

**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Astarior 10 mg/5 mg, hard capsules

[Astarior 20 mg/5 mg, hard capsules]

[Astarior 40 mg/5 mg, hard capsules]

[Astarior 10 mg/10 mg, hard capsules]

[Astarior 20 mg/10 mg, hard capsules]

[Astarior 40 mg/10 mg, hard capsules]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril

[Each hard capsule contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril]

[Each hard capsule contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril]

[Each hard capsule contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril]

[Each hard capsule contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril]

[Each hard capsule contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril]

Excipient with known effect: sucrose (33.9 mg for Astarior 10/5 mg, 46.8 mg for Astarior 20/5 mg, 72.6 mg for Astarior 40/5 mg, 54.9 mg for Astarior 10/10 mg, 67.8 mg for Astarior 20/10 mg, 93.6 mg for Astarior 40/10 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard

Astarior 10/5 mg: Size 2 hard gelatin capsule, with black imprint "10 5" on light blue body and black imprint "S" on light blue cap, containing white to slightly white spherical pellets.

Astarior 20/5 mg: Size 2 hard gelatin capsule, with black imprint "20 5" on light blue body and black imprint "S" on blue cap, containing white to slightly white spherical pellets.

Astarior 40/5 mg: Size 2 hard gelatin capsule, with black imprint "40 5" on blue body and black imprint "S" on blue cap, containing white to slightly white spherical pellets.

Astarior 10/10 mg: Size 2 hard gelatin capsule, with black imprint "10 10" on light green body and black imprint "S" on light green cap, containing white to slightly white spherical pellets.

Astarior 20/10 mg: Size 2 hard gelatin capsule, with black imprint "20 10" on light green body and black imprint "S" on green cap, containing white to slightly white spherical pellets.

Astarior 40/10 mg: Size 2 hard gelatin capsule, with black imprint "40 10" on green body and black imprint "S" on green cap, containing white to slightly white spherical pellets.

Size 2 hard gelatin capsules are approximately 18 mm in length.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Astarior is indicated as substitution therapy as part of cardiovascular risk management (see section 5.1), in adult patients adequately controlled with atorvastatin and perindopril given concurrently at the same dose level but as separate products.

4.2. Posology and method of administration

Posology

Adults

The usual posology is one capsule 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.

The patients should continue a standard cholesterol-lowering diet during treatment with Astarior.

Co-administration with other medicines

Concomitant therapy

In patients taking tipranavir, ritonavir, telaprevir or ciclosporine concomitantly with Astarior, the dose of atorvastatin in Astarior should not exceed 10 mg/day (see sections 4.4 and 4.5).

In patients taking hepatitis C antiviral agents containing boceprevir, elbasvir ~~or~~/grazoprevir concomitantly with Astarior, the dose of atorvastatin in Astarior should not exceed ~~10~~/20 mg/day (see sections 4.4 and 4.5).

Patients with renal impairment

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

Elderly

Older people can be treated with Astarior according to the renal function (*see sections 4.4 and 5.2*).

Patients with hepatic impairment

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

Paediatric population

The safety and efficacy of Astarior 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.

Astarior should be taken as a single dose once daily in the morning before a meal.

The capsules must not be chewed or broken.

4.3. Contraindications

- Hypersensitivity to the active substances or to any other ACE (Angiotensin Converting Enzyme) inhibitor 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);
- Concomitant use with the hepatitis C antivirals glecaprevir/pibrentasvir;
- History of angioedema 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/1.73 m²) (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 and perindopril are applicable to Astarior.

Liver effects

Due to the atorvastatin component in Astarior, 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).

Rarely, ACE inhibitors such as perindopril 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 Astarior who develop jaundice or marked elevations of hepatic enzymes should discontinue the product and receive appropriate medical follow-up (see section 4.8).

Taking into account the effect of atorvastatin and perindopril, Astarior is contra-indicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal or severe hepatic impairment (see section 4.3). Astarior 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.

In situations where pre-disposing factors for rhabdomyolysis have been identified before treatment initiation i.e.:

- 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 need for CK measurement should be considered, taking account of the presence of other predisposing factors for rhabdomyolysis
 - When an increase in plasma CK levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2)
- the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

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

Creatine kinase measurement

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

Whilst on treatment

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing Astarior.
- If such symptoms occur whilst a patient is receiving treatment with Astarior, 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 $\leq 5 \times$ 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.
- Astarior 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 Astarior 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 derivatives, [antivirals for the treatment of hepatitis C \(HCV\) \(boceprevir, telaprevir, elbasvir/grazoprevir\)](#), erythromycin, niacin ~~and/or ezetimibe, the hepatitis C antiviral agents boceprevir, telaprevir, elbasvir, grazoprevir or the combination of tipranavir/ritonavir~~. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with Astarior 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).

Atorvastatin 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 Astarior and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Immune-mediated necrotizing myopathy

There have been very rare reports of an immune-mediated necrotizing 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.

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, Astarior therapy should be discontinued and switching to therapy with only perindopril should be considered.

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 Astarior 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 Astarior.

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 Astarior (see section 4.5).

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 using the individual components or discontinuation of treatment with Astarior may be necessary.

Aortic and mitral valve stenosis/ hypertrophic cardiomyopathy

As with other medicines containing ACE inhibitors such as perindopril, Astarior should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Kidney transplantation

There is no experience regarding the administration of perindopril or Astarior 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

Astarior can be administered in patients with creatinine clearance \geq 60 mL/min, and is not suitable for patients with moderate renal impairment (creatinine clearance between 30 and 60 mL/min) or with severe renal impairment (creatinine clearance < 30 mL/min). 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 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 using the individual components and/or discontinuation of the diuretic and/or Astarior may be required.

The effect of the combination Astarior has not been tested in patients with renal impairment. Astarior 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, Astarior 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 Astarior (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 Astarior 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 such as perindopril during low-density lipoprotein (LDL) apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation

Patients receiving ACE inhibitor-containing medicines, such as Astarior, 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. Astarior 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 Astarior 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. Astarior, 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 Astarior.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Astarior 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 Astarior 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 Astarior, 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 sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Astarior.

Level of sodium

Astarior contains less than 1 mmol sodium (23 mg) per capsule, i.e. essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

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

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).

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	In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase (see section 4.3).

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).
Atorvastatin	Glecaprevir/pibrentasvir
The concomitant therapy with Astarior is contra-indicated due to an increased risk of myopathy.	

Concomitant use not recommended (see section 4.4)

Component	Known interaction with the product	Interaction with other medicinal product
Atorvastatin	Potent CYP3A4 inhibitors	<p>Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2).</p> <p>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 with concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe (see section 4.4).</p> <p>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, <u>some antivirals used in the treatment of HCV (e.g. elbasvir/grazoprevir)</u> and HIV protease inhibitors including, ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) with Astarior should be avoided if possible. In cases where co-administration of these medicinal products with Astarior cannot be avoided, lowest doses of atorvastatin in Astarior should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).</p>

Component	Known interaction with the product	Interaction with other medicinal product
	Inhibitors of Breast Cancer Resistant Protein (BCRP)	Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy; therefore a dose adjustment of atorvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with atorvastatin increases plasma concentrations of atorvastatin 1.9 fold (see Table 1); therefore, the dose of atorvastatin in Astarior should not exceed 20 mg daily in patients receiving concomitant medications with products containing elbasvir or grazoprevir (see sections 4.2 and 4.4).
	Grapefruit or grapefruit juice	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended (see Table 1).
Perindopril	Aliskiren	In patients other than diabetic or impaired renal patients, concomitant treatment with Astarior and aliskiren is not recommended since risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.
	Co-trimoxazole (trimethoprim/sulfamethoxazole)	Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4)
	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 (contained in Astarior) 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 Astarior with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).
	Potassium-sparing diuretics (e.g. triamterene, amiloride,	These drugs are known to induce hyperkalaemia (potentially lethal), especially in conjunction

Component	Known interaction with the product	Interaction with other medicinal product
	epplerenone, spironolactone), potassium salts	with renal impairment (additive hyperkalaemic effects). The combination of Astarior 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.

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 Astarior 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 Astarior 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.

Component	Known interaction with the product	Interaction with other medicinal product
	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 Astarior. Appropriate clinical monitoring of these patients is recommended.
	Fusidic acid	As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. The concomitant use of Astarior and fusidic acid is not recommended, switching a patient to the individual component perindopril when discontinuation of Astarior is required should be considered. Statin therapy could be restarted 7 days after the last dose of fusidic acid.
	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 Astarior 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 Astarior 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 Astarior 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.
	Baclofen	Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.
	Non-potassium-sparing diuretics	Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.
	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).

Component	Known interaction with the product	Interaction with other medicinal product
	Non-steroidal anti-inflammatory medicinal products (NSAIDs) (including acetylsalicylic acid ≥ 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 Astarior 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.

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/Anaesthetics	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).

Component	Known interaction with the product	Interaction with other medicinal product
	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.
Perindopril	Antihypertensive agents and vasodilators	Concomitant use of these agents may increase the hypotensive effects of Astarior. 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 BID, 14 days	10 mg, OD, for 4 days	↑ 2.3 fold	
Nelfinavir 1250 mg	10 mg, OD, for	↑ 1.7 fold [^]	No specific

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose	Change in AUC ^{&}	Clinical recommendation [#]
BID, 14 days	28 days		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	40 mg SD	↑ 2.3 fold	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	↑ 8.3	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).
Elbasvir 50 mg OD / + Grazoprevir 200 mg OD, 13 days	120 mg, SD	↑ 1.95 fold	The dose of atorvastatin should not exceed a daily dose of 20 mg during

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose	Change in AUC ^{&}	Clinical recommendation [#]
			coadministration with products containing elbasvir or grazoprevir.

- 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 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).
- ** Ratio based on a single sample taken 8-16 h post dose.**
- [^] 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

Women of childbearing potential

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

Pregnancy

Based on existing data with the individual components as described below, Astarior is contraindicated during pregnancy (see section 4.3).

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 foetal 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.

Perindopril

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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

For these reasons 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 trimester of pregnancy.

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).

Breast-feeding

Based on existing data with the individual components as described below, Astarior is contra-indicated during breast-feeding (see section 4.3).

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.

Fertility

There are no clinical data on fertility with the use of Astarior

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.

4.7. Effects on ability to drive and use machines

No studies have been performed on the effect of Astarior 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.

As a result the ability to drive or operate machinery may be impaired in patients taking Astarior.

4.8. Undesirable effects

Summary of the profile:

The most commonly reported adverse reactions with atorvastatin and perindopril given separately include: nasopharyngitis, hypersensitivity, hyperglycaemia, dizziness, headache, dysgeusia, paraesthesia, visual impairment, tinnitus, vertigo, hypotension, pharyngolaryngeal pain, epistaxis, cough, dyspnoea, nausea, vomiting, abdominal pain upper and lower, dyspepsia, diarrhoea, constipation, flatulence, rash, pruritus, joint swelling, pain in extremity, arthralgia, muscle spasms, myalgia, back pain, asthenia, liver function test abnormal, blood creatine kinase increased.

Tabulated list of adverse reactions:

The following undesirable effects have been observed during treatment with atorvastatin and perindopril, or given separately and ranked under the MedDRA classification by body system and under heading of frequency using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
Infections and infestation	Nasopharyngitis	Common	-
	Rhinitis	-	Very rare
Blood and lymphatic system disorders	Thrombocytopenia	Rare	Very rare
	Leukopenia/ Neutropenia (see section 4.4)	-	Very rare
	Eosinophilia	-	Uncommon*
	Agranulocytosis /Pancytopenia (see section 4.4)		Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	Very rare
Immune system disorders	Hypersensitivity	Common	-
	Anaphylaxis	Very rare	-
Metabolism and nutrition disorders	Hyperglycaemia	Common	-
	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon	Uncommon*
	Hyponatraemia	-	Uncommon*
	Hyperkalaemia reversible on discontinuation (see section 4.4)	-	Uncommon*
	Anorexia	Uncommon	-
Psychiatric disorders	Insomnia	Uncommon	-
	Mood altered	-	Uncommon
	Sleep disorder		Uncommon
	Nightmare	Uncommon	-
	Confusional state	-	Very rare
Nervous system disorders	Somnolence	-	Uncommon*
	Dizziness	Uncommon	Common
	Headache	Common	Common
	Dysgeusia	Uncommon	Common
	Syncope	-	Uncommon*
	Hypoaesthesia	Uncommon	-
	Paraesthesia	Uncommon	Common

MedDRA System Organ Class	Undesirable effects	Frequency	
		Atorvastatin	Perindopril
	Peripheral neuropathy	Rare	-
	Stroke possible secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Amnesia	Uncommon	-
	Eye disorders	Visual impairment	Rare
	Vision blurred	Uncommon	-
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
	Vertigo	-	Common
	Hearing loss	Very Rare	-
Cardiac disorders	Myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Angina pectoris	-	Very rare
	Arrhythmia	-	Very rare
	Tachycardia	-	Uncommon*
	Palpitations	-	Uncommon*
Vascular disorders	Hypotension (and effects related to hypotension)	-	Common
	Vasculitis	-	Uncommon*
	Raynaud's phenomenon	-	Not known
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	Common	-
	Epistaxis	Common	-
	Cough	-	Common
	Dyspnoea	-	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal disorders	Nausea	Common	Common
	Vomiting	Uncommon	Common
	Abdominal pain upper and lower	Uncommon	Common
	Dyspepsia	Common	Common
	Diarrhoea	Common	Common
	Constipation	Common	Common
	Dry mouth	-	Uncommon
	Pancreatitis	Uncommon	Very rare
	Eructation	Uncommon	-
	Flatulence	Common	-
Hepato-biliary disorders	Hepatitis either cytolytic or cholestatic (see section 4.4)	Uncommon	Very rare
	Cholestasis	Rare	-
	Hepatic failure	Very rare	-
Skin and	Rash	Uncommon	Common

MedDRA System Organ Class	Undesirable effects	Frequency	
		Atorvastatin	Perindopril
subcutaneous tissue disorders	Pruritus	Uncommon	Common
	Urticaria (see section 4.4)	Uncommon	Uncommon
	Hyperhidrosis	-	Uncommon
	Psoriasis aggravation	-	Rare*
	Alopecia	Uncommon	-
	Angioedema (see section 4.4)	Rare	Uncommon
	Pemphigoid	-	Uncommon*
	Stevens-Johnson syndrome	Rare	-
	Photosensitivity reaction	-	Uncommon*
	Toxic epidermal necrolysis	Rare	-
	Erythema multiforme	Rare	Very rare
Musculoskeletal and connective tissue disorders	Joint swelling	Common	-
	Pain in extremity	Common	-
	Arthralgia	Common	Uncommon*
	Muscle spasms	Common	Common
	Myalgia	Common	Uncommon*
	Back pain	Common	-
	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 (see section 4.4)	Not known	-	
Renal and urinary disorders	Renal failure	-	Uncommon
	Acute kidney injury	-	Very rare
Reproductive system and breast disorders	Erectile dysfunction	-	Uncommon
	Gynaecomastia	Very rare	-
General disorders and administration site conditions	Asthenia	Uncommon	Common
	Fatigue	Uncommon	-
	Chest pain	Uncommon	Uncommon*
	Malaise	Uncommon	Uncommon*
	Oedema peripheral	Uncommon	Uncommon*
	Pyrexia	Uncommon	Uncommon*
Investigations	Blood urea increased	-	Uncommon*
	Blood creatinine increased	-	Uncommon*

MedDRA System Organ Class	Undesirable effects	Frequency	
		Atorvastatin	Perindopril
	Hepatic enzymes increased	-	Rare
	Blood bilirubin increased	-	Rare
	Haemoglobin decreased and haematocrit decreased (see section 4.4)	-	Very rare
	Weight increased	Uncommon	-
	White blood cells urine positive	Uncommon	-
	Liver function test abnormal	Common	-
	Blood creatine phosphokinase increased	Common	-
Injury, poisoning and procedural complications	Fall	-	Uncommon*

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

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 section 4.4).

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 > 30 kg/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 Astarior 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG CoA reductase inhibitors, other combinations,
ATC code: C10BX15

Mechanism of action and pharmacodynamics effects

Atorvastatin

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

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin 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

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*.

Heart failure:

Perindopril reduces cardiac work by a decrease in pre-load and after-load.

Clinical efficacy and safety:

Astarior 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.

Atherosclerosis

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

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

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L \pm 0.8 mmol/L (78.9 mg/dl \pm 30 mg/dL) from baseline 3.89 mmol/L \pm 0.7 mmol/L (150 mg/dl \pm 28 mg/dL) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L \pm 0.7 mmol/L (110 mg/dl \pm 26 mg/dL) from baseline 3.89 mmol/L \pm 0.7 mmol/L (150 mg/dL \pm 26 mg/dL) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apolipoprotein B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

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

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

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

Acute coronary syndrome

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

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

Prevention of cardiovascular disease

The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5 mmol/L (251 mg/dL). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C > 6 , peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

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

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

Event	Relative Risk Reduction (%)	No. of Events (atorvastatin vs placebo)	Absolute Risk Reduction ¹ (%)	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006

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

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

In a post-hoc analysis, a subgroup of patients randomised to the amlodipine-based regimen were treated with perindopril and either atorvastatin (n=1,950) or placebo (n=1,926). The risk of total CHD [non-fatal MI (including silent) + fatal CHD] was reduced of 42% (95% CI [0.396;0.837]). There were also a significant reduction of 46% for the risk of cardiovascular mortality (95% CI [0.344, 0.854]), a reduction of 40% for the composite cardiovascular mortality + MI + stroke (95% CI [0.461;0.779]), a reduction of 36% for the composite total CHD + fatal and non-fatal stroke (95% CI [0.490;0.846]), a reduction of 32% for the total coronary events (95% CI [0.516;0.883]) and a reduction of 29% for all cause of mortality (95% CI [0.555;0.915]).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 4.14 mmol/L (160 mg/dL) and TG ≤ 6.78 mmol/L (600 mg/dL). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria. Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years.

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

Event	Relative Risk Reduction (%)	No. of Events (atorvastatin vs placebo)	Absolute Risk Reduction ¹ (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs 64	1.9%	0.0070
Strokes (fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

¹Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

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

Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4,731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI [0.72;1.00]; p=0.05 or 0.84; 95% CI [0.71;0.99]; p=0.03 after adjustment for baseline factors) compared to placebo. All cause mortality was 9.1% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 1.4%, p=0.02) compared to placebo.

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

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

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

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.

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.

Heart failure

Perindopril reduces cardiac work by a decrease in pre-load and after-load.

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2.5 mg of perindopril arginine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo

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.

At randomization, 89.41% of patients with a lipid lowering therapy (LLT) received statins (89.02% in the Perindopril group and 89.80% in the placebo group).

In a subgroup of patients treated with LLT from EUROPA study defined in a post-hoc analysis, the addition of perindopril on top of LLT (n=3534) showed a significant absolute risk reduction of 1.7% (RRR of 21.8%, 95% CI [0.634 ; 0.964] compared to placebo on top of LLT (n=3499) in the composite endpoint of cardiovascular mortality, non-fatal acute myocardial infarction and cardiac arrest with successful resuscitation.

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

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 a 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.

Paediatric population

No data are available with Astarior in children.

The European Medicines Agency has granted a product-specific waiver for Astarior in all subsets of the paediatric population for the treatment of cardiovascular diseases (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, was 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.

In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 40 mg, perindopril arginine 10 mg and acetylsalicylic acid 100 mg resulted in a 32% increase in the maximum concentration of perindopril, but the pharmacokinetics of perindoprilat, the active metabolite were unaffected. No pharmacokinetic interaction was identified for atorvastatin, acetylsalicylic acid and their respective metabolites.

Atorvastatin

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution

Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is $\geq 98\%$ 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 efflux transporter BCRP.

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 C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal 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 C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

SLCO1B1 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 older people, 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.

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).

5.3. Preclinical safety data

No preclinical studies have been performed with Astarior.

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 AUC_{0-24h} 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule content

Talc (E553b)

Atorvastatin pellets

- Calcium carbonate (E170)
- Hydroxypropyl cellulose (E463)
- Polysorbate 80 (E433)
- Croscarmellose sodium (E468)
- Sugar spheres (sucrose and maize starch)

Perindopril arginine pellets

- Hydroxypropyl cellulose (E463)
- Sugar spheres (sucrose and maize starch)

Capsule shell

Astarior 10/5 mg, 20/5 mg and 40/5 mg

- Titanium dioxide (E171)
- Brilliant blue FCF – FD&C Blue 1 (E133)
- Gelatin

Astarior 10/10 mg, 20/10 mg and 40/10 mg

- Titanium dioxide (E171)
- Brilliant blue FCF – FD&C Blue 1 (E133)
- Yellow iron oxide (E172)
- Gelatin

Ink content:

- shellac (E904)
- propylene glycol (E1520)
- strong ammonia solution (E527)
- black iron oxide (E172)
- potassium hydroxide (E525).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store in the original container in order to protect from moisture.

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

6.5. Nature and contents of container

Astarior 10/5 mg

- 10 hard capsules in a PP container closed with a LDPE stopper
- 30 hard capsules in a PP container closed with a LDPE stopper
- 90 (3x30) hard capsules in 3 PP containers closed with a LDPE stopper
- 100 hard capsules in a HDPE bottle closed with a PP stopper

Astarior 20/5 mg, Astarior 40/5 mg, Astarior 10/10 mg, Astarior 20/10 mg, Astarior 40/10 mg

- 30 hard capsules in a PP container closed with a LDPE stopper
- 90 (3x30) hard capsules in 3 PP containers closed with a LDPE stopper
- 100 hard capsules in a HDPE bottle closed with a PP stopper

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<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)}>

|

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Astarior 10 mg/5 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin and 5 mg perindopril arginine equivalent to 3.395 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

10 hard capsules
30 hard capsules
90 hard capsules (3 containers of 30 capsules)
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Astarior 10 mg/5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}

SN: {number}

NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Astarior 10 mg/5 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin and 5 mg perindopril arginine equivalent to 3.395 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

10 hard capsules
30 hard capsules
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Astarior 20 mg/5 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin and 5 mg perindopril arginine equivalent to 3.395 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules
90 hard capsules (3 containers of 30 capsules)
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Astarior 20 mg/5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}

SN: {number}

NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Astarior 20 mg/5 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin and 5 mg perindopril arginine equivalent to 3.395 mg perindopril

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules

100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Astarior 40 mg/5 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin and 5 mg perindopril arginine equivalent to 3.395 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules
90 hard capsules (3 containers of 30 capsules)
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Astarior 40 mg/5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}

SN: {number}

NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Astarior 40 mg/5 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin and 5 mg perindopril arginine equivalent to 3.395 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules

100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Astarior 10 mg/10 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin and 10 mg perindopril arginine equivalent to 6.79 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules
90 hard capsules (3 containers of 30 capsules)
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Astarior 10 mg/10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}

SN: {number}

NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Astarior 10 mg/10 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin and 10 mg perindopril arginine equivalent to 6.79 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules

100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Astarior 20 mg/10 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin and 10 mg perindopril arginine equivalent to 6.79 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules
90 hard capsules (3 containers of 30 capsules)
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Astarior 20 mg/10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}

SN: {number}

NN: {number}

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
CONTAINER**

1. NAME OF THE MEDICINAL PRODUCT

Astarior 20 mg/10 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin and 10 mg perindopril arginine equivalent to 6.79 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules

100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Astarior 40mg/10 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin and 10 mg perindopril arginine equivalent to 6.79 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules
90 hard capsules (3 containers of 30 capsules)
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Astarior 40 mg/10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}

SN: {number}

NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Astarior 40 mg/10 mg, hard capsules
atorvastatin/perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin and 10 mg perindopril arginine equivalent to 6.79 mg perindopril.

3. LIST OF EXCIPIENTS

Contains sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard

30 hard capsules

100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

PACKAGE LEAFLET

Package leaflet: Information for the patient

Astarior 10 mg/5 mg hard capsules
Astarior 20 mg/5 mg hard capsules
Astarior 40 mg/5 mg hard capsules
Astarior 10 mg/10 mg hard capsules
Astarior 20 mg/10 mg hard capsules
Astarior 40 mg/10 mg hard capsules

atorvastatin / perindopril arginine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Astarior is and what it is used for
2. What you need to know before you take Astarior
3. How to take Astarior
4. Possible side effects
5. How to store Astarior
6. Contents of the pack and other information

1. What Astarior is and what it is used for

Astarior contains two active ingredients, atorvastatin and perindopril arginine in one capsule.

Atorvastatin belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines. Atorvastatin is used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and life style changes on their own have failed. If you are at an increased risk of heart disease, atorvastatin can also be used to reduce such risk even if your cholesterol levels are normal.

Perindopril arginine is an angiotensin converting enzyme (ACE) inhibitor. In patients with high blood pressure, it works by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Astarior is intended for adult patients already on treatment with atorvastatin and perindopril arginine as single tablets as part of cardiovascular risk management. Instead of taking atorvastatin and perindopril arginine as single tablets you will receive one capsule of Astarior which contains the two active ingredients in the same strength.

You should maintain a standard cholesterol lowering diet during treatment.

2. What you need to know before you take Astarior

Do not take Astarior :

- if you are allergic to atorvastatin or to any similar medicines used to lower blood lipids, to perindopril or any other ACE inhibitor, or to any of the other ingredients of this medicine (listed in section 6),
- if you have a disease which affects the liver,

- if you have any unexplained abnormal blood tests for liver function,
- if you have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema),
- if you have diabetes or impaired kidney function and you are taking a blood pressure lowering medicine containing aliskiren,
- if you are having dialysis or any other type of blood filtration. Depending on the machine that is used, Astarior may not be suitable for you₂;
- if you have kidney problems where the blood supply to your kidneys is reduced (renal artery stenosis).
- if you are being treated with sacubitril/valsartan, a medicine for heart failure (see “Warning and Precaution” and “Other medicines and Astarior”)₂;
- [if you use the combination of glecaprevir/pibrentasvir in the treatment of hepatitis C,](#)
- if you are pregnant or trying to become pregnant, or if you are a woman able to have children and not using reliable contraception,
- if you are breast-feeding.

Warnings and precautions

Talk to your doctor or pharmacist before taking Astarior if you:

- have a liver problem or a history of liver disease,
- regularly drink a large amount of alcohol,
- are taking or have taken in the last 7 days a medicine called fusidic acid (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and Astarior can lead to serious muscle problems (rhabdomyolysis),
- have had repeated or unexplained muscle aches or pains, have, or if a close family member has a muscle problem which runs in the family,
- have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other ‘-statin’ or ‘-fibrate’ medicines),
- have an under-active thyroid gland (hypothyroidism),
- have severe respiratory failure,
- have diabetes (high blood glucose),
- have heart failure or any other heart problem,
- have recently suffered from diarrhoea or vomiting, or are dehydrated,
- have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood),
- have kidney problems, recently underwent a kidney transplantation or if you are receiving dialysis,
- are elderly (over 70),
- have abnormally increased levels of a hormone called aldosterone in your blood (primary aldosteronism),
- are experiencing a severe allergic reaction with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing (angioedema). This may occur at any time during treatment. If you develop such symptoms, you should stop taking Astarior and see a doctor immediately.
- suffer from a collagen vascular disease (deposits of collagen in your blood vessels), such as systemic lupus erythematosus or scleroderma,
- are of black origin since you may have a higher risk of angioedema and this medicine may be less effective in lowering your blood pressure than in non-black patients,
- are taking any of the following medicines, the risk of angioedema is increased:
 - racecadotril (used to treat diarrhea)
 - sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors (used to avoid rejection of transplanted organs)
 - sacubitril (available as fixed dose combination with valsartan) used to treat long-term heart failure,
- are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine),

- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings,
- are to undergo anaesthesia and/or major surgery
- are on a salt restricted diet or use salt substitutes which contain potassium,
- have been told by your doctor that you have an intolerance to some sugars,
- are taking any of the following medicines used to treat high blood pressure:
 - an angiotensin II receptor blocker (ARBs) (also known as sartans - for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems,
 - aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take Astarior”.

If any of these apply to you, your doctor may need to carry out a blood test before and possibly during your treatment to predict your risk of muscle related side effects. The risk of muscle related side effects e.g. rhabdomyolysis is known to increase when certain medicines are taken at the same time (see section 2 “Other medicines and Astarior”).

Also tell your doctor or pharmacist if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fat in your blood, are overweight and have high blood pressure.

Children and adolescents

The use of Astarior in children and adolescents up to the age of 18 years is not recommended.

Other medicines and Astarior

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

There are some medicines that may change the effect of Astarior or their effect may be changed by Astarior. This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side-effects, including the muscle wasting condition known as rhabdomyolysis described in Section 4.

Astarior must not be used with:

- aliskiren (used for high blood pressure) in diabetic or renal impaired patients,
- sacubitril/valsartan (used to treat long-term heart failure). See sections “Do not take Astarior” and “Warnings and precautions”;
- [glecaprevir/pibrentasvir \(used in the treatment of hepatitis C\)](#).

You should avoid Astarior with:

- immunosuppressants (medicines which reduce the defence mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin, tacrolimus),
- clarithromycin, telithromycin (antibiotics),
- [medicines used in the treatment of HIV or liver disease such as **h**Hepatitis C, e.g. delavirdine, ritonavir, lopinavir, atazanavir, indinavir, darunavir, telaprevir, ~~boceprevir~~, tipranavir, **boceprevir and the combination of elbasvir/grazoprevir, elbasvir, or grazoprevir**](#),
- stiripentol (an anti-convulsant for epilepsy),
- ketoconazole, itraconazole, voriconazole, posaconazole (anti-fungal medicines),
- other medicines for high blood pressure, including aliskiren in patients other than diabetic or renal impaired, angiotensin II receptor blockers (e.g. valsartan) see also information under the headings “Do not take Astarior” and “Warnings and precautions”, or diuretics (medicines which increase the amount of urine produced by the kidneys),

- 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”.
- 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).

Treatment with Astarior can be affected by other medicines. Make sure to tell your doctor if you are taking any of the following medicines as special care may be required:

- fluconazole (anti-fungal medicines),
- rifampicin, erythromycin, fusidic acid, trimethoprim (antibiotics),
- some calcium channel blockers used for angina or high blood pressure, e.g. diltiazem, verapamil,
- efavirenz (medicine used in the treatment of HIV),
- medicine obtained without a prescription: *hypericum perforatum* or St John’s Wort (herbal treatment used for depression),
- medicines to regulate your heart rhythm e.g. digoxin, amiodarone, procainamide,
- other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, colestipol, ezetimibe,
- medicines which reduce blood clotting (anticoagulants, such as warfarin, heparin),
- baclofen (used to treat muscle stiffness in diseases such as multiple sclerosis),
- non-potassium-sparing diuretics (medicines which increase the amount of urine produced by the kidneys),
- medicines to treat diabetes (such as insulin or metformin),
- 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.

If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using Astarior. Your doctor will tell you when it is safe to restart Astarior. Taking Astarior with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in section 4.

The use of Astarior should be taken into consideration with:

- 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. colestipol,
- oral contraceptives,
- medicines used for the treatment of low blood pressure, shock (e.g. ephedrine, noradrenaline or adrenaline),
- some calcium channel blockers used for angina or high blood pressure, e.g. amlodipine, medicines to treat mental disorders such as depression, anxiety, schizophrenia etc (e.g. tricyclic antidepressants, antipsychotics),
- gold salts, especially by intravenous administration (used to treat symptoms of rheumatoid arthritis),
- vasodilators including nitrates (products that make the blood vessels become wider),
- cimetidine (used for heartburn and peptic ulcers),
- phenazone (a painkiller),
- antacids (indigestion products containing aluminium or magnesium),
- allopurinol (for the treatment of gout).

Astarior with food, drink and alcohol

It is preferable to take Astarior in the morning before breakfast.

Grapefruit and grapefruit juice

If you are taking Astarior, you should 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. See Section 2 “Warnings and precautions” for details.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Do not take Astarior if you are pregnant, if you are trying to become pregnant or if able to become pregnant unless you use reliable contraceptive measures (see “Do not take Astarior”).

This medicine must not be used during pregnancy.

Breast-feeding

You must not take Astarior if you are breast-feeding. Tell your doctor immediately if you are breast-feeding or about to start breast-feeding.

Driving and using machines

Astarior may cause dizziness or weakness. If you are affected in this way, your ability to drive or to operate machinery may be impaired.

Astarior contains sucrose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Astarior contains sodium

Astarior contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

3. How to take Astarior

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one capsule per day. Swallow your capsule whole with a glass of water preferably at the same time each day, in the morning and before a meal. Do not chew or crush the capsules.

Use in children and adolescents

Use in children and adolescents younger than 18 years is not recommended.

If you take more Astarior than you should

If you take more capsules than prescribed, contact your nearest accident and emergency department or tell your doctor immediately. Taking too many capsules may cause your blood pressure to become low which can make you feel dizzy, lightheaded, faint or weak. If this happens, lying down with the legs raised can help. ~~Taking too many capsules may also cause dizziness, headache, ringing in ears, confusion, nausea, vomiting and abdominal pain. A large overdose can lead to more rapid breathing than normal (hyperventilation), fever, passing less urine than is normal, agitation, seizures, hallucinations, low blood sugar, coma, shock and respiratory arrest.~~

If you forget to take Astarior

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

If you stop taking Astarior

As the treatment with Astarior is usually life-long, you should discuss with your doctor before stopping this medicinal product.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking the medicinal product and see a doctor immediately, if you experience any of the following side effects or symptoms that can be serious:

- swelling of eyelids, the face, lips, mouth, tongue or throat, difficulty in breathing (angioedema) (See section 2 “Warnings and precautions”),
- severe dizziness or fainting due to low blood pressure,
- severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions,
- muscle weakness, tenderness, ~~or~~ pain, rupture or red-brown discolouration of urine and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown (rhabdomyolysis) which can be life-threatening and lead to kidney problems,
- weakness of arms or legs, or problems speaking which could be a sign of a possible stroke,
- unusual fast or irregular heartbeat, chest pain (angina) or heart attack,
- sudden wheeziness, chest pain, shortness of breath, or difficulty in breathing (bronchospasm),
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell,
- if you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver failure,
- yellowing of the skin or eyes (jaundice) which could be a sign of inflammation of the liver (hepatitis)
- skin rash which often starts with red itchy patches on your face, arms or legs (erythema multiforme),
- lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

Tell your doctor if you notice any of the following side effects:

Common (may affect up to 1 in 10 people):

- inflammation of the nasal passages,
- increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels), increase in blood creatine kinase,
- vertigo, dizziness,
- headache,
- sensation of pins and needles in the skin,
- vision disturbances,
- tinnitus (sensation of noises or ringing in the ears),
- pain in the throat,
- nose bleed,
- cough, shortness of breath (dyspnoea),
- joint pain, pain in the extremities, joint swelling, muscle spasms, muscle pain, and back pain,
- feeling of weakness,
- blood test results that show your liver function can become abnormal,
- gastro-intestinal disorders: feeling sick (nausea), being sick (vomiting), constipation, wind, indigestion, diarrhoea, upper and lower abdominal pain, taste disturbances.

Uncommon (may affect up to 1 in 100 people):

- excess of eosinophils (a type of white blood cells),
- anorexia (loss of appetite),
- insomnia,

- mood swings,
- sleep disturbances,
- having nightmares,
- somnolence,
- fainting,
- reductions of sensation to pain or touch,
- loss of memory,
- blurred vision,
- tachycardia (fast heart beat),
- palpitations (awareness of your heart beat),
- vasculitis (inflammation of blood vessels),
- dry mouth,
- belching,
- increased sweating,
- hair loss,
- formation of blister clusters over the skin,
- photosensitivity reaction (increased sensitivity of the skin to sun),
- neck pain,
- muscle fatigue,
- kidney problems,
- inability to obtain an erection, impotence,
- fatigue,
- chest pain,
- malaise,
- localised swelling (oedema peripheral),
- raised temperature (fever),
- weight gain,
- urine tests that are positive for white blood cells,
- fall,
- change in laboratory parameters: high blood level of potassium reversible on discontinuation, low level of sodium, very low blood sugar level (if you have diabetes you should continue careful monitoring of your blood sugar levels), increased blood urea, and increased blood creatinine.

Rare (may affect up to 1 in 1,000 people):

- low blood platelet count which may result in unusual bruising or easy bleeding,
- disorder of the nerves which can cause weakness, tingling or numbness,
- cholestasis (yellowing of the skin and whites of the eyes),
- psoriasis worsening,
- muscle inflammation,
- tendon injury,
- changes in laboratory parameters: increased liver enzymes, increased serum bilirubin.

Very rare (may affect up to 1 in 10,000 people):

- sneezing/running nose caused by inflammation of the lining of the nose (rhinitis),
- changes in blood values such as a lower number of white and red blood cells, lower haemoglobin, illness resulting from the destruction of red blood cells,
- confusion,
- hearing loss,
- eosinophilic pneumonia (a rare type of pneumonia),
- acute kidney failure,
- discomfort or enlargement of the breasts in men.

Not known (frequency cannot be estimated from the available data):

- muscle weakness that is constant,

- discoloration, numbness and pain in fingers or toes (Raynaud's phenomenon).

Concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion can occur with ACE inhibitors. If you have these symptoms contact your doctor as soon as possible.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Astarior

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and capsule container after EXP. The expiry date refers to the last day of that month.

Store in the original container in order to protect from moisture.

This medicine does not require any special temperature storage conditions.

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.

6. Contents of the pack and other information

What Astarior contains

- **The active substances are** atorvastatin and perindopril arginine.

Each hard capsule of Astarior 10 mg/5 mg contains 10.82 mg atorvastatin calcium trihydrate equivalent to atorvastatin 10 mg, 5 mg perindopril arginine equivalent to 3.395 mg perindopril

Each hard capsule of Astarior 20 mg/5 mg contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril

Each hard capsule of Astarior 40 mg/5 mg contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril

Each hard capsule of Astarior 10 mg/10 mg contains 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril

Each hard capsule of Astarior 20 mg/10 mg contains 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril

Each hard capsule of Astarior 40 mg/10 mg contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril

- **The other ingredients are:**

- **Pellets of atorvastatin:** calcium carbonate (E170), hydroxypropyl cellulose (E463), polysorbate 80 (E433), croscarmellose sodium (E468), sugar spheres (sucrose and maize starch).

- **Pellets of perindopril:** hydroxypropyl cellulose (E463), sugar spheres (sucrose and maize starch).

- **Talc**

- **Capsule shell:**

- **Astarior 10 mg/5 mg, 20 mg/5 mg and 40 mg/5 mg:** titanium dioxide (E171), brilliant blue FCF – FD&C Blue 1 (E133), gelatin.

- **Astarior 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg:** titanium dioxide (E171), brilliant blue FCF – FD&C Blue 1 (E133), yellow iron oxide (E172), gelatin.

- **Printing ink** : shellac (E904), propylene glycol (E1520), strong ammonia solution (E527), black iron oxide (E172), potassium hydroxide (E525).

What Astarior looks like and contents of the pack

Astarior are hard gelatin size 2 capsules containing spherical white to slightly white spherical pellets.

Astarior 10 mg/5 mg hard capsules have a light blue body with a black imprint “10 5” and a light blue cap with a black imprint “☞”.

Astarior 20 mg/5 mg hard capsules have a light blue body with black imprint “20 5” and a blue cap with a black imprint “☞”.

Astarior 40 mg/5 mg hard capsules have a blue body with black imprint “40 5” and a blue cap with a black imprint “☞”.

Astarior 10 mg/10 mg hard capsules have a light green body with a black imprint “10 10” and a light green cap with a black imprint “☞”.

Astarior 20 mg/10 mg hard capsules have a light green body with a black imprint “20 10” and a green cap with a black imprint “☞”.

Astarior 40 mg/10 mg hard capsules have a green body with a black imprint “40 10” and a green cap with a black imprint “☞”.

The hard capsules are available in containers of 10 (available for 10 mg/5 mg strength only), 30 and 100. A presentation containing 90 capsules (3 containers of 30 capsules) is also available.

10, 30 and 100 hard capsules containers are closed with a stopper.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

< [To be completed nationally] >

Manufacturer

Les Laboratoires Servier Industrie
905, route de Saran
45520 Gidy - France

and

Przedsiębiorstwo Farmaceutyczne ANPHARM S.A.
ul. Annopol 6B – 03-236 Warszawa – Poland

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

Bulgaria	Parvaxor капсула, твърда
Czech Republic, Poland	Parvaxor
Finland	Astarior kapseli, kova
France	Astarior gélule
Greece	Astarior Καψάκιο, σκληρό
Hungary	Parvaxor Lipcover kemény kapszula
Latvia	Parvaxor cietās kapsulas
Lithuania	Tacernol kietoji kapsulės
Netherlands	Astarior capsule, hard
Portugal	Astarior
Romania	Parvaxor capsulă
Slovakia	Parvaxor tvrdá kapsula

This leaflet was last revised in <{MM/YYYY}>.

< [To be completed nationally] >

<Other sources of information>

Detailed information on this medicine is available on the website of {MS/Agency}>