] is not recommended in these populations.

Elderly: It is unnecessary to adjust the dose in elderly patients (see section 5.2).

Co-administration with other medicines

If co-administered with ciclosporin, the dose of atorvastatin should not exceed 10 mg (see section 4.5).

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day (see sections 4.4 and 4.5).

Method of administration
Doses may be taken at any time of day with or without food.

4.3 Contraindications

[Invented name] is contra-indicated in patients:
- who have hypersensitivity to dihydropyridines*, the active substances amlodipine and atorvastatin or to any of the excipients listed in section 6.1;
- who have active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal;
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6);
- in combination with itraconazole, ketoconazole and telithromycin (see section 4.5);
- who have severe hypotension;
- who have shock (including cardiogenic shock);
- who have obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis);
- who have haemodynamically unstable heart failure after acute myocardial infarction;
- treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

* amlodipine is a dihydropyridine calcium channel blocker.

4.4 Special warnings and precautions for use

Cardiac failure: Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Liver effects: Liver tests should be performed before initiation of treatment, periodically thereafter, and in patients who develop any signs or symptoms suggestive of liver injury. In case of increased transaminase levels monitoring should be performed until the abnormalities resolve.

Should an increase in ALT or AST of greater than 3 times the upper limit of normal (ULN) persist, treatment should be discontinued.

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Due to the atorvastatin component, [Invented name] should be used with caution in patients who consume substantial quantities of alcohol, in patients with hepatic impairment and/or have a history of liver disease.

Skeletal muscle effects: As with other HMG-CoA reductase inhibitors, atorvastatin may affect the skeletal muscle and cause myalgia, myositis, and myopathy that may rarely progress to rhabdomyolysis, characterised by markedly elevated CK levels (>10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure and may be fatal on rare occasion.

A regular control of CK levels or other muscular enzymes is not recommended in asymptomatic patients treated by statin. CK monitoring is recommended before starting any statin treatment, in patients with pre-disposing factors for rhabdomyolysis and in those with muscular symptoms, and whilst treated by a statin (see below).

Before treatment

[Invented name] should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine kinase (CK) level should be measured before starting statin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of predisposing factors for rhabdomyolysis.
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2).

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

If CK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started.

Creatine kinase measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (>5 times ULN), levels should be systematically remeasured within 5 to 7 days later to confirm the results.

Whilst on treatment

- Patients must be asked to promptly report unexplained muscle pain, muscle cramps or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with [Invented name], their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.

- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of [Invented name] may be considered at the lowest dose and with close monitoring.
- [Invented name] must be discontinued if clinically significant elevation of CK levels (>10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

There is no effect of amlodipine on laboratory parameters.

Concomitant treatment with other medicinal products
As with other drugs in the statin class, risk of rhabdomyolysis is increased when [Invented name] is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In cases where co-administration of these medicinal products with [Invented name] is necessary, the benefit and the risk of concurrent treatment should be carefully considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

[Invented name] must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.
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 [Invented name] and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischaemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to the combination drug
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. No effect of amlodipine on the C_{max} of atorvastatin was shown but the AUC of atorvastatin increased by 18% (IC 90% [109-127%]) in the presence of amlodipine.

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

Interactions related to amlodipine

Unadvisable combination

Dantrolene (infusion): in animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
By extrapolation combination of amlodipine and dantrolene should be avoided (see section 4.4).

Combinations needing precaution

Baclofen: increase in the anti-hypertensive effect. Monitoring of the arterial pressure and dose adjustment of the anti-hypertensive drug if necessary.

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
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: Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Combinations to be taken into account

Alpha-1 blockers in urology (prazosin, alfuzosin, doxazosin, tamsulozin, terazosin): increase in the hypotensive effect. Risk of severe orthostatic hypotension.

Amifostin: increase in the hypotensive effect by addition of adverse effects.

Imipramine antidepressants, neuroleptics: antihypertensive effect and risk of orthostatic hypotension increased (additive effect).

Beta-blockers in heart failure (bisoprolol, carvedilol, metoprolol): risk of hypotension and heart failure in patients with latent or un-controlled heart failure (*in vitro* negative inotropic effect of the dihydropyridines, variable depending on the products, which may add to the negative inotropic effects of beta-blockers). The presence of a beta-blocker treatment can minimise the reflex sympathetic reaction set into action in case of excessive hemodynamic repercussion.

Corticosteroid, tetracosactid: decrease in the antihypertensive effect (water and sodium retention effect of the corticosteroids).

Other antihypertensive agents: the concomitant use of amlodipine with another antihypertensive drug (beta-blocker, angiotensin II blocker, diuretic, ACE inhibitor) can increase the hypotensive effect of amlodipine. Treatment with trinitrate, nitrates or other vasodilatators needs to be considered with caution.

Sildenafil: a single 100mg 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 blood pressure lowering effect.

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, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

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.

In interaction studies it has also been shown that cimetidine, atorvastatin, aluminium/magnesium salts and digoxin have not affected the pharmacokinetics of amlodipine.

Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2).

Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4).

CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatement of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors: (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

CYP3A4 inducers

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A 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. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport inhibitors

Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

Gemfibrozil / fibric acid derivatives

The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

Ezetimibe

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

Effect of atorvastatin on co-administered medicinal products

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives

Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

Warfarin

In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Clinical Recommendation[#]
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑ 9.4 fold	In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin

Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	daily. Clinical monitoring of these patients is recommended
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	No specific recommendation. [Invented name] contains 10 mg atorvastatin.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑ 4.4 fold	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑ 3.9 fold	No specific recommendation. [Invented name] contains 10 mg atorvastatin.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg SD	↑ 3.3 fold	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	↑ 2.5 fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	↑2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	↑ 1.7 fold^	No specific recommendation
Grapefruit Juice, 240 mL OD *	40 mg, SD	↑ 37%	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑ 51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑33%^	Clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	↑18%	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 4 weeks	↓ less than 1%^	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg OD for 4 weeks	↓ 35%^	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓ 41%	No specific recommendation.
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	↑ 30%	If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80%	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	Lower starting dose and clinical monitoring of these patients is recommended.

Fenofibrate 160 mg OD, 7 days	40 mg SD	↑ 3%	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	↑ 2.3 fold	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	↑8.3 fold	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).
Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days	10 mg SD	↑1.95 fold	The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.

[&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

[#] See sections 4.4 and 4.5 for clinical significance.

[*] Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).

[^] Total atorvastatin equivalent activity

Increase is indicated as "↑", decrease as "↓"

OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily

Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

Atorvastatin and dosing regimen	Co-administered medicinal product		
	Medicinal product/Dose (mg)	Change in AUC[&]	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	↑15%	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months - norethindrone 1 mg -ethinyl estradiol 35 µg	↑28% ↑19%	No specific recommendation.
80 mg OD for 15 days	* Phenazone, 600 mg SD	↑3%	No specific recommendation

[&] Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)

[*] Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

Increase is indicated as "↑", decrease as "↓"
OD = once daily; SD = single dose

4.6 Fertility, pregnancy and lactation

[Invented name] is contraindicated in pregnancy and while breast-feeding.

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy

Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction (see section 5.3).

Maternal treatment with atorvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, [Invented name] should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with [Invented name] should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3.).

In case of discovery of a pregnancy during the treatment, [Invented name] must be discontinued immediately.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.
It is not known whether atorvastatin (and its metabolites) is excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3). Because of the potential for serious adverse reactions, women taking [Invented name] should not breast-feed their infants (see section 4.3). Atorvastatin is contraindicated during breastfeeding (see section 4.3).

Fertility

In animal studies atorvastatin had no effect on male or female fertility (see section 5.3).

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No study has been performed to establish the effect of amlodipine/atorvastatin fixed combination on ability to drive and use machines.

The atorvastatin component of [Invented name] has negligible influence on the ability to drive and use machines.
However based on the pharmacodynamic properties of the amlodipine component of [Invented name], the possible occurrence of dizziness, headache, fatigue or nausea needs to be taken into account while driving or using machines (see section 4.8).

4.8 Undesirable effects

Amlodipine/atorvastatin fixed combination has been evaluated for safety in 1092 patients in double blind placebo controlled studies treated for concomitant hypertension and dyslipidaemia. In clinical trials with product containing amlodipin / atorvastatin, no adverse events peculiar to this combination have been observed. Adverse events have been limited to those that were reported previously with amlodipine and/or atorvastatin (please see respective adverse event tables below).

In controlled clinical trials, discontinuation of therapy due to clinical adverse events or laboratory abnormalities was only required in 5.1% of patients treated with both amlodipine and atorvastatin compared to 4.0% of patients given placebo.

The following adverse events, listed according to the MedDRA system organ class and frequencies, are for amlodipine and atorvastatin individually:
Very common: ≥1/10, common: ≥1/100 and <1/10, uncommon: ≥1/1000 and <1/100, rare: ≥1/10,000 and <1/1000, very rare: < 1/10,000, not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**	
		Amlodipine	**Atorvastatin**
Infections and infestations	Nasopharyngitis	-	Common
Blood and the Lymphatic System Disorders	Leucopenia	Very rare	-
	Thrombocytopenia	Very rare	Rare
Immune System Disorders	Hypersensitivity	Very rare	Common
	Anaphylaxis	-	Very rare
Metabolism and Nutrition Disorders	Hypoglycaemia	-	Uncommon
	Hyperglycaemia*	Very rare	Common
	Weight increase	Uncommon	Uncommon
	Weight decrease	Uncommon	-
	Anorexia	-	Uncommon
Psychiatric Disorders	Insomnia	Uncommon	Uncommon
	Mood changes (including anxiety)	Uncommon	-
	Nightmare	-	Uncommon
	Depression	Uncommon	Not known
	Confusion	Rare	-
Nervous System Disorders	Somnolence	Common	-
	Dizziness	Common	Uncommon
	Headache (especially at the beginning of the treatment)	Common	Common
	Tremor	Uncommon	-
	Hypoesthesia, paresthesia	Uncommon	Uncommon
	Syncope	Uncommon	-
	Hypertonia	Very rare	-
	Peripheral neuropathy	Very rare	Rare
	Amnesia	-	Uncommon
	Dysgeusia	Uncommon	Uncommon
	Extrapyramidal disorder	Not known	-
	Vision blurred	-	Uncommon

Eye Disorders	Visual disturbances (including diplopia)	Uncommon	Rare
Ear and Labyrinth Disorders	Tinnitus	Uncommon	Uncommon
	Hearing loss	-	Very rare
Cardiac Disorders	Palpitations	Common	-
	Angina pectoris	Rare	-
	Myocardial infarction	Very rare	-
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	-
Vascular Disorders	Flushing	Common	-
	Hypotension	Uncommon	-
	Vasculitis	Very rare	-
Respiratory, Thoracic and Mediastinal Disorders	Pharyngolaryngeal pain	-	Common
	Epistaxis	-	Common
	Dyspnoea	Uncommon	-
	Rhinitis	Uncommon	-
	Coughing	Very rare	-
	Interstitial lung disease, especially with long term therapy	-	Not known
Gastrointestinal Disorders	Gingival hyperplasia	Very rare	-
	Nausea	Common	Common
	Abdominal pain upper and lower	Common	Uncommon
	Vomiting	Uncommon	Uncommon
	Dyspepsia	Uncommon	Common
	Change of bowel habits (including diarrhoea and constipation)	Uncommon	-
	Dry mouth	Uncommon	-
	Dysgeusia	Uncommon	-
	Diarrhoea, constipation, flatulence	-	Common
	Gastritis	Very rare	-
	Pancreatitis	Very rare	Uncommon
	Eructation	-	Uncommon
Hepatobiliary Disorders	Hepatitis	Very rare	Uncommon
	Cholestasis	-	Rare
	Hepatic failure	-	Very rare
	Jaundice	Very rare	-
Skin and Subcutaneous Tissue Disorders	Dermatitis bullous including erythema multiforme	Very rare	Rare
	Quincke's oedema	Very rare	-
	Erythema multiforme	Very rare	-
	Alopecia	Uncommon	Uncommon
	Purpura	Uncommon	-
	Skin discoloration	Uncommon	-
	Pruritus	Uncommon	Uncommon
	Rash	Uncommon	Uncommon
	Hyperhidrosis	Uncommon	-
	Exanthema	Uncommon	-
	Urticaria	Very rare	Uncommon
	Angioneurotic oedema	Very rare	Rare
	Exfoliative dermatitis	Very rare	-

	Photosensitivity	Very rare	-
	Stevens-Johnson syndrome	Very rare	Rare
	Toxic epidermal necrolysis	Not known	Rare
Musculoskeletal and Connective Tissue Disorders	Joint swelling (including ankle swelling)	Common	Common
	Arthralgia, Myalgia (see section 4.4)	Uncommon	Common
	Muscle cramps, muscle spasms	Uncommon	Common
	Back pain	Uncommon	Common
	Neck pain	-	Uncommon
	Pain in extremity	-	Common
	Muscle fatigue	-	Uncommon
	Myositis (see section 4.4)	-	Rare
	Rhabdomyolysis, myopathy (see section 4.4)	-	Rare
	Tendinopathy, in rare cases tendon rupture	-	Rare
	Muscle rupture	-	Rare
	Lupus-like syndrome	-	Very rare
	Immune-mediated necrotizing myopathy (see section 4.4)	-	Not known
Renal and Urinary Disorders	Micturition disorder, nocturia, increased urinary frequency	Uncommon	-
Reproductive System and Breast Disorders	Impotence	Uncommon	Uncommon
	Gynaecomastia	Uncommon	Very rare
General Disorders and Administration Site Conditions	Oedema	Common	Uncommon
	Peripheral oedema	-	Uncommon
	Fatigue	Common	Uncommon
	Chest pain	Uncommon	Uncommon
	Asthenia	Uncommon	Uncommon
	Pain	Uncommon	-
	Malaise	Uncommon	Uncommon
	Pyrexia	-	Uncommon
Investigations	Hepatic enzyme increased, alanine aminotransferase and aspartate aminotransferase (mostly consistent with cholestasis)	Very rare	Common
	Blood CK increased (see section 4.4)	-	Common
	White blood cells urine positive	-	Uncommon

*diabetes mellitus has been reported with some statins: frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI>30 kg/m^2, raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with [Invented name] in humans.

Amlodipine
For amlodipine, experience with intentional overdose in humans is limited. Gross overdose 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. Any hypotension due to amlodipine overdose calls for a monitoring in cardiologic intensive care unit. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Atorvastatin
Specific treatment is not available for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA-reductase inhibitors, other combinations (atorvastatin and amlodipine), ATC code: C10BX03

[Invented name] has a dual mechanism 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 [Invented name] inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of [Invented name] is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts –03-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

No modification of amlodipine's effect on systolic blood pressure during the administration of amlodipine/atorvastatin fixed combination, compared to amlodipine used alone.

In the same way, no modification of atorvastatin's effect on LDL-C has been observed in the effect of atorvastatin on serum LDL cholesterol fraction during the administration of amlodipine/atorvastatin fixed combination ,in comparison to atorvastatin used alone.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a randomised 2x2 factorial design study comparing two antihypertensive regimens in a total of 19,257 patients (blood pressure lowering arm – ASCOT-BPLA), as well as the effect of addition of 10 mg atorvastatin compared to placebo in 10,305 patients (lipid-lowering arm - ASCOT-LLA) on fatal and non-fatal coronary events:

The effect of atorvastatin on fatal and non-fatal coronary events was assessed in a randomised double blind placebo controlled study (ASCOT-LLA) in 10,305 hypertensive patients 40-79 years of age with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5 mmol/l (251 mg/dl). All patients had at least 3 of the following predefined cardiovascular risk factors: male gender, age (≥55 years), smoking, diabetes, history of premature CHD in a first-degree relative, TC:HDL ≥6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormalities, proteinuria/albuminuria.

Patients were treated with anti-hypertensive regimens based on amlodipine (5-10 mg) or atenolol (50-100 mg). To attain further blood pressure (BP) goals (<140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients), perindopril (4-8 mg) could be added to the amlodipine group and bendroflumethiazide potassium (1.25-2.5 mg) to the atenolol group. Third line therapy was doxazosin GITS (4-8 mg) in both arms. There were 5168 patients in the atorvastatin group (2584 patients received amlodipine and 2584 patients received atenolol) and 5137 in the placebo group (2554 patients received amlodipine and 2583 patients received atenolol).

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

- 53% (95% confidence interval 31% to 68%, p<0.0001) compared with amlodipine + placebo,
- 39% (95% confidence interval 8% to 59%, p<0.016) compared with atenolol + atorvastatin.

Blood pressure decreased significantly on both treatment regimens and significantly more with the amlodipine based regimen plus atorvastatin than with the atenolol based plus atorvastatin regimen (-26.5/-15.6 mmHg versus -24.7/-13.6 mmHg respectively). The p values on differences between two groups were 0.0036 (for SBP) and <0.0001 (for DBP).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT):
A randomized double-blind study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare the effects of amlodipine or lisinopril to chlorthalidone as first-line therapies in patients with mild to moderate hypertension.

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

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. 11.3% of patients in the amlodipine group reached the primary endpoint versus 11.5% in the chlorthalidone-group (RR of 0.98, 95% CI [0.90-1.07] p=0.65).
Among secondary endpoints:

- all-cause mortality rates were 17.3% in the chlorthalidone group and 16.8% in the amlodipine group (amlodipine versus chlorthalidone RR 0.96, 95% CI [0.89-1.02] p=0.20)
- the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% % vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001).

The trial did not show superiority of any drug with respect to the primary endpoint, an analysis of the results performed *a posteriori* has shown that amlodipine reduces the primary endpoint fatal CHD and non-fatal myocardial infarctions, and the secondary endpoint all cause mortality, to a similar extent as chlorthalidone.

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

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. All cause mortality was 9.1% (216/2365) for atorvastatin versus 8.9% (211/2366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo.

- The risk of hemorrhagic stroke was increased in patients who entered the study with prior hemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57), and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

- The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.71-14.61), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57-1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke. All cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

5.2 Pharmacokinetic properties

Fixed combination of amlodipine and atorvastatin data

Following oral administration, 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 the fixed combination of amlodipine and atorvastatin are not significantly different from the bioavailability of amlodipine and atorvastatin from co-administration of amlodipine and atorvastatin tablets.

The bioavailability of amlodipine from the fixed combination of amlodipine and atorvastatin was not affected under the fed state. Although food decreases the rate and extent of absorption of atorvastatin from the fixed combination of amlodipine and atorvastatin by approximately 32% and 11%, respectively, as assessed by C_{max} and AUC similar reductions in plasma concentrations in the fed state have been seen with atorvastatin without a reduction in LDL-C effect (see below).

Amlodipine data

Absorption

After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 -12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/Kg. The bioavailability of amlodipine is not altered by the presence of food.

Distribution

In vitro studies with amlodipine have shown that approximately 97.5% of the circulating drug is bound to plasma proteins in hypertensive patients.

Biotransformation

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Elimination
Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels are reached after 7 to 8 days of consecutive dosing. 10% of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.

Atorvastatin data
Absorption
Atorvastatin is rapidly absorbed, maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution
The mean volume of distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥95% bound to plasma proteins.

Biotransformation
Atorvastatin is extensively metabolised to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination
Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism. However, the drug does not appear to undergo significant 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, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Data on amlodipine and atorvastatin in special populations

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 in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of atorvastatin in the elderly population compared to younger adults (see section 4.4).

Paediatric: Pharmacokinetic data in the paediatric population are not available.

Gender: Concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal insufficiency: The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Amlodipine is not dialyzable. Therefore, patients with renal failure can receive the usual initial amlodipine dose.

In studies with atorvastatin, renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary.

Hepatic insufficiency: Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%.Therapeutic response to atorvastatin is unaffected in patients with moderate to severe hepatic dysfunction, but exposure to the drug is greatly increased. Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

5.3 Preclinical safety data

No non-clinical studies have been performed with the fixed combination of amlodipine and atorvastatin.

Pre-clinical data on amlodipine revealed no special hazard for humans based on conventional studies of safety, pharmacology, repeat dose toxicity, genotoxicity or carcinogenic potential. In reproduction toxicology studies with amlodipine, an increased duration of parturition and a higher perinatal mortality was observed in rat.

Atorvastatin was not genotoxic (in vitro and in vivo) nor carcinogenic in rats. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, for which the systemic exposure was 6- to 11-fold higher than the highest human dose based on $AUC_{(0-24)}$. There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or foetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure). The concentration of atorvastatin and its active metabolites in rat milk were about equal to that in dams' plasma. Atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
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). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Starch pregelatinised
Cellulose, microcrystalline
Magnesium carbonate, heavy
Polysorbate 80
Hydroxypropylcellulose
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Coating
[Invented name] 5 mg / 10 mg:
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol
Talc

[Invented name] 10 mg / 10 mg:
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol
Talc
Indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Al//OPA/Al/PVC blister foil. 30 tablets in carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmaceutical Works POLPHARMA SA
19 Pelplińska Street, 83-200 Starogard Gdański, Poland

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT