ATORVASTATIN + PERINDOPRIL ARGININE + AMLODIPINE

TRIVERAM® INITIO 10 mg/5 mg/5 mg film-coated tablet
TRIVERAM® 20 mg/5 mg/5 mg film-coated tablet
TRIVERAM® 20 mg/10 mg/5 mg film-coated tablet
TRIVERAM® 20 mg/10 mg/10 mg film-coated tablet
TRIVERAM® FORTE 40 mg/10 mg/10 mg film-coated tablet

HMG CoA reductase inhibitors, other combinations

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

FORMULATION
Atorvastatin + Perindopril arginine + Amlodipine (Triveram INITIO) 10mg/5mg/5mg: 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.

Atorvastatin + Perindopril arginine + Amlodipine (Triveram) 20mg/5mg/5mg: 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.

Atorvastatin + Perindopril arginine + Amlodipine (Triveram) 20mg/10mg/5mg: 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.

Atorvastatin + Perindopril arginine + Amlodipine (Triveram) 20mg/10mg/10mg: 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.

Atorvastatin + Perindopril arginine + Amlodipine (Triveram FORTE) 40mg/10mg/10mg: 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 INITIO 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 FORTE 40/10/10 mg).

PHARMACODYNAMICS AND PHARMACOKINETICS
Pharmacodynamics
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 hypercholesterolemia, 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 ischemic burden by the following two actions:
1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions.
This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacokinetics
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.
Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

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. 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 the 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.

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 metabolized 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.

INDICATION
Atorvastatin + Perindopril arginine + Amlodipine (Triveram) is indicated for the treatment of essential hypertension and/or stable coronary artery disease, in association with primary hypercholesterolemia or mixed hyperlipidemia, as substitution therapy in adult patients adequately controlled with atorvastatin, perindopril and amlodipine given concurrently at the same dose level as in the combination.

DOSAGE AND ADMINISTRATION
Oral use.

Tablet should be taken as a single dose once daily in the morning before a meal.
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: Atorvastatin + Perindopril arginine + Amlodipine (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: elderly can be treated with Atorvastatin + Perindopril arginine + Amlodipine (Triveram) according to the renal function.

Hepatic impairment: Atorvastatin + Perindopril arginine + Amlodipine (Triveram) should be used with caution in patients with hepatic impairment. This medicine is contraindicated in patients with active liver disease.

Pediatric population: The safety and efficacy of Atorvastatin + Perindopril arginine + Amlodipine (Triveram) in children and adolescents have not been established. No data are available. Therefore, use in children and adolescents is not recommended.

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;
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal;
- During pregnancy, while breastfeeding and in women of child-bearing potential not using appropriate contraceptive measures;
- Concomitant use with the hepatitis C antivirals glecaprevir/pibrentasvir;
- 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);
- Hemodynamically unstable heart failure after acute myocardial infarction;
- History of angioedema (Quincke's edema) 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).
- Concomitant use with sacubitril/valsartan,
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces;
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney.

WARNINGS AND PRECAUTIONS
Special warnings and precautions related to atorvastatin, perindopril and amlodipine are applicable to Atorvastatin + Perindopril arginine + Amlodipine (Triveram)
Liver effects:
Due to the atorvastatin component in Atorvastatin + Perindopril arginine + Amlodipine (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. Atorvastatin + Perindopril arginine + Amlodipine (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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram) who develop jaundice or marked elevations of hepatic enzymes should discontinue Atorvastatin + Perindopril arginine + Amlodipine (Triveram) and receive appropriate medical follow-up.

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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram) and suffering from severe hepatic impairment.

Taking into account the effect of atorvastatin, perindopril and amlodipine, Atorvastatin + Perindopril arginine + Amlodipine (Triveram) is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal. Atorvastatin + Perindopril arginine + Amlodipine (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 characterized by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinemia 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 predisposing 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 and special populations including genetic subpopulations

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 Atorvastatin + Perindopril arginine + Amlodipine (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.
- Atorvastatin + Perindopril arginine + Amlodipine (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 Atorvastatin + Perindopril arginine + Amlodipine (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, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.
There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.
In cases where co-administration of these medicinal products with Atorvastatin + Perindopril arginine + Amlodipine (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.

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. 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. Presenting features can include dyspnea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, Atorvastatin + Perindopril arginine + Amlodipine (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 hyperglycemia 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 Atorvastatin + Perindopril arginine + Amlodipine (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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram).
In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with medicines containing an ACE inhibitor, such as Atorvastatin + Perindopril arginine + Amlodipine (Triveram).

Cardiac failure:
Atorvastatin + Perindopril arginine + Amlodipine (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 edema was higher in the amlodipine treated group than in the placebo group. 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, diarrhea or vomiting, or who have severe renin-dependent hypertension. 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, hyponatremia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients who suffer from ischemic 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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram) may be necessary.

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

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. 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:
Atorvastatin + Perindopril arginine + Amlodipine (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.
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 Atorvastatin + Perindopril arginine + Amlodipine (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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram) has not been tested in patients with renal impairment. Atorvastatin + Perindopril arginine + Amlodipine (Triveram) doses should respect the dosing recommendations of the individual components taken separately.

Hemodialysis 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. This may occur at any time during therapy. In such cases, Atorvastatin + Perindopril arginine + Amlodipine (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 edema 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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram).
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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram) presenting with abdominal pain.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. 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. Concomitant use of other NEP inhibitors (*e.g.* racecadotril) and ACE inhibitors may also increase the risk of angioedema. 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).

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 desensitization:
Patients receiving ACE inhibitor-containing medicines, such as Atorvastatin + Perindopril arginine + Amlodipine (Triveram), during desensitization 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/Anemia:
Neutropenia/agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Atorvastatin + Perindopril arginine + Amlodipine (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 Atorvastatin + Perindopril arginine + Amlodipine (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. Atorvastatin + Perindopril arginine + Amlodipine (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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram).

Surgery/Anesthesia:
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Atorvastatin + Perindopril arginine + Amlodipine (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.

Hyperkalemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalemia 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). 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. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents with Atorvastatin + Perindopril arginine + Amlodipine (Triveram) is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Combination with lithium:
The combination of lithium and medicines containing perindopril, such as Atorvastatin + Perindopril arginine + Amlodipine (Triveram), is not recommended.

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, hyperkalemia 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.
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 the total lactase deficiency should not take Atorvastatin + Perindopril arginine + Amlodipine (Triveram).
Level of sodium
Triveram contains less than 1 mmol sodium (23 mg) per tablet, *i.e.* essentially 'sodium-free'.

Effects on ability to drive and use machines
No studies have been performed on the effect of Atorvastatin + Perindopril arginine + Amlodipine (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 Atorvastatin + Perindopril arginine + Amlodipine (Triveram). Caution is recommended especially at the start of treatment.

PREGNANCY AND LACTATION
Atorvastatin + Perindopril arginine + Amlodipine (Triveram) is contraindicated during pregnancy and lactation.

Women of childbearing potential
Women of child-bearing potential should use appropriate contraceptive measures during treatment with Atorvastatin + Perindopril arginine + Amlodipine (Triveram).

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.
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 hypercholesterolemia.
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.

Perindopril
The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimesters of pregnancy.
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 fetoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). 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.

Amlodipine
Safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding:
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. Because of the potential for serious adverse reactions, women taking atorvastatin should not breastfeed their infants. Atorvastatin is contraindicated during breastfeeding.

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 breastfeeding 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.

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.

INTERACTIONS
Patient should tell the doctor if taking, have recently taken or might take any other medicines.

Atorvastatin + Perindopril arginine + Amlodipine (Triveram) may affect or be affected by other medicines, such as:
- immunosuppressants (medicines which reduce the defense mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (*e.g.* ciclosporin, tacrolimus),
- ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole (anti-fungal medicines),
- rifampicin, erythromycin, clarithromycin, telithromycin, fusidic acid*, trimethoprim (antibiotics for infection caused by bacteria),
- colchicine (used in the treatment of gout, a disease with painful, swollen joints caused by uric acid crystals),
- other medicines to regulate lipid levels, *e.g.* gemfibrozil, other fibrates, colestipol, ezetimibe,
- some calcium channel blockers used for angina or high blood pressure, *e.g.* diltiazem,
- medicines to regulate the heart rhythm *e.g.* digoxin, verapamil, amiodarone,
- medicines used in the treatment of HIV or liver disease such as Hepatitis C e.g. delavirdine, efavirenz, ritonavir, lopinavir, atazanavir, indinavir, darunavir, telaprevir, boceprevir and the combination of elbasvir/grazoprevir,
- warfarin (which reduces blood clotting),
- oral contraceptives,
- stiripentol (an anti-convulsant for epilepsy),
- cimetidine (used for heartburn and peptic ulcers),
- phenazone (a painkiller),
- antacids (indigestion products containing aluminium or magnesium),
- medicine obtained without a prescription *hypericum perforatum* or St John's Wort (herbal treatment used for depression),
- dantrolene (infusion for severe body temperature abnormalities),
- other medicines for high blood pressure, including aliskiren, angiotensin II receptor blockers (*e.g.* valsartan), see also information under Contraindications and Warnings and Precautions,
- potassium-sparing drugs (*e.g.* triamterene, amiloride, eplerenone, spironolactone), potassium supplements or potassium-containing salt substitutes, other drugs which can increase potassium in your body (such as heparin and co-trimoxazole also known as trimethoprim/sulfamethoxazole),
- estramustine (used in cancer therapy),
- lithium for mania or depression,
- medicines, which are most often used to treat diarrhea (racecadotril) or avoid rejection of transplanted organs (sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors). See section "Warnings and precautions",medicines used to treat diabetes (such as insulin, metformin or gliptines),
- sacubitril/valsartan (used to treat long-term heart failure),
- baclofen (used to treat muscle stiffness in diseases such as multiple sclerosis),
- non-steroidal anti-inflammatory drugs (*e.g.* ibuprofen) for pain relief or treatment of inflammation (*e.g.* in case of rheumatoid arthritis) or high dose aspirin,
- vasodilators including nitrates (products that make the blood vessels become wider),
- medicines to treat mental disorders such as depression, anxiety, schizophrenia, etc. (*e.g.* tricyclic antidepressants, antipsychotics),
- medicines used for the treatment of low blood pressure, shock or asthma (*e.g.* ephedrine, noradrenaline or adrenaline),
- gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis),
- allopurinol (for the treatment of gout),
- procainamide (for the treatment of an irregular heart beat).

*If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using Triveram. Your doctor will tell you when it is safe to restart Triveram. Taking Triveram with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis).

Grapefruit and grapefruit juice
Grapefruit juice and grapefruit should not be consumed by people who are taking Atorvastatin + Perindopril arginine + Amlodipine (Triveram). This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of this medicine.
If taking this medicine, do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice will lead to an increased effect of the active ingredient atorvastatin.

Alcohol
Avoid drinking too much alcohol while taking this medicine.

ADVERSE DRUG REACTIONS
Summary of the profile:
The most commonly reported adverse reactions with atorvastatin, perindopril and amlodipine given separately include: nasopharyngitis, hypersensitivity, hyperglycemia, headache, pharyngolaryngeal pain, epistaxis, constipation, flatulence, dyspepsia, nausea, diarrhea, 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, edema, fatigue, paresthesia, visual impairment, diplopia, tinnitus, vertigo, hypotension, cough, dyspnea, 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	-
	Hemolytic anemia 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	Hyperglycemia	Common	-	Very rare
	Hypoglycemia	Uncommon	Uncommon*	-
	Hyponatremia	-	Uncommon*	-
	Hyperkalemia reversible on discontinuation	-	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
Nervous system disorders	Somnolence	-	Uncommon*	Common
	Dizziness	Uncommon	Common	Common
	Headache	Common	Common	Common
	Tremor	-	-	Uncommon
	Dysgeusia	Uncommon	Common	Uncommon
	Syncope	-	Uncommon*	Uncommon
	Hypoesthesia	Uncommon	-	Uncommon
	Paresthesia	Uncommon	Common	Uncommon
	Hypertonia	-	-	Very rare
	Neuropathy peripheral	Rare	-	Very rare
	Stroke possible secondary to excessive hypotension in high-risk patients	-	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	-	Very rare	Very rare
	Angina pectoris	-	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
	Dyspnea	-	Common	Common
	Bronchospasm	-	Uncommon	-
	Eosinophilic pneumonia	-	Very rare	-
Gastro-intestinal disorders	Nausea	Common	Common	Common
	Vomiting	Uncommon	Common	Uncommon
	Abdominal pain upper and lower	Uncommon	Common	Common
	Dyspepsia	Common	Common	Common
	Diarrhea	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	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 discoloration	-	-	Uncommon
	Hyperhidrosis	-	Uncommon	Uncommon
	Exanthema	-	-	Uncommon
	Alopecia	Uncommon	-	Uncommon
	Angioedema	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

MedDRA System Organ Class	Undesirable effects	Frequency		
		Atorvastatin	Perindopril	Amlodipine
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	-	-
	Muscle fatigue	Uncommon	-	-
	Myopathy	Rare	-	-
	Myositis	Rare	-	-
	Rhabdomyolysis	Rare	-	-
	Muscle rupture	Rare	-	-
	Tendinopathy sometimes complicated by rupture	Rare	-	-
	Lupus-like syndrome	Very rare	-	-
	Immune-mediated necrotizing myopathy	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
	Gynecomastia	Very rare	-	Uncommon
General disorders and administration site conditions	Asthenia	Uncommon	Common	Common
	Fatigue	Uncommon	-	Common
	Edema	-	-	Very common
	Chest pain	Uncommon	Uncommon*	Uncommon
	Pain	-	-	Uncommon
	Malaise	Uncommon	Uncommon*	Uncommon
	Edema 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	-	-
	Hemoglobin decreased and hematocrit 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.

The following adverse events have been reported with some statins:
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy.
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m^2, 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.

OVERDOSE AND TREATMENT

If more tablets were taken than prescribed, contact the nearest accident and emergency department or tell the doctor immediately. Taking too many tablets may cause the blood pressure to become low or even dangerously low. It can make the patient feel dizzy, lightheaded, faint or weak. If this happens, lying down with the legs raised can help. If blood pressure drop is severe enough shock can occur. The skin could feel cool and clammy and patient could lose consciousness.

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

Perindopril: Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.
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 hemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Amlodipine: Available data suggest that gross overdosage could result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
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.

MISSED DOSE

It is important to take the medicine every day as regular treatment works better. However, if a dose is forgotten, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

DISCONTINUATION OF TREATMENT

As the treatment with Atorvastatin + Perindopril arginine + Amlodipine (Triveram) is usually life-long, patient should discuss with the doctor before stopping this medicinal product.

REPORTING OF ADVERSE DRUG REACTION

For suspected adverse drug reaction, report to the FDA at www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

PACKAGING

Box of 1 polypropylene tablet container closed with LDPE stopper with dessicant x 30's.
10/5/5 mg tablet container contains a LDPE flow reducer.

Manufactured by:
Les Laboratoires Servier Industrie
905 route de Saran, 45520 Gidy, France

Imported by:
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Unit AD, 11th Floor, 8 Rockwell, Hidalgo Drive, Rockwell Center, Brgy. Poblacion, Makati, Metro Manila

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