National Institute for Quality- and Organizational Development in Healthcare and Medicines
National Institute of Pharmacy
Directorate

Public Assessment Report

Decentralised Procedure

Amlator-P

atorvastain L-lysine/amlodipine besilate

10 mg/5 mg
10 mg/10 mg
20 mg/5 mg
20 mg/10 mg
film-coated tablets

DC Number: HU/H/0248/001-004/DC

Applicant: Gedeon Richter plc.

Table of contents

Modul 1

Information about the initial procedure

Product name	Amlator-P
Type of application:	
level 1	Known active substances
level 2	Initial application
level 3	Fixed combination, Art 10b (Dir. 2001/83/EC)
level 4	Chemical substances
level 5	Prescription only
Active substance	atorvastatin l-lysine, amlodipine besílate
Pharmaceutical form	film-coated tablets
Strength	10mg/5 mg, 10 mg/10 mg, 20 mg/5 mg, 20 mg/20 mg
MA holder	Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary
RMS	Hungary
CMS	BG, CZ, EE, LT, LV, RO and SK
Procedure number	HU/H/0248/001-004/DC
Timetable	Start of the procedure: 17-02-2010 End of the European procedure: 09-03-2011

Modul 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 10 mg/5 mg film-coated tablets
{(Invented) name} 10 mg/10 mg film-coated tablets
{(Invented) name} 20 mg/5 mg film-coated tablets
{(Invented) name} 20 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{(Invented) name} 10 mg/5 mg film-coated tablets: each film-coated tablet contains 10 mg atorvastatin (as atorvastatin L-lysine) and 5 mg amlodipine (as amlodipine besylate).
{(Invented) name} 10 mg/10 mg film-coated tablets: each film-coated tablet contains 10 mg atorvastatin (as atorvastatin L-lysine) and 10 mg amlodipine (as amlodipine besylate).
{(Invented) name} 20 mg/5 mg film-coated tablets: each film-coated tablet contains 20 mg atorvastatin (as atorvastatin L-lysine) and 5 mg amlodipine (as amlodipine besylate).
{(Invented) name} 20 mg/10 mg film-coated tablets: each film-coated tablet contains 20 mg atorvastatin (as atorvastatin L-lysine) and 10 mg amlodipine (as amlodipine besylate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

{(Invented) name} 10 mg/5 mg film-coated tablets are white, round, biconvex film-coated tablets. Engraving on one side: “CE3”, other side is without engraving.
{(Invented) name} 10 mg/10 mg film-coated tablets are white, round, biconvex film-coated tablets. Engraving on one side: “CE5”, other side is without engraving.
{(Invented) name} 20 mg/5 mg film-coated tablets are white, oblong, biconvex film-coated tablets. Engraving on one side: “CE4”, other side is without engraving.
{(Invented) name} 20 mg/10 mg film-coated tablets are white, oblong, biconvex film-coated tablets. Engraving on one side: “CE6”, other side is without engraving.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{(Invented) name} film-coated tablets are indicated as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination for the treatment of hypertension (with or without chronic stable coronary artery disease) in adult patients with oneof the following coincident conditions:

- primary hypercholesterolaemia (including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification),

- homozygous familial hypercholesterolaemia.

4.2 Posology and method of administration

{(Invented) name} is not recommended for initial therapy. The dose of {(Invented) name} should be determined by the titration of individual components on the basis of the posology and method of administration of amlodipine and atorvastatin.

In agreement with the results of dose titration the recommended dose is one tablet {(Invented) name} 10 mg/5 mg, one tablet {(Invented) name} 10 mg/10 mg, one tablet {(Invented) name} P 20 mg/5 mg or one tablet {(Invented) name} 20 mg/10 mg daily. The maximum daily dose is one tablet {(Invented) name} 20 mg/10 mg daily.

{(Invented) name} may be taken any time of the day and irrespective of meals.

Use in the elderly
Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Use in children and adolescents
{(Invented) name} is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Patients with hepatic impairment
Atorvastatin should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). Atorvastatin is contraindicated in patients with active liver disease (see section 4.3).

Patients with renal impairment:
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, while renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. Therefore no adjustment of dose is required (see section 4.4).

Amlodipine is not dialysable.

4.3 Contraindications

- Hypersensitivity to the active substances or any dihydropyridines or statins or to any of the excipients
- Severe hypotension
- Shock (including cardiogen shock)
- Outflow obstruction of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see section 4.4)
- During pregnancy, while breast feeding and in women of child bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

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 in patients with NYHA grade III and IV heart failure amlodipine was associated with increased reports of pulmonary oedema despite no

significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

Hypertensive crisis
The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Liver Effects
Liver function tests should be performed before the initiation of atorvastatin treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury during {(Invented) name} therapy should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases (ALT or AST) of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of {(Invented) name} is recommended (see section 4.8).

The half life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients.

(Invented) name} should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

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 ischemic 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).

Use in elderly patients
In the elderly increase of the dosage should take place with care (see section 5.2).

Use in children
{(Invented) name} is not indicated in children.

Use in renal failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

Skeletal muscle effects
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

Before treatment
Before the use of {(Invented) name}, at the beginning of atorvastatin as monocomponent, the drug should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A 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 other 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 remeasured within 5 to 7 days later to confirm the results.

Whilst on treatment

- Patients must be asked to promptly report muscle pain, weakness or cramps 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 times 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.
- Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products

Risk of rhabdomyolysis is increased when atorvastatin 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, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, erythromycin, niacin and ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where coadministration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy (see section 4.5).

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.

4.5 Interaction with other medicinal products and other forms of interaction

In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in atorvastatin AUC. Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin. No drug interaction studies have been conducted with atorvastatin and amlodipine combination and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Interactions with amlodipine

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors: With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. 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. However, no adverse events attributable to such interaction have been reported.

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

In clinical interaction studies grapefruit juice, cimetidine, aluminium/ magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, ethanol (alcohol), warfarin or cyclosporin.

There is no effect of amlodipine on laboratory parameters.

Interactions with atorvastatin

Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. 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 and HIV protease inhibitors including ritonavir, lopi-

navir, 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 protein 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
Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

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 co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
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	In cases where co-administration with atorvastatin

Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑ 3.3 fold	is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
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%^	Lower maximum dose and 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	40mg SD	↑ 35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40mg SD	↑ 3%	Lower starting dose and clinical monitoring of these patients is recommended.

[&] 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).
** Single sample taken 8-16 h post dose.
^ Total atorvastatin equivalent activity
Increase is indicated as "↑", decrease as "↓"
OD = once daily; SD = single dose; BID = twice 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 (see section 4.3).

Women of childbearing potential

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

Pregnancy

The safety of atorvastatin and amlodipine in human pregnancy has not been established.

Reproductive studies in rats with amlodipine have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans.

Atorvastatin is contraindicated during pregnancy (see section 4.3). 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, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with atorvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3.)

Breastfeeding

It is unknown whether amlodipine, atorvastatin and their metabolites are excreted in human breast 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).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse events, that have been seen with either atorvastatin or amlodipine alone may be potential side effects with {(Invented) name}.

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

Based on data from clinical studies and extensive post marketing experience, the following table presents the adverse reaction profile for atorvastatin.

Estimated frequencies of reactions are ranked according to the following convention: common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

System Organ Class MedDRA 12.0	**Frequency**	**Adverse reactions of Atorvastatin**	**Adverse reactions of Amlodipine**
Infections and infestations	*Common*	Nasopharyngitis	
Blood and the lymphatic system disorders	*Rare*	Thrombocytopenia	
	Very rare		Thrombocytopenia, Leukopenia
Immune system disorders	*Common*	Allergic reactions	
	Very rare	Anaphylaxis	Hypersensitivity
	Common	Hyperglycaemia	

System Organ Class MedDRA 12.0	Frequency	Adverse reactions of Atorvastatin	Adverse reactions of Amlodipine
Metabolism and nutrition Disorders	*Uncommon*	Hypoglycaemia, Anorexia	
	Very rare		Hyperglycaemia
Psychiatric disorders	*Uncommon*	Insomnia Nightmare	Insomnia, Mood altered (including anxiety), De-pression
	Rare		Confusion
Nervous system disorders	*Common*	Headache	Somnolence, Dizziness, Headache (especially at the beginning of the treatment)
	Uncommon	Dizziness, Paraesthesia, Hypoesthesia, Dysgeusia, Amnesia,	Syncope, Tremor, Dys-geusia, Hypoaesthesia, Paraesthesia
	Rare	Peripheral neuropathy NOS	
	Very rare		Hypertonia (in muscles). Neuropathy peripheral
Eye disorders	*Uncommon*	Vision blurred	Visual impairment (includ-ing diplopia)
	Rare	Visual disturbances	
Ear and labyrinth disorders	*Uncommon*	Tinnitus	Tinnitus
	Very rare	Hearing loss	
Cardiac Disorders	*Uncommon*		Palpitations
	Very rare		Myocardial infarction, Arrhythmia (including Bradycardia, Ventricular tachycardia and Atrial fibrillation)
Vascular disorders	*Common*		Flushing
	Uncommon		Hypotension
	Very rare		Vasculitis
Respiratory, thoracic and mediastinal disorders	*Common*	Pharyngolaryngeal pain, Epistaxis	
	Uncommon		Dyspnoea, Rhinitis
	Very rare		Cough
Gastrointestinal disorders	*Common*	Diarrhoea, Constipation, Flatulence, Nausea, Dyspepsia	Abdominal pain, Nausea
	Uncommon	Vomiting, Abdominal pain upper and lower, Eructa-tion, Pancreatitis	Vomiting, Dyspepsia, Change of bowel habits (including Diarrhoea and Constipatio), Dry mouth
	Very rare		Pancreatitis, Gastritis, Gingival hyperplasia

System Organ Class MedDRA 12.0	Frequency	Adverse reactions of Atorvastatin	Adverse reactions of Amlodipine
Hepatobiliary disorders	*Uncommon*	Hepatitis	
	Rare	Cholestasis	
	Very rare	Hepatic failure	Hepatitis, Jaundice
Skin and subcutaneous tissue disorders	*Uncommon*	Urticaria, Alopecia, Skin rash, Pruritus	Alopecia, Purpura, Skin discolouration, Hyperhidrosis, Pruritus, Rash, Exanthema
	Rare	Angioneurotic oedema, Dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	
	Very rare		Angioedema, Erythema multiforme, Urticaria, Exfoliative dermatitis, Stevens-Johnson syndrome, Quincke-oedema Photosensitivity reaction
Musculoskeletal and connective tissue disorders	*Common*	Myalgia, Arthralgia Pain in extremity, Muscle spasms, Joint swelling, Back pain	Ankle oedema
	Uncommon	Neck pain, Muscle fatigue	Arthralgia, Myalgia, Muscle spasms, Back pain
	Rare	Myopathy, Myositis, Rhabdomyolysis, Tendon disorder sometimes complicated by tendon rupture	
Renal and urinary disorders	*Uncommon*		Micturition disorder, Nocturia, Pollakiuria
Reproductive system and breast disorders	*Uncommon*		Erectile dysfunction, Gynaecomastia
	Very rare	Gynaecomastia	
General disorders and administration site conditions	*Common*		Oedema, Fatigue
	Uncommon	Malaise, Asthenia, Chest pain, Periferal oedema, Fatigue, Pyrexia	Chest pain, Asthenia, Pain, Malaise
Investigations	*Common*	Liver function test abnormal * Blood creatine phosphokinase increased**	
	Uncommon	Weight gain White blood cells urine positive	Weight increase, Weight decrease
	Very rare		Hepatic enzymes increased***

*As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose related and were reversible in all patients.
**Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin treated patients (see section 4.4).
***mostly in connection with cholestasis

The following adverse events have been reported with some statins: sexual dysfunction, depression and exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

4.9 Overdose

No case of overdose has been reported.

Amlodipine

Symptoms:
Available data 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.

Treatment:
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 blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Atorvastatin

Specific treatment is not available for atorvastatin overdosage. 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 atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents HMG CoA reductase inhibitors, combinations (atorvastatin and amlodipine). ATC code: C10BX03

Atorvastatin

Atorvastatin is a selective, competitive inhibitor of HMG – CoA reductase, the rate-limiting enzyme responsible for the conversion of 3 – hydroxy-3 – methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG – CoA reductase and subsequently cholesterol biosynthesis in the liver and increases 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 iss effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of total – C (30%-46%), LDL – C (41% - 61%), apolipoprotein B (34% -50%), and triglycerides (14% -33%), while producing variable increases in HDL – C and apolipoprotein A1 in a dose-response study.

These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total C, LDL C, and apolipoprotein B have been proven to reduce the risk for cardiovascular events and cardiovascular mortality.

Homozygous familial hypercholesterolaemia

In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double- blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e. g. need for revascularisation, non fatal myocardial infarction, coronary death) was not investigated in this study.

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L ± 0.8 (78.9 mg/dl ± 30) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/l ± 0.7 (110 mg/dl ± 26) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apolipopro-

tein B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.

The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in this study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

Acute coronary syndrome

In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Q-wave MI or unstable angina). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring hospitalization, indicating a risk reduction by 16% (p=0.048). This was mainly due to a 26% reduction in re-hospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).

The safety profile of atorvastatin in the MIRACL study was consistent with what is described in section 4.8.

Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non fatal coronary heart disease was assessed in a randomized, double blind, placebo controlled study, the Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT LLA). Patients were hypertensive, 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 predefined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first degree relative, TC:HDL C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with antihypertensive therapy (either amlodipine or atenolol based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

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

Event	***Relative Risk reduction (%)***	***Number of events (Atorvastatin vs Placebo)***	***Absolute risk reduction[1] (%)***	***p-value***
Fatal CHD plus non-fatal MI)	36%	100 vs 154	1.1%	0,0005
Total cardiovascular events and revascularisation procedures	20%	389 vs 483	1.9%	0,0008
Total coronary events	29%	178 vs 247	1.4%	0,0006

[1]Based on difference in crude events rates occurring over a median follow up of 3.3 years.
CHD = coronary heart disease
MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32 0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59 1.17), p=0.287).

The effect of atorvastatin on fatal and nonfatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes 40-75 years of age, without prior history of cardiovascular disease and with LDL-C ≤4.14 mmol/l (160 mg/dl) and TG ≤6.78mmol/l (600mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

Patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

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

Event	Relative Risk Reduction (%)	Absolute Risk Reduction[1] (%)	Number of Events (Atorvastatin vs.Placebo)	*p*-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	37%	3.2%	83 vs. 127	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	1.9%	38 vs. 64	0.0070
Strokes (Fatal and non-fatal)	48%	1.3%	21 vs. 39	0.0163

[1]Based on difference in crude events rates occurring over a median follow-up of 3.9 years.
AMI= acute myocardial infarction; CABG= coronary artery bypass graft; CHD=coronary heart disease; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4,731 patients who had a stroke or 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% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 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.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (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 ischaemic burden by the following two actions.

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since amodipine doesn't cause reflex tachycardia, the unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of Amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

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

In patients with angina, once daily administration of Amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate 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: Haemodynamic 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 with heart failure.

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

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: Amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension."

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

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between Amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the Amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between Amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

The effects of amlodipine on cardioavascular morbidity and mortality, and the progression of coronary artery and carotid artery sclerosis was investigated in the PREVENT (Prospective Randomized

Evaluation of the Vascular Effects of Norvasc Trial) trial.
In this multicenter, randomized, placebo-controlled, double-masked clinical trial, 825 patients with angiographically documented coronary artery disease were followed up for three years. In the medical history of the patients randomized into the treatment group, the rate of MI (myocardial infarction) was 45%, the rate of PTCA (Percutaneous transluminal coronary angioplasty) was 42%, and the rate of angina pectoris was 69%. The severity of coronary artery disease ranged from one artery influenced (45% of the patients) to more than three artery influenced (21% of the patients). Patients with uncontrolled hypertension (diastolic hypertension >95Hgmm) were excluded. The assessment of the major cardiovascular events was performed by an outcome evaluating committee that was blinded for the treatment. Although there wasn't any demonstrable effect on the progression of the coronary artery atherosclerotic laesions found, amlodipine could halt the progression of carotid artery intima-media thickening.In patients treated with amlodipine, .a significant (31%) reduction of the outcome combinied of the cardiovascular mortality, myocardial infarction, stroke, percutaneous transluminal coronary angioplasty (PTCA) coronary artery bypass graft

(CABG) implantation, hospitalization due to instable angina pectoris and the progression of congestive heart failure.

In patients treated with amlodipine, the need for revascularization prodecures (PTCA and CABG) was also reduced significantly (-42%).Compared to placebo group, the need for hospitalization due to instable agina was reduced (-33%) in the amlodipine group.

5.2 Pharmacokinetic properties

Atorvastatin

Absorption:
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin 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.

Distribution:
Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.

Biotransformation:
Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized viaglucuronidation. 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.

Excretion:
Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG - CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Special populations

Elderly:
Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

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

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

Renal insufficiency:

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic insufficiency:
Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in Cmax and approx. 11 – fold in AUC) in patients with chronic alcoholic liver disease (Child – 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.

<u>*Amlodipine*</u>

Absorption:
After oral administration amlodipine is well absorbed, and peak plasma concentration is achieved between 6-12 hours. Absolute bioavailability has been estimated between 64-80%. The bioavailability of Amlodipine is not altered by the presence of food.

Distribution:
Distribution volume is about 21 l/kg. Approximately 97 % of the circulating drug is bound to plasma proteins. Steady-state plasma levels of Amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Metabolism and Elimination:
Amlodipine is extensively converted to inactive metabolites via hepatic metabolism, and 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life about 30-50 hours.

<u>Special Populations</u>
Effects of Age and Disease States on Pharmacokinetics

Elderly patients:
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.

Renal Impairment:
The pharmacokinetics of Amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

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

5.3 Preclinical safety data

<u>*Atorvastatin*</u>

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

Amlodipine

In two-year preclinical studies with rats and mice, receiving amlodipine in doses of 0.5 mg, 1.25 mg 2.5 mg per kg body weight, amlodipine was not carcinogen. In mice the highest dose was similar to the advised maximum daily human dose of 10 mg counted in mg/ m^2, while in rats it was the double. This dose was near the maximum tolerated dose in mice, while in rats it was lower.

Amlodipine was not mutagen neither in the study of the chromosomes or gens.

In rats amlodipine did not show any effect on fertility up to 10 mg/kg body weight, which was eight times higher than the maximum human dose counted according to body surface.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
calcium carbonate,
cellulose, microcrystalline,
starch, pregelatinised (maize),
croscarmellose sodium,
calcium oxide,
sodium starch glycolate, type A,
hydroxypropylcellulose,
polysorbate 80,
silica, colloidal anhydrous,
magnesium stearate.

Tablet coating:
poly(vinyl alcohol)-partially hydrolyzed,
titanium dioxide (E171),
macrogol 4000,
talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 25°C.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

30 and 90 film-coated tablets are in white, opaque PA/Aluminium/PVC//Aluminium blister and carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

Modul 3

Package leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

{(Invented) name} 10 mg/5 mg film-coated tablets
{(Invented) name} 10 mg/10 mg film-coated tablets
{(Invented) name} 20 mg/5 mg film-coated tablets
{(Invented) name} 20 mg/10 mg film-coated tablets

(atorvastatin/amlodipine)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT {(INVENTED) NAME} IS AND WHAT IT IS USED FOR

{(Invented) name} is a combination product that contains two active substances called atorvastatin and amlodipine.

{(Invented) name} is indicated as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination for the treatment of hypertension (with or without chronic stable coronary artery disease) in adult patients with one of the following coincident conditions:
- elevated cholesterol levels (called primary hypercholesterolaemia), or elevated cholesterol and triglyceride levels at the same time (called combined or mixed hyperlipidaemia)
- elevated cholesterol levels of hereditary origin (called homozygous hypercholesterolaemia).

{(Invented) name} is not intended for initial therapy. You should stop taking the components (medicinal products that contain amlodipine and atorvastatin) when you start taking {(Invented) name}.

You should maintain a standard cholesterol lowering diet during treatment.

If your doctor thinks that both active substances alone are appropriate for you, or you have already taken medicines with these active substances, he can prescribe {(Invented) name} for you.

2. BEFORE YOU TAKE {(INVENTED) NAME}

Do not take {(Invented) name}
- if you are allergic (hypersensitive) to amlodipine or to atorvastatin or any of the other ingredients of the medicine, or if you are allergic (hypersensitive) to a group of substances called "calcium channel blockers" or to any similar medicines to atorvastatin used to lower blood lipids;
- if you have very low blood pressure;
- if you suffer from shock, including cardiogenic shock (not enough blood supply to your tissues);
- if you have serious narrowing of the aortic heart valve (aortic stenosis);
- if you suffer from a certain type of heart failure after heart attack;
- if you have or have ever had a disease which affects the liver;
- if you have had any unexplained abnormal blood tests for liver function;
- if you are pregnant or trying to become pregnant;
- if you are a woman able to have children and not using reliable contraception;
- if you are breast-feeding.

Take special care with {(Invented) name}
- if you have cardiac insufficiency;
- if you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes;
- if you have kidney problems;
- if you have an under-active thyroid gland (hypothyroidism);
- if you have had any repeated or unexplained muscle aches or pains, a personal or family history of muscle problems;
- if you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines);
- if you regularly drink large amounts of alcohol;
- if you have a history of liver disease;
- if you are older than 70 years.

Check with your doctor or pharmacist before taking {(Invented) name}
- if you have severe respiratory failure.

If any of these apply to you, your doctor will need to carry out a blood test before and possibly during your {(Invented) name} treatment to predict your risk of muscle related side effects. The risk of muscle related side effects e.g. rhabdomyolysis is known to increase when certain medicines are taken at the same time (see Section 2 "Taking other medicines").

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

There are some medicines that may change the effect of {(Invented) name} or their effect may be changed by {(Invented) name}. This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side-effects, including the important muscle wasting condition known as rhabdomyolysis described in Section 4:
- certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid;
- other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, colestipol;

- some calcium channel blockers used for angina or high blood pressure, e.g. amlodipine, diltiazem,; medicines to regulate your heart rhythm e.g. digoxin, verapamil, amiodarone;
- medicines used to alter the way your immune system works, e.g. ciclosporin;
- medicines used in the treatment of HIV e.g. ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.,
- other medicines known to interact with {(Invented) name} include ezetimibe (which lowers cholesterol), warfarin (which reduces blood clotting), oral contraceptives, stiripentol (an anti-convulsant for epilepsy), cimetidine (used for heartburn and peptic ulcers), phenazone (a painkiller) and antacids (indigestion products containing aluminium or magnesium);
- medicines for the treatment of cardiac insufficiency, e.g. beta-blockers;
- medicines used to treat high blood pressure such as angiotensin-II receptor blockers, angiotensin-converting enzyme inhibitors;
- medicine to treat high blood pressure and prostate problems such as alpha-1-blockers;
- medicines obtained without a prescription: St John's Wort.

Taking {(Invented) name} with food and drink:
You can take {(Invented) name} with or without food.

Grapefruit juice
Do not take more than one or two glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effect of {(Invented) name}.

Alcohol
Avoid drinking too much alcohol while taking this medicine. For other information see section 2 "Take special care with {(Invented) name}".

Pregnancy and breast-feeding
Do not take {(Invented) name} if you are pregnant, or if you are trying to become pregnant.
Do not take {(Invented) name} if you are able to become pregnant unless you use reliable contraceptive measures.
Do not take {(Invented) name} if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Normally this medicine does not affect your ability to drive or operate machines. However, do not drive if this medicine affects your ability to drive. Do not use any tools or machines if your ability to use them is affected by this medicine. Do not drive or use machines if you feel dizzy after taking this medicine.

3. HOW TO TAKE {(INVENTED) NAME}

Always take {(Invented) name} exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with {(Invented) name}.

Adults
The dose of {(Invented) name} as determined by the doctor can be one {(Invented) name} 10 mg/5 mg, {(Invented) name} 10 mg/10 mg, {(Invented) name} 20 mg/5 mg or one {(Invented) name} 20 mg/10 mg film-coated tablet per day.

The maximum daily dose is: one {(Invented) name} 20 mg/10 mg film-coated tablet.

Swallow each tablet whole with a drink of water. You can take it at any time of the day with or without food. Try to take your tablet at the same time every day.

Follow the dietary advice of the doctor particularly about the low-fat diet; do physical exercises regularly and do not smoke.

The duration of treatment with {(Invented) name} is determined by your doctor.

Please ask your doctor if you think that the effect of {(Invented) name} is too strong or too weak.

Elderly patients
There is no need to modify the dose for elderly patients.

Children and adolescents
For children and adolescent {(Invented) name} is not recommended.

Patients with kidney impairment
Dose change is not necessary in these patients.

Patients with liver impairment
{(Invented) name} should be administered with caution in these patients and regular medical follow-up should include frequent monitoring of liver function.

If you have take more {(Invented) name} than you should have
If you have take more {(Invented) name} than you should have, contact your doctor or the nearest hospital for advice. Take along any tablets that are left, the container and the label so that the hospital can easily tell what medicine you have taken.

If you forget to take {(Invented) name}
If you forget to take a dose, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

If you stop taking {(Invented) name}
Do not stop taking your medicine unless your doctor tells you to do so.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, {(Invented) name} can cause side effects, although not everybody gets them.

If you experience any of the following serious side effects, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department.

Rare: affects 1 to 10 users in 10,000:
- serious allergic reaction which causes swelling of the face, tongue and/or throat, which can cause considerable difficulty in breathing;
- serious illness with severe peeling and swelling of the skin, blistering of the skin, mouth, eyes genitals and fever. Skin rash with pink-red blotches especially on palms of hands or soles of feet which may blister;

- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown which can be life-threatening and lead to kidney problems.

Very rare: affect less than 1 user in 10,000:
- if you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. You should consult your doctor as soon as possible.

Other possible side effects with {(Invented) name}:

Common (affects 1 to 10 users in 100):
- drowsiness, headache, dizziness (especially at the beginning of the treatment), tiredness, weakness;
- inflammation of the nasal passages, pain in the throat, nose bleed;
- flush;
- abdominal pain, nausea, constipation, wind, indigestion, diarrhoea;
- rashes, itching;
- muscle pain, ankle oedema/swelling, joint pain and back pain;
- allergic reactions;
- oedema;
- increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels), increase in blood creatine kinase;
- blood test results that show your liver function can become abnormal.

Uncommon (affects 1 to 10 users in 1,000):
- inflammation of the nasal cavity (rhinitis/running nose);
- anorexia (loss of appetite), weight gain, weight decrease, decreases in blood sugar levels (if you have diabetes you should continue careful monitoring of your blood sugar levels);
- change of mood (anxiety), depression, trembling;
- dizziness, numbness or tingling in the fingers and toes, reductions of sensation to pain or touch, change in sense of taste, loss of memory;
- eye disturbances (including double vision), blurred vision;
- ringing in the ears and/or head;
- strong heartbeat;
- chest pain;
- breathlessness, faint, increased sweat, hypotension;
- dry mouth, vomiting, belching, abdominal pain upper and lower, pancreatitis (inflammation of the pancreas leading to stomach pain);
- hepatitis (liver inflammation);
- hair loss, bruise-like injuries or damage to small blood vessels causing blotches on the skin; discoloration of the skin, rash, skin rash and itching, hives, exanthema;
- neck pain, muscle fatigue;
- myopathy;
- urination problems (including the big amount of night urination and the increased need to urinate);
- impotence, gynecomastia (breast enlargement in men and women);
- fatigue, raised temperature, feeling unwell, cramps, asthenia, pain, peripheral oedema;
- having nightmares, insomnia;
- urine tests that are positive for white blood cells.

Rare (affects 1 to 10 users in 10,000):
- unexpected bleeding or bruising;
- cholestasis (yellowing of the skin and whites of the eyes);

- confusion;
- tendon injury.

Very rare (affects less than 1 user in 10,000):
- decrease of white blood cells in the blood;
- muscle stiffness or muscle tension;
- arrhythmias, heart attack, inflammation of the small blood vessels, increased growth of gum, cough;
- an allergic reaction - symptoms may include sudden wheezing and chest pain or tightness, swelling of the eyelids, face, lips, mouth, tongue or throat, difficulty breathing, collapse;
- photosensitivity;
- hearing loss;
- gastritis;
- hepatic failure;
- angioedema.

Possible side effects reported with some statins (medicines of the same type):
- sexual difficulties;
- depression;
- breathing problems including persistent cough and/or shortness of breath or fever.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE {(INVENTED) NAME}

Keep out of the reach and sight of children.

Do not use {(Invented) name} after the expiry date. The expiry date refers to the last day of that month.

Store below 25°C.

Store in the original package in order to protect from light and moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What {(Invented) name} contains

The active substances of {(Invented) name} are atorvastatin and amlodipine.

{(Invented) name} 10 mg/5 mg film-coated tablets contain 10 mg atorvastatin (as atorvastatin L-lysine) and 5 mg amlodipine (as amlodipine besylate) in each film-coated tablet.

{(Invented) name} 10 mg/10 mg film-coated tablets contain 10 mg atorvastatin (as atorvastatin L-lysine) and 10 mg amlodipine (as amlodipine besylate) in each film-coated tablet.

{(Invented) name} 20 mg/5 mg film-coated tablets contain 20 mg atorvastatin (as atorvastatin L-lysine) and 5 mg amlodipine (as amlodipine besylate) in each film-coated tablet.

{(Invented) name} 20 mg/10 mg film-coated tablets contain 20 mg atorvastatin (as atorvastatin L-lysine) and 10 mg amlodipine (as amlodipine besylate) in each film-coated tablet.

The other ingredients are:

Tablet core:
calcium carbonate,
cellulose, microcrystalline,
starch, pregelatinised (maize),
croscarmellose sodium,
calcium oxide,
sodium starch glycolate, type A,
hydroxypropylcellulose,
polysorbate 80,
silica, colloidal anhydrous,
magnesium stearate

Tablet coating:
poly(vinyl alcohol)-partially hydrolyzed,
titanium dioxide (E171),
macrogol 4000,
talc.

What {(Invented) name} looks like and content of the pack

{(Invented) name} 10 mg/5 mg film-coated tablets are white, round, biconvex film-coated tablets. Engraving on one side: “CE3”, other side is without engraving.

{(Invented) name} 10 mg/10 mg film-coated tablets are white, round, biconvex film-coated tablets. Engraving on one side: “CE5”, other side is without engraving.

{(Invented) name} 20 mg/5 mg film-coated tablets are white, oblong, biconvex film-coated tablets. Engraving on one side: “CE4”, other side is without engraving.

{(Invented) name} 20 mg/10 mg film-coated tablets are white, oblong, biconvex film-coated tablets. Engraving on one side: “CE6”, other side is without engraving.

30 and 90 film-coated tablets are in white, opaque PA/Aluminium/PVC//Aluminium blister and carton box.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

<[To be completed nationally]>

Manufacturer

<[To be completed nationally]>

This medicinal product is authorised in the Member States of the EEA under the following names

<[To be completed nationally]>

This leaflet was last approved in MM/YYYY

<[To be completed nationally]>

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

Modul 4

Labelling

The 10 mg/5 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 10 mg/5 mg film-coated tablets
atorvastatin/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg atorvastatin (as atorvastatin L-lysine) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER (S)

<[To be completed nationally]>

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{(Invented) name} 10 mg/5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Blister

1.NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 10 mg/5 mg film-coated tablets
atorvastatin/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

[Exp.:]

4. BATCH NUMBER

[Batch:]

5. OTHER

The 10 mg/10 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 10 mg/10 mg film-coated tablets
atorvastatin/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg atorvastatin (as atorvastatin L-lysine) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER (S)

<[To be completed nationally]>

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{(Invented) name} 10 mg/10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Blister

1.NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 10 mg/10 mg film-coated tablets
atorvastatin/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

[Exp.:]

4. BATCH NUMBER

[Batch:]

5. OTHER

The 20 mg/5 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 20 mg/5 mg film-coated tablets
atorvastatin/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg atorvastatin (as atorvastatin L-lysine) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER (S)

<[To be completed nationally]>

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{(Invented) name} 20 mg/5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Blister

1.NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 20 mg/5 mg film-coated tablets
atorvastatin/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

[Exp.:]

4. BATCH NUMBER

[Batch:]

5. OTHER

The 20 mg/10 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 20 mg/10 mg film-coated tablets
atorvastatin/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg atorvastatin (as atorvastatin L-lysine) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER (S)

<[To be completed nationally]>

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{(Invented) name} 20 mg/10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Blister

1.NAME OF THE MEDICINAL PRODUCT

{(Invented) name} 20 mg/10 mg film-coated tablets
atorvastatin/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

[Exp.:]

4. BATCH NUMBER

[Batch:]

5. OTHER

Modul 5

Scientific discussion during the initial procedure

I. INTRODUCTION

I.1 Problem statement

The rationale of developing fixed-dose combination products for the concomitant treatment of two concomitant diseases like hypertension and dyslipidaemia is that risk factors for cardiovascular disease often coexist. With the average population prevalence of concomitant hypertension and dyslipidemia estimated at 18% of men and 20% of women aged years or older, the shortcomings of medical intervention result in an enormous excess burden of morbidity and mortality. Guidelines (NCEP 2003, ESC *Guidelines on CVD prevention in clinical practice* 2007), stress this therapeutic approach i.e. the simultaneous management of multiple cardiovascular risk factors.

I.2 About the product

Amlator-P (this name will be used throughout this discussion) tablets contain the known active substances atorvastatin L-lysine/amlodipine besilate in 10mg/5mg; 20mg/5mg; 10mg/10mg; 20mg/10mg dose strengths.

Atorvastatin is an inhibitor of HMG-CoA reductase approved for the reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification). It is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments and for prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event as an adjunct to correction of other risk factors.

Amlodipine is indicated in the treatment of hypertension and in stable and Prinzmetal's anginas.

Pharmacological class
ATC code: C10BX03

Pharmacotherapeutic group
HMG CoA reductase inhibitors, combinations (atorvastatin and amlodipine).

The Applicant's rationale of developing fixed-dose combination products for the concomitant treatment of two concomitant diseases like hypertension and dyslipidaemia is that risk factors for CVD often coexist.

Amlator-P is indicated as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination for the treatment of hypertension (with or without chronic stable coronary artery disease) in adult patients with one of the following coincident conditions:

- primary hypercholesterolaemia (including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification),

- homozygous familial hypercholesterolaemia.

The proposed posology:

Amlator-P is not recommended for initial therapy. The dose of Amlator-P should be determined by the titration of individual components on the basis of the posology and method of administration of amlodipine and atorvastatin.

In agreement with the results of dose titration the recommended dose is one tablet Amlator-P 10 mg/5 mg, one tablet Amlator-P 10 mg/10 mg, one tablet Amlator-P 20 mg/5 mg or one tablet Amlator-P 20 mg/10 mg daily. The maximum daily dose is one tablet Amlator-P 20 mg/10 mg daily.

Amlator-P may be taken any part of the day and irrespective of meals.

Use in the elderly
Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Use in children and adolescents
Amlator-P is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Patients with hepatic impairment
Atorvastatin should be used with caution in patients with hepatic impairment. Atorvastatin is contraindicated in patients with active liver disease.

Patients with renal impairment:
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, while renal disease has no influence on the plasma concentrations nor lipid effects of atorvastatin. Therefore no adjustment of dose is required.

Amlodipine is not dialysable.

I.3 General comments on the submitted dossier

Gedeon Richter Plc. has applied for marketing authorisation for Amlator-P according to the Article 10.b in Directive 2001/83/EC as amended, with HU acting as the reference member state and with concerned member states BG, CZ, EE, LT, LV, PL, RO and SK.

On the basis of the Article 7 of the Paediatric Regulation the application included a product-specific waiver from paediatric investigation. The waiver decision number was (pending): EMEA-000719-PIP01-09.

Scientific advice was not given by either reference or concerned member states for this medicinal product.

In line with the *Question and Answers document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention* (CHMP/EWP/191583/2005) and the revised *Guideline on Clinical Development of Fixed Combination Medicinal Products* (CHMP/EWP/240/95 Rev.1) the Applicant has conducted one clinical trial, Study no. 80395 entitled “Randomised, open-label, 2-way crossover, bioequivalence study of atorvastatin-amlodipine 20mg-10mg tablet (Gedeon

Richter Romania S.A., Romania) and coadministration of Sortis (reference, Pfizer Ltd. Hungary) 20mg tablet / Norvasc (reference, Pfizer Europe MA EEIG, Romania) 10mg tablet following a 20mg-10mg dose in healthy subjects under fasting conditions".

I.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The applicant had provided adequate GCP statement for the bioequivalence study submitted in the dossier. The analytical laboratory participated was GLP compliant.

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerning the decentralised application of Amlator® 10/5 mg, 10/10/ mg, 20/5 mg and 20/10 mg film-coated tablets is based on Article 10.b of consolidated Directive 2001/83/EC (i.e. a fixed combination). The products have been developed by Gedeon Richter Plc. The product to which references have been made have been Sortis® film-coated tablets (containing 10 mg and 20 mg atorvastatin as active ingredient in form of the calcium salt) and Norvasc® tablets (containing 5 mg and 10 mg amlodipine besilate as active ingredient), both original products of Pfizer Inc.

Amlator is indicated as substitution therapy for patients adequately controlled with amlodipine and atorvastatin given concurrently at the same dose levels. The product is a combination for the treatment of essential hypertension and dyslipidaemia consistent with global cardiovascular risk assessment and management recommendations. The maximum daily dose is once a 20 mg/10 mg tablet.

The film-coated tablets will be marketed in dosage strengths of atorvastatin/amlodipine 10 mg/5 mg, 10 mg/10 mg, 20 mg/5 mg and 20mg/10 milligram and packaged in PA/Al/PVC//Al blisters and box.

II.2 Drug Substances (active pharmaceutical ingredients)

The active substances are amlodipine besilate and atorvastatin L-lysine.

Amlodipine besilate

It is described in the European Pharmacopoeia (Ph. Eur.) and the CEP procedure has been followed for this substance. The CEP indicates the suitability of the Ph. Eur. monograph to control the purity of the substance, provided that it is supplemented with a test for residual solvents by GC.

- INN name: amlodipine besilate.
- Compendial names: amlodipine besilate (Ph. Eur., BP and USP).
- Chemical name: 3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene-sulphonate.

The API is a white or almost white powder, slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

The substance is specified according to the requirements of the current Ph. Eur. monograph. Additional requirements have been set for residual solvents.

The Ph. Eur. specification includes the following tests: appearance, solubility, identification (IR), optical rotation, related substances (HPLC), water content, sulphated ash, assay (HPLC). Residual solvents (GC) are also controlled. The specification is in accordance also with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline. Moreover, the API specifications of both the substance and the medicinal product manufacturers were completed with limit for particle size distribution.

The specifications reflect all relevant quality attributes of the API and were found to be adequate to control the quality of the drug substance. The limits set are properly justified. The in-house ana-

lytical methods and the validation of these additional tests have been presented. This is considered to be acceptable.

Batch analysis data also justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period of 5 years and the packaging (double polyethylene bag in multiple coated paper-bag or fibre drum) have been mentioned in the CEP.

GMP compliance of the API manufacture has been demonstrated by the applicant.

Atorvastatin L-lysine

Data on the quality and manufacture of the active substance were provided in the applicant's dossier using the ASMF procedure. The Quality Overall Summary is adequate.

- INN name: atorvastatin
- Chemical name: (3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4 (phenylcarbamoyl)pyrrol-1-yl]- 3,5-dihydroxyheptanoic acid L-lysine salt

The API is a white or almost white powder, is slightly soluble in methanol, DMF and water, insoluble in acetone and dichloromethane. It shows polymorphism.

Evidence of the structure has been confirmed by NMR, MS, FT-IR, TG, XRDP, DSC and by UV spectroscopy. The molecule has two chiral centers, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

The ASMF holder supplied complete details of the manufacturing process including the new steps. Description of the manufacturing process of the API is adequate.

Atorvastatin L-lysine is not official in the Ph. Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: characteristics, identification by IR and HPLC, water content, sulphated ash, heavy metals, lysine content, related substances, residual solvents, assay and microbiological purity. The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the API manufacturer and the medicinal product manufacturer for the control of the substance are adequately characterised.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the API. As a result of the presented stability data a retest period of 24 months is acceptable if stored below 30 °C in a sealed double polyethylene bags in paper.

GMP compliance of the API manufacture has been demonstrated by the applicant.

II.3 Medicinal Product

The aim of the formulation development was to develop a single formulation containing atorvastatin lysin and amlodipine besilate in different dosage strengths.

A satisfactory package of data on development pharmaceutics has been presented. A short but acceptable discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profiles, the product has been proven to be similar to the reference product. A description and flow chart of the manufacturing method has been provided with appropriate indication of in-process controls included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies products with the following composition, appearance and packaging were obtained. The excipients used in the finished products are calcium carbonate, microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, calcium oxide, sodium starch glycolate, hydroxypropylcellulose, polysorbate, colloidal anhydrous silica, magnesium stearate and opadry white (talc, macrogol, titanium dioxide and poly(vinyl alcohol). All excipients used comply with their respective European Pharmacopoeia monographs. Compliance of the product with the general monograph of the European Pharmacopoeia on the *Products with the risk of TSE* has been demonstrated by the applicant.

The 10 mg/5 mg and 10 mg/10 mg film-coated tablets are white, round, biconvex film-coated tablets, engraving “CE3” or “CE5”on one side, respectively.

The 20 mg/5 mg and 20 mg/10 mg film-coated tablets are white, oblong, biconvex film-coated tablets, engraving “CE4” or “CE6” on one side, respectively.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as required by the relevant dosage form monograph of the European pharmacopoeia and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been, as appropriate, adequately validated. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is as follows: PA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 18 months with storage conditions “Do not store above 25 °C. Store in the original package in order to protect from light and moisture” has been approved.

The SPC, PIL and label texts are, from pharmaceutical point of view, acceptable.

II.4 Discussion on chemical and biological aspects

Conclusion: the product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmaco-toxicological properties of both atorvastatin and amlodipine are well-known. The non clinical overview is therefore based on a review of data available in several scientific databases or published in relation to atorvastatin and amlodipine given either alone or in combination.

III.2 Pharmacology

No specific new non-clinical studies have been performed, which is acceptable for this type of application.

III.3 Pharmacokinetics

No specific new non-clinical studies have been performed, which is acceptable for this type of application.

III.4 Toxicology

As for toxicological issues related to atorvastatin-L-lysine, see sections IV.5 and IV.6.

Repeated dose toxicity
N/A

Genotoxicity and carcinogenicity
N/A

Reproductive and developmental toxicity
N/A

III.5 Ecotoxicity/environmental risk assessment

Since Amlator–P is intended to substitute other similar products on the market, its storage, distribution, use and disposal will not result in an increase of risk to the environment.

III.6 Discussion on the non-clinical aspects

This fix combination product contains atorvastatin lysine salt, in contrast to the marketed atorvastatin products containing atorvastatin calcium salt. Lysine, the natural amino acid being present in foods and human proteins is an acceptable salt-forming substance in human medicines.

The Applicant overviewed the literature with regard to non-clinical data of atorvastatin L-lysine and concluded that it has not been tested in non-clinical studies. As in bioequivalence study, comparing the fix-combination of atorvastatin-amlodipine content with the monocom-

ponent tablets containing amlodipine and atorvastatin, the main pharmacokinetic parameters for atorvastatin L-lysine in the fixed combination and for atorvastatin-calcium in the tested reference preparation were found to be equivalent, no additional studies were needed to be performed to demonstrate the similar non-clinical profile of atorvastatin lysine salt to that of the calcium salt.

Pharmacodynamics, pharmacokinetics and toxicology of both atorvastatin and amlodipine are well-known. As the combination is only for substitution therapy there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The rationale of developing fixed-dose combination products for the concomitant treatment of two concomitant diseases like hypertension and dyslipidaemia is that risk factors for cardiovascular disease often coexist. With the average population prevalence of concomitant hypertension and dyslipidemia estimated at 18% of men and 20% of women aged years or older, the shortcomings of medical intervention result in an enormous excess burden of morbidity and mortality Guidelines (NCEP 2003, ESC *Guidelines on CVD prevention in clinical practice* 2007), stress this therapeutic approach i.e. the simultaneous management of multiple cardiovascular risk factors.

In line with the *Question and Answers document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention* (CHMP/EWP/191583/2005) and the recently adopted revised *Guideline on Clinical Development of Fixed Combination Medicinal Products* (CHMP/EWP/240/95 Rev.1) the Applicant has conducted one clinical trial, Study no. 80395 entitled "Randomised, open-label, 2-way crossover, bioequivalence study of atorvastatin-amlodipine 20mg-10mg tablet (Gedeon Richter Romania S.A., Romania) and coadministration of Sortis (reference, Pfizer Ltd. Hungary) 20mg tablet / Norvasc (reference, Pfizer Europe MA EEIG, Romania) 10mg tablet following a 20mg-10mg dose in healthy subjects under fasting conditions".

IV.2 Pharmacokinetics

To support the application, the applicant submitted one bioequivalence study report.

The bioequivalence study was carried out with the highest strength (Atorvastatin-Amlodipine 20/10 mg film-coated tablets) and the Applicant seeks biowaiver for all other strengths. The Applicant states that all requirements of the *Note for Guidance on Investigation of bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98) concerning biowaivers were met:

1. the pharmaceutical products are manufactured by the same manufacturing process;
2. atorvastatin and amlodipine do have a linear drug input over the developed dose range;
3. dose-proportional formulations;
4. in vitro dissolution testing at the required pH values have shown similarity of dissolution profiles.

GCP aspects
The applicant states that the bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

Study design
The clinical development performed by the Applicant comprised of an open-label, single-dose, two-way, crossover study, during which the subjects received a single dose of 20mg/10mg atorvastatin/amlodipine (as fixed combination Atorvastatin+Amlodipine 20mg/10mg film-coated tablets {containing atorvastatin L-lysine and amlodipine besylate}, as 'Treatment A' or co-administered Sortis 20mg film-coated tablets {containing atorvastatin

calcium} plus Norvasc 10mg tablets {containing amlodipine besylate}, as 'Treatment B') in a randomized order. The two treatment phases were separated by a washout period of at least 21 days. For atorvastatin and metabolites, blood samples were collected prior to drug administration and 0.250, 0.500, 0.667, 0.833, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 11.0, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0, and 60.0 hours post-dose in each period. For amlodipine, blood samples were collected prior to drug administration and 2.50, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0, 36.0. 48.0, 72.0, 120, 168, and 216 hours post-dose in each period.

Population(s) studied

Enrolled and randomised: 60 (17 females and 43 males)
Drop-out: 1 (withdrew himself)
Withdrawals: 3 (were withdrawn)
Completed: 56
Safety population: 60

Analytical methods

Plasma concentrations of atorvastatin and its active metabolites ortho-hydroxy atorvastatin and para-hydroxy atorvastatin as well as of amlodipine were determined by validated HPLC-MS/MS methods.

Pharmacokinetic Variables

The pharmacokinetic parameters analysed were AUC_{0-T}, AUC_{0-inf}, C_{max}. The bioequivalence assessment is based on pharmacokinetic parameters of atorvastatin and amlodipine. Data of the active metabolites, 2-OH-atorvastatin and 4-OH-atorvastatin are provided but bioequivalence assessment is based on the pharmacokinetic analysis of the parent compounds.

Statistical methods

ANOVA was performed on log-transformed pharmacokinetic parameters $C_{max,}$ AUC^{0-t} and AUC_{inf}. To conclude bioequivalence two one sided 90% confidence intervals were calculated for test by reference ratio of geometric least square mean of C_{max} and AUC_{0-T}.

Results

Atorvastatin - Amlodipine (A) vs Sortis - Norvasc (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	96.68%	96.15%	110.34%
90 % Geometric C.I.[2]	92.16 % to 101.41 %	91.78 % to 100.73 %	98.57 % to 123.50 %
Intra-Subject CV	15.21 %	14.78 %	36.81 %

Atorvastatin - Amlodipine (A) vs Sortis - Norvasc (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	102.86%	102.97%	103.99%
90 % Geometric C.I.[2]	99.96 % to 105.84 %	100.04 % to 105.99 %	100.93 % to 107.15 %
Intra-Subject CV	9.04 %	9.15 %	9.48 %

The results of the study show that the 90% Confidence Intervals for the log-transformed parameters AUC_{0-T} and C_{max} for atorvastatin and amlodipine were all within the 80-125% acceptable range.

Conclusion
Based on these results, it can be concluded that the test atorvastatin-amlodipine combination product (Treatment A) is bioequivalent to the individual atorvastatin and amlodipine reference products coadministered (Sortis and Norvasc, Treatment B), following a 20 mg-10 mg dose under fasting conditions.

IV.3 Pharmacodynamics

Not applicable

IV.4 Clinical efficacy

Monocomponents alone

The efficacy of atorvastatin and amlodipine has already been demonstrated during the clinical development of both substances.

Atorvastatin/amlodipine combination

The Company's supportive efficacy analysis was restricted to randomized and controlled studies in the treatment of concommitant hypertension and dyslipidaemia. These studies showed the lack of negative pharmacodynamic interaction between the two drugs: the lipid lowering efficacy of atorvastatin was preserved when concomitant amlodipine therapy was added, and the blood pressure lowering efficacy of amlodipine was preserved when concomitant atorvastatin therapy was added to the patients.

The rationale of developing a fixed combination product of atorvastatin and amlodipine was further supported by extensive co-prescription data of amlodipine and atorvastatin in the clinical practice. Co-prescription data of amlodipine and atorvastatin were obtained from IMS Health Ltd, a reliable international provider of business intelligence and strategic consulting services for the pharmaceutical and healthcare industries (www.imshealth.com).

IV.5 Clinical safety

Monocomponents alone
The safety of atorvastatin and amlodipine has already been demonstrated during the clinical development of both substances.

Atorvastatin/amlodipine combination
The Applicant's supportive safety analysis deals with all available published data on the combined use of atorvastatin and amlodipine. In brief, the supportive safety analysis of the published data (on more than 10,000 exposed patients) found that the discontinuation rates were similar between arms in the comparative studies, and the reported adverse event frequencies with the combination were similar to those in the comparator arms (monotherapy or placebo)

or to the reported frequencies of the approved monotherapy products according to their approved Summary of Product Characteristics.

IV.6 Discussion on the clinical aspects

The application concerns a fixed combination of atorvastatin and amlodipine. The indication is as substitution therapy for those patients who are adequately controlled with amlodipine and atorvastatin given concurrently, at the same dose level as in the combination for the treatment of hypertension (with or without chronic stable coronary artery disease) in adult patients with one of the following coincident conditions:

- primary hypercholesterolaemia (including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification),
- homozygous familial hypercholesterolaemia.

The Amlator-P product contains atorvastatin lysine salt, in contrast to the marketed atorvastatin products containing atorvastatin calcium salt. Lysine is an acceptable salt-forming substance in human medicines, being a natural amino acid, an essential component of food and one of the building blocks of all human proteins. The mean daily uptake of lysine is about 5.3 g/day {National Academy of Sciences, Institute of Medicine, Food and Nutrition Board, 2005 157 /id}, which far exceeds the maximal lysine exposure using our Products (about 4 mg/day). Therefore, the lysine salt of atorvastatin is considered to be safe unless it alters the pharmacokinetics of atorvastatin. In line with the applicable Regulatory guidance documents (i.e. CHMP/EWP/240/95, Rev. 1 and the *Question and Answers document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention* (CHMP/EWP/191583/05)), the Applicant's clinical development programme has targeted demonstration of bioequivalence between the new fixed-dose combination product and the free combination of the recognized reference formulations.

For supporting the absence of any clinically significant difference between the present salt alternatives of atorvastatin, the Applicant performed a systematic review of the related scientific literature. As a result of the literature search, up to now, no published study was identified dealing with the clinical investigation of atorvastatin L-lysine. However, publicly available data on the L-lysine itself and the review of general aspects of using alternative salt forming agents, supplemented with human pharmacokinetic data and the results of in vitro tests examining the degree of ionization of both salts in media at bio-relevant pHs led to the conclusion that no other separate clinical study is needed for supporting the proof of similarity of efficacy/safety of the two different atorvastatin salt forms. The Applicant compiled a brief summary from literature findings and own laboratory data in order to support the statement above.

As suggested by authors Stahl and Wermuth (2002) and Verbeek (2006) the following aspects shall be taken into account when changing salt form of an active entity:

- Influence on pharmacokinetics
    - Absorption (solubility, dissolution rate),
    - first-pass effect,
    - distribution, metabolism and elimination.
- Influence on safety

- toxicology.

The Applicant performed in vitro comparative dissolution tests in media of three different pHs and found that dissolution profiles of test (atorvastatin L-lysine) and reference (atorvastatin calcium) preparations are similar.

In addition, the Applicant performed in vitro tests examining the degree of ionization of salts in media at bio-relevant pHs.

On the basis of the calculated results, atorvastatin calcium and lysine salts do not differ in ionization degree in the biologically relevant pH range (i.e. gastrointestinal tract's pH). The above results are modelling that practically atorvastatin and calcium as well as L-lysin salts are dissociated completely in the duodeno-jejunal section of the gastrointestinal tract. It is also apparent from the data that the dissociation of both salt forms is complete in the pH range of the blood (pH 7.38-7.42). In other words, atorvastatin molecules are present in the blood circulation in a free (deprotonated) acid form but not as calcium or lysine salt.

Toxicology
Proteins consist of L-amino acids. Lysine cannot be synthesized by mammals and, as a consequence, is an indispensable amino acid. The lysine dose associated with no observed adverse effect level (NOAEL) was estimated at 3.3–4.0 g/kg/day in rats. As a consequence, an upper limit of 300–400 mg/kg/day can be considered in humans. L-Lysine is an acceptable salt-forming substance and flavouring agent in human medicines, being a natural amino acid, an essential component of food and one of the building blocks of all human proteins. Joint WHO/FAO/UNU Expert Consultation attributed "No safety concern" to the use of L-lysine as a flavouring agent. The Consultation has not evaluated L-lysine using the Procedure for the Safety Evaluation of Flavouring Agents, since the substance is a macronutrient and normal component of protein and, as such, human exposure through food is orders of magnitude higher than the anticipated level of exposure from use as flavouring agent. The same conclusion can be reached when considering the ratio between the above mentioned intake in the Western human diet and the maximal lysine exposure using the Applicant's product (5.24mg/day): it is around 5.0 ‰ for a person 70kg in weight.

Of the nitrogen bases, the essential basic amino acids (e.g. L-lysine) are of no concern.

Based on kinetic considerations, agents of high solubility, dissolution rate and absorption rate may cause unwanted or toxic effects earlier or more strongly expressed when compared to less soluble, hence slow-dissolving, and, in consequence, slow-absorbed salts. The toxicological profile of an active ingredient may, therefore, vary with the selected salt form and provide opportunities to modulate the pharmacodynamic as well as toxic effects. Conversely, when drug salts with similar solubility and dissolution rates are compared, the same safety profiles may be expected, provided the typical difference in the time course of plasma concentrations resulting from different absorption rates for identical doses of a drug entity, but the same value of the elimination rate constant.

To support the application the Applicant has adequately demonstrated bioequivalence between the combination and the monocomponent originators given at the same time.

The applicant has not performed dose-finding studies.

However, the published studies identified in the literature could help the Applicant's dose selection, since some studies reported the relative proportions of the different dose pairs after a free individual dose titration period. The percentage of patients receiving the 5mg/10mg, 5mg/20mg, 10mg/10mg, and 10mg/20mg dose pairs after the individual dose titration period in the GEMINI study were 17.8%, 19.5%, 13.0%, and 12.5%, respectively (all together, 62.8%). In the AVALON study (part 3), at the end of the free dose titration period, similar number of patients were treated with 5 mg or 10 mg of amlodipine (50.2% and 49.8%) while with respect to atorvastatin, the majority of patients were treated with 10 mg (32.1%) or 20 mg (32.0%), and only 23.2% received 40 mg and 12.7% received 80 mg.

For further justification the Applicant has provided co-prescription data from HU, PL, CZ, SK and UK between 2007-2009 or 2006-2008. Co-prescription data support the widespread and generally increasing concomitant use of atorvastatin and amlodipine in the RMS and some CMSs, as well, as in the UK.

There is no objection against granting the marketing authorization from a clinical point of view.

IV.7 Pharmacovigilance system

The RMS considers that the new version of the Pharmacovigilance system of Gedeon Richter Plc. (Version 11.1 as of 12 January 2011) fulfils the requirements described in Volume 9A of the *Rules Governing Medicinal Products in the European Union*.

The Applicant has also provided adequate evidence that the proposed Marketing Authorisation Holders

Gedeon Richter Plc. (H-1103 Budapest, Gyömrői Street 19-21, Hungary
Gedeon Richter Romania SA (Gedeon Richter Romania Ltd., 540306, Tg Mures, Cuza Voda Street 99-105, Romania)
Gedeon Richter Polska Sp. z. o.o (ul. ks. J.Poniatowskiego 5, 05-825 Grodzisk Mazowiecki, Poland)

have the services of a qualified person, Judit Széll (Gedeon Richter Plc.), responsible for pharmacovigilance and also have the necessary means for the notification of any suspected adverse reaction occurring either in the Community or in a third country.

IV.8 Risk Management Plan

The RMS, taking into account the Applicant's arguments mentioned in the RMP, namely

- Amlator-P is intended to be used solely as substitution therapy (in patients adequately controlled with atorvastatin and amlodipine, given concurrently, at the same dose levels as in the fixed combination);
- compared to the individual (or free-combination) use of amlodipine and atorvastatin, no new safety concerns are established for the fixed-dose combination use of these active ingredients;
- in line with a recently approved Summary of Product Characteristics of an atorvastation containing medicinal productclosing an Article 30 referral of atorvastatin (approved by CHMP on 24/09/2010), neither special recommendation are required when amlodipine and atorvastatin are not administered concomitantly, nor dosage limitations are recommended.

can accept the conclusion of the Risk Management Plan that there is no need for additional risk minimisation besides the routine risk minimisation activities (Summary of Product Characteristics, Patient Information Leaflet).

IV.9 Periodic Safety Update Report (PSUR) cycle

The Applicant requested the following: taking into account that the present fixed dose combinations have been extensively used worldwide as free combinations and as the Amlator-P fix-combination film-coated tablets are intended for substitution indication exclusively (for patients who are adequately controlled with atorvastatin and amlodipine, given concurrently, at the same dose levels as in the fixed combination), no additional risks are expected besides those known with the administration of the free combinations. As both atorvastatin and amlodipine have been on the market for more than ten years and their PSUR cycles follow a three-yearly scheme, it is intended to follow a three-yearly PSUR cycle for Amlator-P film-coated tablets using the EU harmonised DLP of one of the active substances, namely atorvastatin active substance (next DLP: 31 October 2011).

Taking the conclusion of the above mentioned (IV.8) Risk Management Plan also into account, although this product is a new fixed combination in the intended indication, the RMS suggests that the first PSUR should be submitted within 60 days after three years calculated from the date of the final letter of the Decentralised Procedure common phase plus one month.

Common renewal date: after 5 years calculated from the date of the final letter of the Decentralised Procedure common phase plus one month.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application contains an adequate overview of the current non-clinical and clinical data. The bioequivalence has been shown. The risk-benefit balance of Amlator-P is therefore favourable and approval is recommended from non-clinical and clinical points of view.

Modul 6

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Change in the SmPC and PIL of Amlator/Duplecor 5/10, 10/10, 5/20 10/20 mg filmcoated tablets in accordance with Article 30 of Directive 2001/83/EC referral procedure of the reference product Norvasc (EMEA/H/A-30/1288, 07-10-2011).	HU/H/0248/001-004/IB/002	Yes	10-01-2012	09-02-2012	Approval	N
Type II Cl.6.a.: Change(s) to therapeutic indication(s). Addition of a new therapeutic indication or modification of an approved one. Addition of a new indication for atorvastatin (prevention of cardiovascular events)	HU/H/0248/001-004/II/004	Yes	20-02-2012	20-05-2012	Approval	N
Type IB C.I.3.a. Submission of updated SmPCs and PILs, completed with informations according to the recommendations of PhVWP (Doc. Ref.: CMDh/PhVWP/042/2012) in connection with risk of new onset diabetes/impaired glucose metabolism.	HU/H/0248/001-004/IB/005	Yes	30-05-2012	29-06-2012	Approval	N