Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	– Drug-induced hepatitis – Rhabdomyolysis / myopathy – New onset of diabetes in patients with increased risk of diabetes – Stevens-Johnson syndrome and toxic epidermal necrolysis – Interstitial lung disease – Hyperkalaemia – Increased risk of hypotension, hyperkalaemia and acute renal failure when combining RAS-agents – Neutropenia /agranulocytosis/ thrombocytopenia – Foetotoxicity / e mbryotoxicity / u se during pregnancy – Angioedema
Important potential risks	– Haemorrhagic stroke – Autoimmune events
Missing information	– Children and adolescents – Lactating women – Patients with severe hepatic impairment – Patients with severe renal impairment

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk		
Drug-induced hepatitis	Information included in the sections 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC	None proposed
Rhabdomyolysis / myopathy	Information included in the sections 4.4, 4.5, 4.8 and 5.2 of the SmPC	None proposed
New onset of diabetes in patients with increased risk of diabetes	Information included in the sections 4.4 and 4.8 of the SmPC	None proposed
Stevens-Johnson syndrome and toxic epidermal necrolysis	Information included in the sections 4.8 of the SmPC	None proposed

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Interstitial lung disease	Information included in the sections 4.4 and 4.8 of the SmPC	None proposed
Hyperkalaemia	Information included in the sections 4.4, 4.5, 4.6 and 4.8 of the SmPC	None proposed
Increased risk of hypotension, hyperkalaemia and acute renal failure when combining RAS-agents	Information included in the sections 4.3,4.4, 4.5, 4.8 and 5.1 of the SmPC	None proposed
Neutropenia /agranulocytosis/ thrombocytopenia	Information included in the sections 4.4 and 4.8 of the SmPC	None proposed
Foetotoxicity / embryotoxicity / use during pregnancy	Information included in the sections 4.3 and 4.6 of the SmPC	None proposed
Angioedema	Information included in the sections 4.3, 4.4, 4.5 and 4.8 of the SmPC	None proposed
Important potential risk		
Haemorrhagic stroke	Information included in the section 5.1 of the SmPC	None proposed
Autoimmune events	Information included in the sections 4.4 and 4.8 of the SmPC	None proposed
Missing information		
Children and adolescents	Information included in the sections 4.2 and 5.1 of the SmPC	None proposed
Lactating women	Information included in the sections 4.3 and 4.6 of the SmPC	None proposed
Patients with severe hepatic impairment	Information included in the sections 4.2, 4.3, 4.4 and 5.2of the SmPC	None proposed
Patients with severe renal impairment	Information included in the sections 4.2, 4.3, 4.4 and 5.2 of the SmPC	None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Cardiovascular diseases, i.e. diseases involving the heart or blood vessels, are the major cause of death in both developed and developing countries. People are at increased risk if they have elevated lipids levels, high blood pressure and the risk is further increased if they have had one or both of the following conditions:

- a first myocardial infarction, also known as a heart attack, which occurs when the supply of blood to the heart is suddenly blocked, causing damage to the heart muscle;
- a revascularization which is a restoration of blood supply typically accomplished by surgical means.

Scientific data have demonstrated that the combination of medical therapy with lifestyle modifications could reduce this risk.

VI.2.2 Summary of treatment benefits

Euvascor/Astarior contains atorvastatin, a product used to regulate lipid levels and perindopril, a medicine used to lower blood pressure which works by widening the blood vessels and makes it easier for the heart to pump blood through them. Euvascor/Astarior provides a combination of well-known medicinal substances, which are used for cardiovascular risk management in a single capsule and reduces the formation of atherosclerotic lesion, hence cardiovascular events. The benefit of a single capsule compared to taking each of these products separately (in other words, taking two tablets) is to simplify treatment and to improve the correct use of the medicines.

VI.2.3 Unknowns relating to treatment benefits

The populations where experience is limited such as children and adolescents (< 18 years old), pregnant and lactating women, patients with severe kidney problems and patients with severe liver problems are reflected in the Summary of Product Characteristics (SmPC).

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Abnormal blood tests for liver function (drug-induced hepatitis)	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 t imes 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. Liver disease (hepatitis) is an uncommon side effect of atorvastatin (seen between 1 and 10 patients in 1000). Cholestasis, a condition where bile cannot flow from the liver to the duodenum, is a rare side effect (seen up to 1 patient in 1000) and hepatic failure is a very rare side effect (seen up to 1 pa tient in 10000) of atorvastatin.	Yes by following the contraindication to not use Euvascor/Astarior in patients with history of active liver disease or unexplained persistent abnormal blood tests for liver function or severe hepatic impairment, as well as the special warnings and precautions for use; by monitoring for symptoms suggestive of liver dysfunction e.g. jaundice or marked elevations of liver enzymes. Patients should talk to their doctor or pharmacist before taking the product if they have a liver problem and if they regularly drink a large amount of alcohol.
Abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis); pain or weakness in muscles (myopathy)	Severe muscle weakness, tenderness or pain and at the same time, malaise and fever occur rarely with atorvastatin (seen up to 1 patient in 1000); it may be caused by an abnormal muscle breakdown which can be life-threatening and lead to kidney problems (rhabdomyolysis; seen up to 1 patient in 1000 taking atorvastatin). These side effects may also occur with Euvascor. The risk of rhabdomyolysis is increased when Euvascor/Astarior is administered concomitantly with certain medicinal products.	Yes by following the contraindications, special warnings and precautions for use and the interactions with other medicinal products. Whilst on treatment, patients should stop taking the medicinal product and see a doctor immediately, if they experience muscle weakness, tenderness or pain and particularly, if at the same time, they feel unwell or have a high temperature.

Risk	**What is known**	**Preventability**
New onset of diabetes (high blood sugar) in patients with increased risk of diabetes	Increases in blood sugar levels is a common side effect with atorvastatin (seen between 1 and 10 patients in 100). This side effect may also occur with Euvascor. There is a risk of developing diabetes in patients with high levels of sugars and fat in blood, in those who are overweight and in patients who have high blood pressure.	Yes by following the special warnings and precautions for use. While a patient is on this medicine his doctor should monitor him closely if he has diabetes or is at risk of developing diabetes.
Severe skin r eactions 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 and toxic epidermal necrolysis)	People taking atorvastatin rarely (may affect up to 1 in 1000 people) experienced serious skin reactions.	Yes by following the recommendation to stop taking Euvascor/Astarior and see a doctor immediately if you experience severe skin reactions .
Injury to the lung tissue that leads to breathing problems (interstitial lung disease)	Breathing problems including persistent cough and/or shortness of breath or fever can exceptionally occur with a group of medicines known as statins, which are lipid (fat) regulating medicines, to which atorvastatin belongs to. This side effect may also occur with Euvascor/Astarior.	Yes by following the special warnings and precautions for use. Checking with a doctor or pharmacist before taking a statin in case of severe respiratory symptoms. Reporting to a doctor of any symptoms such as persistent dry cough, shortness of breath, and/or deterioration in general health (fatigue, weight loss and fever).
High level of potassium in the blood (hyperkalaemia)	High level of potassium in the blood is an uncommon side effect with perindopril (seen between 1 and 10 patients in 1000). This may cause serious, sometimes fatal, irregular heartbeat. This side effect may also occur with Euvascor/Astarior.	Yes by following the special warnings and precautions for use and the interactions with other medicinal products.
Increased risk of low blood pressure (hypotension), increased potassium in the blood (hyperkaliemia) and possible damage to the kidney (Dual blockade of the of the renin-angiotensin-aldosterone system)	Combination of Euvascor/Astarior (containing perindopril, an ACE inhibitor) with an ARB (also known as sartan), or a direct renin inhibitor (such as aliskiren) does not increase the benefits, and may increase the risks of low blood pressure, increased potassium in the blood and possible damage to the kidney.	Yes by following the contraindications, special warnings and precautions for use, and the interactions with other medicinal products.
Changes in blood values such as a lower number of white cells of blood platelets (neutropenia/agranulocytosis/ thrombocytopenia)	Disorders of the blood are very rare side effects with perindopril (seen up to 1 patient in 10000). These side effects may also occur with Euvascor/Astarior.	Yes by following the special warnings and precautions for use. Euvascor/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.

Risk	What is known	Preventability
Foetotoxicity / embryotoxicity / use during pregnancy	Euvascor may cause serious harm to baby if used during pregnancy.	Yes by following the contra-indication to not use Euvascor/Astarior during pregnancy, while breast feeding and in women of childbearing potential not using appropriate contraceptive measures. You must tell your doctor if you think you are pregnant or if you plan to have a baby.
Angioedema	Swelling of eyelids, face, lips, tongue or throat are uncommon side effects with perindopril (seen between 1 and 10 patients in 1000).	Yes by following the contra-indication to not use Euvascor/Astarior in patients with history of angioedema associated with previous ACE inhibitor therapy and with hereditary or idiopathic angioedema; as well as following the special warnings and precautions for use. In case of swelling, treatment must be immediately discontinued and patient should seek urgent advice from a doctor. Euvascor/Astarior must not be re-started at any time in patients who have developed swelling.

Important potential risks

Risk	What is known	Preventability
Rupture in a weakened blood vessel in the brain (Haemorrhagic stroke)	After the experiment, data concluded that atorvastatin 80 mg reduced the incidence of ischemic stroke (an obstruction within a blood vessel supplying blood to the brain) and increased the incidence of hemorrhagic stroke (a weakened blood vessel leak).	Yes by carefully consider the risk of hemorrhagic stroke before initiating atorvastatin treatment. Your doctor will monitor you while you are taking this medicine.
Events occuring when the body tissues are attacked by its own immune system (Autoimmune events)	People taking atorvastatin had developed muscle weakness caused by an autoimmune response with unknown frequency.	Yes by following the special warnings and precautions for use. Patients should stop taking the medicinal product and see a doctor immediately, if they experience muscle weakness.

Missing information

Risk	What is known
Children and adolescents	The efficacy and safety of Euvascor/Astarior has not been studied in this population.
Lactating women	The efficacy and safety of Euvascor/Astarior has not been studied in this population.
Patients with severe hepatic impairment	The efficacy and safety of Euvascor/Astarior has not been studied in this population.

Risk	What is known
Patients with severe renal impairment	The efficacy and safety of Euvascor/Astarior has not been studied in this population.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.
The Summary of Product Characteristics and the Package leaflet for Euvascor/Astarior can be found on the website of your national health agency. If you do not know how to find this website, you can find it by selecting your country in the search function on t he following website: http://www.hma.eu/66.html.
This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No clinical studies are planned to be conducted following the approval of this product.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, this is the first version of the Euvascor Risk Management Plan.