SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Triveram 10mg/5mg/5mg film-coated tablets
[Triveram 20mg/5mg/5mg film-coated tablets]
[Triveram 20mg/10mg/5mg film-coated tablets]
[Triveram 20mg/10mg/10mg film-coated tablets]
[Triveram 40mg/10mg/10mg film-coated tablets]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.40 mg perindopril and 6.94 mg amlodipine besilate equivalent to 5 mg amlodipine
[One film-coated tablet contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.40 mg perindopril and 6.94 mg amlodipine besilate equivalent to 5 mg amlodipine]
[One film-coated tablet contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril and 6.94 mg amlodipine besilate equivalent to 5 mg amlodipine]
[One film-coated tablet contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine]
[One film-coated tablet contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine]

Excipient with known effect: lactose monohydrate (27.46 mg for Triveram 10/5/5 mg, 54.92 mg for Triveram 20/5/5 mg, 20/10/5 mg and 20/10/10 mg, and 109.84 mg for Triveram 40/10/10 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Triveram 10/5/5 mg: Yellow, round, film-coated tablet of 7 mm diameter, with a curvature radius of 25 mm, engraved with "1" on one face and "  "on the other.
[Triveram 20/5/5 mg: Yellow, round, film-coated tablet of 8.8 mm diameter, with a curvature radius of 32 mm, engraved with "2" on one face and "  "on the other.]
[Triveram 20/10/5 mg: Yellow, square-shaped, film-coated tablet of 9 mm side length, with a curvature radius of 16 mm, engraved with "3" on one face and "  "on the other.]
[Triveram 20/10/10 mg: Yellow, oblong-shaped, film-coated tablet of 12.7 mm length and 6.35 mm width, engraved with "4" on one face and "  "on the other.]
[Triveram 40/10/10 mg: Yellow, oblong-shaped, film-coated tablet of 16 mm length and 8 mm width, engraved with "5" on one face and "  "on the other.]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Triveram is indicated for the treatment of essential hypertension and/or stable coronary artery disease, in association with primary hypercholesterolaemia or mixed hyperlipidaemia, as substitution therapy in adult patients adequately controlled with atorvastatin, perindopril and amlodipine given concurrently at the same dose level as in the combination.

4.2 Posology and method of administration

Posology

The usual posology is one tablet once daily.

The fixed dose combination is not suitable for initial therapy.
If a change of posology is required, titration should be done with the individual components.

Renal impairment (see section 4.4)
Triveram can be administered in patients with creatinine clearance ≥ 60mL/min, and is not suitable for patients with creatinine clearance < 60mL/min. In these patients, an individual dose titration with the monocomponents is recommended.

Elderly (see sections 4.4 and 5.2)
Elderly can be treated with Triveram according to the renal function.

Hepatic impairment (see sections 4.3, 4.4 and 5.2)
Triveram should be used with caution in patients with hepatic impairment. Triveram is contraindicated in patients with active liver disease.

Paediatric population
The safety and efficacy of Triveram in children and adolescents have not been established. No data are available. Therefore, use in children and adolescents is not recommended.

Method of administration
Oral use.
Triveram tablet should be taken as a single dose once daily in the morning before a meal.

4.3 Contraindications

- Hypersensitivity to the active substances or to any other ACE inhibitor or dihydropyridine derivatives or statin or to any of the excipients of this medicinal product listed in section 6.1;
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal;
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6);
- Severe hypotension;
- Shock (including cardiogenic shock);
- Obstruction of the outflow tract of the left ventricle (e.g., hypertrophic obstructive cardiomyopathy and high grade aortic stenosis);
- Haemodynamically unstable heart failure after acute myocardial infarction;
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy;
- Hereditary or idiopathic angioedema;
- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m²) (see sections 4.5 and 5.1),
- Concomitant use with sacubitril/valsartan (see sections 4.4 and 4.5),
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5);
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).

4.4 Special warnings and precautions for use

Special warnings and precautions related to atorvastatin, perindopril and amlodipine are applicable to Triveram

Liver effects:
Due to the atorvastatin component in Triveram, liver function tests should be performed periodically. Patients who develop any signs or symptoms suggestive of hepatic dysfunction 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 of greater than 3 times the upper limit of normal (ULN) persist, reduction of atorvastatin dose using the individual components or withdrawal of atorvastatin is recommended (see section 4.8). Triveram should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Triveram who develop jaundice or marked elevations of hepatic enzymes should discontinue Triveram and receive appropriate medical follow-up (see section 4.8).

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Careful monitoring may be required in patients treated with Triveram and suffering from severe hepatic impairment.

Taking into account the effect of atorvastatin, perindopril and amlodipine, Triveram is contra-indicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal. Triveram should be used with caution in patients with hepatic impairment and in patients who consume substantial quantities of alcohol and/or have a history of liver disease. If a change of posology is required, titration should be done with the individual components.

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.

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.

Before the treatment:
Atorvastatin 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.

Whilst on treatment:

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with Triveram, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Triveram must be discontinued immediately if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products:
Due to atorvastatin component, risk of rhabdomyolysis is increased when Triveram 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, telaprevir, or the combination of tipranavir/ritonavir. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.
There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.
In cases where co-administration of these medicinal products with Triveram 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, hence down-titration with the individual components should be considered. 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).
Due to atorvastatin component, Triveram must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.
Statin therapy may be re-introduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Triveram and fusidic acid should only be considered on a case by case basis and under close medical supervision.

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, Triveram therapy should be discontinued.

Diabetes Mellitus:
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping Triveram treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30kg/m², raised

triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines when treated with Triveram.

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with medicines containing an ACE inhibitor, such as Triveram (see section 4.5).

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

Hypotension:
ACE inhibitors, such as perindopril, may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see sections 4.2 and 4.8). Similar considerations apply to patients who suffer from ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/mL (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of treatment with Triveram may be necessary.

Aortic and mitral valve stenosis:
As with other medicines containing ACE inhibitors such as perindopril, Triveram should be given with caution to patients with mitral valve stenosis or significant aortic stenosis that is not high grade. The use of Triveram is contraindicated in patients with severe obstruction of the outflow tract of the left ventricle (see section 4.3).

Kidney transplantation:
There is no experience regarding the administration of perindopril arginine in patients with a recent kidney transplantation.

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see section 4.3). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Renal impairment:
Triveram can be administered in patients with creatinine clearance ≥ 60mL/min, and is not suitable for patients with creatinine clearance < 60mL/min (moderate to severe renal impairment). In these patients, an individual dose titration with the monocomponents is recommended. Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors, such as perindopril, may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency.
Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Triveram may be required.

Amlodipine may be used at normal doses in patients with renal failure. Changes in amlodipine plasma concentration are not correlated with degree of renal impairment. Amlodipine is not dialysable.

The effect of the combination Triveram has not been tested in patients with renal impairment. Triveram doses should respect the dosing recommendations of the individual components taken separately.

Haemodialysis patients:
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Triveram should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving Triveram (see section 4.3).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients treated with Triveram presenting with abdominal pain.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE inhibitors may also increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitisation:
Patients receiving ACE inhibitor-containing medicines, such as Triveram, during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Triveram should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Triveram is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Race:
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.
Triveram, which contains the ACE inhibitor perindopril, may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough:
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough in patients treated with Triveram.

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Triveram may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents with Triveram is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Combination with lithium:
The combination of lithium and medicines containing perindopril, such as Triveram, is not recommended (see section 4.5).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Primary aldosteronism:
Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Excipients:
Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or total lactase deficiency should not take Triveram.

Level of sodium
Triveram contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

No drug interaction studies have been conducted with Triveram and other drugs, although studies have been conducted with atorvastatin, perindopril and amlodipine separately. The results of these studies are provided below.

Drugs inducing hyperkalaemia:
Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporine or tacrolimus, trimethoprim. The combination of these drugs increases the risk of hyperkalaemia.

Concomitant use contraindicated (see section 4.3):

Component	Known interaction with the product	Interaction with other medicinal product
Perindopril	Aliskiren	The concomitant therapy with Triveram and aliskiren is contra-indicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m²), due to the risk of hyperkalaemia, worsening of renal function and increase in cardiovascular morbidity and mortality.
	Extracorporeal treatments	Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.
	Sacubitril/valsartan	The concomitant use of perindopril with sacubitril/valsartan is contra-indicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see section 4.3 and 4.4).

Concomitant use not recommended (see section 4.4):

Component	Known interaction with the product	Interaction with other medicinal product
Atorvastatin	Potent CYP3A4 inhibitors	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). Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) with Triveram should be avoided if possible. In cases where co-administration of these medicinal products with Triveram cannot be avoided lower doses of atorvastatin in Triveram should be considered and appropriate clinical monitoring of the patient is recommended (see table 1).
Perindopril	Aliskiren	In patients other than diabetic or impaired renal patients, concomitant treatment with Triveram and aliskiren is not recommended.
	Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker	It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with an ACE inhibitor, such as perindopril in Triveram, and an angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g, by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.
	Estramustine	Risk of increased adverse effects such as angioneurotic oedema (angioedema).
	Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of Triveram with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).
	Co-trimoxazole	Patients taking concomitant co-trimoxazole

Component	Known interaction with the product	Interaction with other medicinal product
	(trimethoprim/sulfamethoxazole)	(trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).
	Potassium-sparing diuretics (e.g. triamterene,amiloride, eplerenone, spironolactone), potassium salts	These drugs are known to induce hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of Triveram with these drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium and creatinine.
Amlodipine	Dantrolene (infusion)	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blocker-containing medicines such as Triveram be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
Atorvastatin/ Amlodipine	Grapefruit or grapefruit juice	Co-administration of large quantities of grapefruit juice and atorvastatin is not recommended (see table 1). Administration of Triveram, containing amlodipine, with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Concomitant use which requires special care:

Component	Known interaction with the product	Interaction with other medicinal product
Atorvastatin	Moderate CYP3A4 inhibitors	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 the atorvastatin component in Triveram 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, rifampicin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin (see table 1). Due to the dual interaction mechanism of rifampicin (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of Triveram with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampicin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.
	Digoxin	When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly (see table 2). Patients taking digoxin should be monitored appropriately.
	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 Triveram. Appropriate clinical monitoring of these patients is recommended.

Component	Known interaction with the product	Interaction with other medicinal product
	Fusidic acid	The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, Triveram treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).
	Gemfibrozil / fibric acid derivatives	The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis (see table 1). 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 in Triveram to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).
	Transport protein inhibitors	Inhibitors of transport proteins (e.g. ciclosporine) 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.

Component	Known interaction with the product	Interaction with other medicinal product
	Warfarin	In a clinical study in patients receiving chronic warfarin therapy, co-administration 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 Triveram 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 the atorvastatin component in Triveram 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.
Perindopril	Antidiabetic agents (insulins, oral hypoglycaemic agents)	Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. Glycaemic control should be closely monitored during the first month of treatment.
	Baclofen	Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Component	Known interaction with the product	Interaction with other medicinal product
	Non-steroidal anti-inflammatory medicinal products (NSAIDs) (including aspirin ≥ 3 g/day)	When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination of Triveram with NSAIDs should be administered with caution, especially in elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
	Racecadotril	ACE inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a drug used against acute diarrhea).
	mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)	Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).
Amlodipine	CYP3A4 inhibitors	Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in elderly. Clinical monitoring and dose adjustment may thus be required. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.
	CYP3A4 inducers	Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Concomitant use to be taken into consideration:

Component	Known interaction with the product	Interaction with other medicinal product
Atorvastatin	Colchicine	Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.
	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.
	Oral contraceptives	Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol (see table 2).
Perindopril	Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin)	Increased risk of angio-oedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin, in patients co-treated with an ACE inhibitor.
	Sympathomimetics	Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.
	Tricyclic antidepressants/ Antipsychotics/Anesthetics	Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).
	Gold	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.
Amlodipine	Digoxin, atorvastatin or warfarin .	In clinical interactions studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin.
	Tacrolimus:	There is a risk of increased tacrolimus blood levels when co administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.
	Mechanistic Target of Rapamycin (mTOR) Inhibitors	mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Component	Known interaction with the product	Interaction with other medicinal product
	Ciclosporine:	No drug interaction studies have been conducted with ciclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of ciclosporine were observed. Consideration should be given for monitoring ciclosporine levels in renal transplant patients on amlodipine, and ciclosporine dose reductions should be made as necessary.
Perindopril / Amlodipine	Antihypertensive agents and vasodilators	Concomitant use of these agents may increase the hypotensive effects of Triveram. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Table 1. Effect of co-administered medicinal product on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	**Atorvastatin**		
	Dose	**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.
Telaprevir 750 mg, q8h, 10 days	20 mg, SD	↑ 7.9 fold	
Ciclosporine 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 4-18, 30 min after atorvastatin dosing	40 mg, OD, for 4 days	↑ 3.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg, OD, for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg, SD	↑ 3.3 fold	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg, OD, for 4 days	↑ 2.5 fold	
Fosamprenavir 1400 mg	10 mg, OD, for 4	↑ 2.3 fold	

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose	**Change in AUC[&]**	**Clinical recommendation[#]**
BID, 14 days	days		
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.
Colestipol 10 g BID, 24 weeks	40 mg OD for 8 weeks	0.74**	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.
Rifampicin 600 mg OD, 7 days (co-administered)	40 mg SD	↑ 30%	If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampicin is recommended, with clinical monitoring.
Rifampicin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80%	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	↑ 3%	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40mg SD	↑ 2.3 fold	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.

OD= once daily, SD = single dose, BID = twice daily, QID = Four times daily, TID = three times daily

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

[&] 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

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose	**Change in AUC[&]**	**Clinical recommendation[#]**

metabolized by CYP3A4. Intake of one 240 mL glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).

^ Total atorvastatin equivalent activity

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

Atorvastatin 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.
10 mg, SD	Tipranavir 500 mg, BID/ritonavir 200 mg BID, 7 days	No change	No specific recommendation.
10 mg, OD, for 4 days	Fosamprenavir 1400 mg, BID, 14 days	↓ 27%	No specific recommendation.
10 mg, OD, for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No specific recommendation.

OD= once daily, SD = single dose, BID = twice daily

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

[&] 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.

4.6 Fertility, pregnancy and lactation

Triveram is contraindicated during pregnancy and lactation (see section 4.3).

Women of childbearing potential

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

Pregnancy:

Atorvastatin

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 suspected to be pregnant. Treatment with atorvastatin should be suspended for the duration of pregnancy or until confirmation of the absence of pregnancy (see section 4.3.)

Perindopril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimesters of pregnancy (see section 4.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also sections 4.3 and 4.4).

Amlodipine

Safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Breast-feeding:

Atorvastatin

It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3). Because of the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants. Atorvastatin is contraindicated during breastfeeding (see section 4.3).

Perindopril

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Amlodipine

Amlodipine is excreted in human milk . The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Fertility:

Atorvastatin

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

Perindopril

There was no effect on reproductive performance or fertility.

Amlodipine

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

4.7 Effects on ability to drive and use machines

No studies have been performed on the effect of Triveram on the ability to drive and use machines.

- Atorvastatin has negligible influence on the ability to drive and use machines.Perindopril has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure

may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.
- 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.

As a result the ability to drive or operate machinery may be impaired in patients taking Triveram. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Summary of the profile:
The most commonly reported adverse reactions with atorvastatin, perindopril and amlodipine given separately include: nasopharyngitis, hypersensitivity, hyperglycaemia, headache, pharyngolaryngeal pain, epistaxis, constipation, flatulence, dyspepsia, nausea, diarrhoea, change of bowel habit, myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, ankle swelling, back pain, liver function test abnormal, blood creatine kinase increased, somnolence, dizziness, palpitations, flushing, abdominal pain, oedema, fatigue, paraesthesia, visual impairment, diplopia, tinnitus, vertigo, hypotension, cough, dyspnoea, vomiting, dysgeusia, rash, pruritus, asthenia.

Tabulated list of adverse reactions:
The following undesirable effects have been observed during treatment with atorvastatin, perindopril, amlodipine, or given separately and ranked under the MedDRA classification by body system and under heading of frequency using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data)).

MedDRA System Organ Class	**Undesirable effects**	**Frequency**		
		Atorvastatin	**Perindopril**	**Amlodipine**
Infections and infestation	Nasopharyngitis	Common	-	-
	Rhinitis	-	Very rare	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia	Rare	Very rare	Very rare
	Leucopenia/neutropenia	-	Very rare	Very rare
	Eosinophilia	-	Uncommon*	-
	Agranulocytosis or pancytopenia	-	Very rare	-
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH	-	Very rare	-
Immune system disorders	Hypersensitivity	Common	-	Very rare
	Anaphylaxis	Very rare	-	-
Metabolism and nutrition disorders	Hyperglycaemia	Common	-	Very rare
	Hypoglycaemia	Uncommon	Uncommon*	-
	Hyponatraemia	-	Uncommon*	-
	Hyperkalaemia reversible on discontinuation (see section 4.4)	-	Uncommon*	-
	Anorexia	Uncommon	-	-
Psychiatric disorders	Insomnia	Uncommon	-	Uncommon
	Mood altered (including anxiety)	-	Uncommon	Uncommon
	Sleep disorder		Uncommon	-
	Depression	-	-	Uncommon
	Nightmares	Uncommon	-	-
	Confusional state	-	Very rare	Rare

MedDRA System Organ Class	Undesirable effects	Frequency		
		Atorvastatin	Perindopril	Amlodipine
Nervous system disorders	Somnolence	-	Uncommon*	Common
	Dizziness	Uncommon	Common	Common
	Headache	Common	Common	Common
	Tremor	-	-	Uncommon
	Dysgeusia	Uncommon	Common	Uncommon
	Syncope	-	Uncommon*	Uncommon
	Hypoaesthesia	Uncommon	-	Uncommon
	Paraesthesia	Uncommon	Common	Uncommon
	Hypertonia	-	-	Very rare
	Neuropathy peripheral	Rare	-	Very rare
	Stroke possible secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare	-
	Amnesia	Uncommon	-	-
	Extrapyramidal disorder (extrapyramidal syndrome)	-	-	Not known
Eye disorders	Visual impairment	Rare	Common	Common
	Diplopia	-	-	Common
	Vision blurred	Uncommon	-	-
Ear and labyrinth disorders	Tinnitus	Uncommon	Common	Uncommon
	Vertigo	-	Common	-
	Hearing loss	Very Rare	-	-
Cardiac disorders	Myocardial infarction secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare	Very rare
	Angina pectoris (see section 4.4)	-	Very rare	-
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	-	Very rare	Uncommon
	Tachycardia	-	Uncommon*	-
	Palpitations	-	Uncommon*	Common
Vascular disorders	Hypotension (and effects related to hypotension)	-	Common	Uncommon
	Vasculitis	-	Uncommon*	Very rare
	Flushing	-	-	Common
	Raynaud's phenomenon	-	Not known	-
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	Common	-	-
	Epistaxis	Common	-	-
	Cough	-	Common	Uncommon
	Dyspnoea	-	Common	Common
	Bronchospasm	-	Uncommon	-
	Eosinophilic pneumonia	-	Very rare	-
Gastro-intestinal disorders	Nausea	Common	Common	Common
	Vomiting	Uncommon	Common	Uncommon

MedDRA System Organ Class	Undesirable effects	Frequency		
		Atorvastatin	Perindopril	Amlodipine
	Abdominal pain upper and lower	Uncommon	Common	Common
	Dyspepsia	Common	Common	Common
	Diarrhoea	Common	Common	Common
	Constipation	Common	Common	Common
	Dry mouth	-	Uncommon	Uncommon
	Pancreatitis	Uncommon	Very rare	Very rare
	Gastritis	-	-	Very rare
	Gingival hyperplasia	-	-	Very rare
	Change of bowel habit	-	-	Common
	Eructation	Uncommon	-	-
	Flatulence	Common	-	-
Hepato-biliary disorders	Hepatitis either cytolytic or cholestatic (see section 4.4)	Uncommon	Very rare	Very rare
	Jaundice	-	-	Very rare
	Cholestasis	Rare	-	-
	Hepatic failure	Very rare	-	-
Skin and subcutaneous tissue disorders	Rash	Uncommon	Common	Uncommon
	Pruritus	Uncommon	Common	Uncommon
	Urticaria	Uncommon	Uncommon	Uncommon
	Purpura	-	-	Uncommon
	Skin discolouration	-	-	Uncommon
	Hyperhidrosis	-	Uncommon	Uncommon
	Exanthema	-	-	Uncommon
	Alopecia	Uncommon	-	Uncommon
	Angioedema (see section 4.4)	Rare	Uncommon	Very rare
	Exfoliative dermatitis	-	-	Very rare
	Pemphigoid	-	Uncommon*	-
	Psoriasis aggravation	-	Rare*	-
	Stevens-Johnson syndrome	Rare	-	Very rare
	Photosensitivity reactions	-	Uncommon*	Very rare
	Toxic epidermal necrolysis	Rare	-	Not known
	Erythema multiforme	Rare	Very rare	Very rare
Musculoskeletal and connective tissue disorders	Joint swelling	Common	-	-
	Ankle swelling	-	-	Common
	Pain in extremity	Common	-	-
	Arthralgia	Common	Uncommon*	Uncommon
	Muscle spasms	Common	Common	Common
	Myalgia	Common	Uncommon*	Uncommon
	Back pain	Common	-	Uncommon
	Neck pain	Uncommon	-	-

MedDRA System Organ Class	Undesirable effects	Frequency		
		Atorvastatin	**Perindopril**	**Amlodipine**
	Muscle fatigue	Uncommon	-	-
	Myopathy	Rare	-	-
	Myositis	Rare	-	-
	Rhabdomyolysis	Rare	-	-
	Tendinopathy sometimes complicated by rupture	Rare	-	-
	Immune-mediated necrotizing myopathy (see section 4.4)	Not known	-	-
Renal and urinary disorders	Micturition disorder	-	-	Uncommon
	Nocturia	-	-	Uncommon
	Pollakiuria	-	-	Uncommon
	Renal failure	-	Uncommon	-
	Renal failure acute	-	Very rare	-
Reproductive system and breast disorders	Erectile dysfunction	-	Uncommon	Uncommon
	Gynaecomastia	Very rare	-	Uncommon
General disorders and administration site conditions	Asthenia	Uncommon	Common	Common
	Fatigue	Uncommon	-	Common
	Oedema	-	-	Very common
	Chest pain	Uncommon	Uncommon*	Uncommon
	Pain	-	-	Uncommon
	Malaise	Uncommon	Uncommon*	Uncommon
	Oedema peripheral	Uncommon	Uncommon*	-
	Pyrexia	Uncommon	Uncommon*	-
Investigations	Blood urea increased	-	Uncommon*	-
	Blood creatinine increased	-	Uncommon*	-
	Hepatic enzymes increased	-	Rare	Very rare**
	Blood bilirubin increased	-	Rare	-
	Weight increased	Uncommon	-	Uncommon
	White blood cells urine positive	Uncommon	-	-
	Weight decreased	-	-	Uncommon
	Liver function test abnormal	Common	-	-
	Blood creatine kinase increased	Common	-	-
	Haemoglobin decreased and haematocrit decreased	-	Very rare	-
Injury, poisoning and procedural complications	Fall	-	Uncommon*	-

***** *Frequency calculated from clinical trials for adverse events detected from spontaneous report*

********Mostly consistent with cholestasis*

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).

The following adverse events have been reported with some statins:
• Sexual dysfunction.
• Depression.
• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
• Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

Cases of SIADH have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy including perindopril.

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

4.9 Overdose

There is no information on overdose with Triveram in humans.

Atorvastatin:

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

Perindopril:

Symptoms:
Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Management:
The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/mL (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Amlodipine:

In humans experience with intentional overdose is limited.

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.

Management:
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG CoA reductase inhibitors, other combinations**, ATC code:** C10BX11

Mechanism of action:

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).

Perindopril
Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).
Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

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.

Pharmacodynamic effects:

Atorvastatin

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 is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

Perindopril
Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.
Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.
Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.
Heart failure:
Perindopril reduces cardiac work by a decrease in pre-load and after-load.

Amlodipine
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:

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

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

Clinical efficacy and safety:

Triveram has not been studied on morbidity and mortality.

Atorvastatin
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 non-insulin-dependent diabetes mellitus.
Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce 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.

Prevention of cardiovascular disease
ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) is an international randomised trial with a 2x2 factorial design. ASCOT aimed to compare the effects of two antihypertensive treatment regimens in 19,257 patients (Blood Pressure Lowering Arm – ASCOT-BPLA) and the effects of the addition of atorvastatin 10 mg, compared with placebo, in 10,305 patients (Lipid Lowering Arm – ASCOT-LLA) on non-fatal and fatal coronary events.

These effects of atorvastatin on fatal and non-fatal coronary events was evaluated on hypertensive patients aged 40-79 years with no history of 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.
Patients received antihypertensive treatment with either amlodipine or atenolol. To achieve the goal of blood pressure control (< 140/90 mmHg in non-diabetic patients, < 130/80 mmHg in patients with diabetes), perindopril could be added in the amlodipine group and bendroflumethiazide in the atenolol group.
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 combination of atorvastatin and amlodipine showed a significant reduction in the primary endpoint of fatal coronary events and non-fatal myocardial infarction of 53% (95%CI [0.31; 0.69], p <0.0001) compared to placebo + amlodipine arm and of 39% (95%CI [0.08; 0.59], p <0.016) compared to atorvastatin + atenolol arm.
In a subgroup of patients from ASCOT-LLA defined in a post-hoc analysis concurrently treated with atorvastatin, perindopril and amlodipine (n=1,814), there was a 38% reduction of fatal coronary events and non-fatal myocardial infarction (95%CI [0.36; 1.08]) in comparison with atorvastatin, atenolol and bendroflumethiazide (n=1,978). There were also a significant reduction of 24% for total cardiovascular events and procedures (95%CI [0.59;0.97]), a reduction of 31% for total coronary events (95%CI [0.48;1.00]) and a significant reduction of 50% for fatal and non-fatal stroke (95%CI [0.29;0.86]), 39% for the composite of non-fatal myocardial infarction, fatal coronary events and coronary revascularization procedures (95%CI (0.38;0.97]) and 42% for the composite of cardiovascular mortality, myocardial infarction and stroke (95%CI [0.40;0.85]).

Perindopril
Hypertension:
The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.
The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.
Discontinuation of treatment does not lead to a rebound effect.
Perindopril reduces left ventricular hypertrophy.
In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media:lumen ratio of small arteries.
An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.
Twelve thousand two hundred and eighteen (12,218) patients aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n=6,110) or placebo (n=6,108).
The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.
The main efficacy criterion was the composite of cardiovascular mortality, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Amlodipine:
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 coronary artery disease (CAD)
The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double- blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in the table below. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Incidence of significant clinical outcomes for CAMELOT

	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	0.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	0.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	0.002

Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	0.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	0.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	0.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	0.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	0.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	0.24

Abbreviations: CHF = congestive heart failure; CI = confidence interval; MI = myocardial infarction; TIA = transient ischemic attack.

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.

Treatment to prevent heart attack trial (ALLHAT)
A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 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 enrolment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).
The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. 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).

Paediatric population
No data are available with Triveram in children.
The European Medicines Agency has granted a product-specific waiver for Triveram in all subsets of the paediatric population for the treatment of ischemic coronary artery disorders, hypertension and elevated cholesterol (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 40 mg, perindopril arginine 10 mg and amlodipine 10 mg resulted in a 23% increase in atorvastatin AUC, which is not clinically meaningful. The maximum concentration of perindopril was increased by about 19%, but the pharmacokinetics of perindoprilat, the active metabolite were unaffected. The rate and extent of absorption

of amlodipine when co-administered with atorvastatin and perindopril were not significantly different from the rate and extent of absorption of amlodipine when taken alone.

Atorvastatin:

Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) 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 via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination
Atorvastatin 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.
Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for Cmax 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 impairment: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
Hepatic impairment: 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.

Perindopril:

Absorption
After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Biotransformation
Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.
As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

Linearity
It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Distribution
The volume of distribution is approximately 0.2 L/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Elimination
Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Special populations
Elderly: Elimination of perindoprilat is decreased in elderly, and also in patients with heart or renal failure.
Renal impairment: Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

Dialysis clearance of perindoprilat is equal to 70 mL/min.

In patients with cirrhosis: Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

Amlodipine:

Absorption
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The bioavailability of amlodipine is not affected by food intake.

Distribution
The volume of distribution is approximately 21 L/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation and elimination
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing.
Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Special populations
Hepatic impairment: Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.
Elderly: The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

5.3 Preclinical safety data

No preclinical studies have been performed with Triveram.

Atorvastatin:
Reproductive toxicology and effect on fertility: 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.
Carcinogenesis, mutagenesis: 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.

Perindopril:
Chronic toxicity: In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.
Reproductive toxicology and effect on fertility: Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. Fertility was not impaired either in male or in female rats.
Carcinogenesis, mutagenesis: No mutagenicity has been observed in *in vitro* or *in vivo* studies. No carcinogenicity has been observed in long term studies in rats and mice.

Amlodipine:
Reproductive toxicology: Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.
Impairment of fertility: There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.
Carcinogenesis, mutagenesis: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Calcium carbonate (E170)
Hydroxypropylcellulose (E463)
Sodium starch glycolate (type A)
Cellulose, microcrystalline (E460)
Maltodextrin
Magnesium stearate (E572)

Tablet film-coating:
Glycerol (E422)
Hypromellose (E464)
Macrogol 6000
Magnesium stearate (E572)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Tablets are stable 10 days after opening in the 10-tablet polypropylene container (available for 10/5/5 mg strength only)
Tablets are stable 30 days after opening in the 28-tablet polypropylene container
Tablets are stable 30 days after opening in the 30-tablet polypropylene container
Tablets are stable 100 days after opening in the 100-tablet high density polyethylene container

6.4 Special precautions for storage

PP Container: This medicinal product does not require any special temperature storage conditions.

HDPE Container (all except the 40/10/10 mg strength): This medicinal product does not require any special temperature storage conditions.

HDPE container (40/10/10 mg strength): Store below 30°C.

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

10 film-coated tablets in polypropylene tablet container closed with a LDPE stopper (available for 10/5/5 mg strength only). The stopper contains a desiccant. 10/5/5 mg tablet container contains a LDPE flow reducer

28 film-coated tablets in polypropylene tablet container closed with a LDPE stopper. The stopper contains a desiccant. 10/5/5 mg tablet container contains a LDPE flow reducer.

30 film-coated tablets in polypropylene tablet container closed with a LDPE stopper. The stopper contains a desiccant. 10/5/5 mg tablet container contains a LDPE flow reducer.

100 film-coated tablets in high density polyethylene tablet container with a polypropylene screwcap. The screwcap contains a desiccant. The tablet container contains dessicant capsules.

Box of 10, 28, 30, 84 (3 tablet containers of 28), 90 (3 tablet containers of 30) or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

For RMS (Finland):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<[To be completed nationally]>

<Detailed information on this medicinal product is available on the website of {name of MS/Agency (link)}>