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	– Hypotension – Drug-induced hepatitis – Hyperkalaemia – Neutropenia / agranulocytosis / thrombocytopenia – Angioedema / hypersensitivity – Myopathy / rhabdomyolysis – Foetotoxicity / embryotoxicity / use during pregnancy – New onset of diabetes in patients with increased risk of diabetes
Important potential risks	– Interstitial lung disease
Missing information	– Children and adolescents (< 18 years of age) – 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

No post-authorisation studies are planned.

VI.1.3 Summary of Post authorisation efficacy development plan

No post-authorisation studies are planned.

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk		
Hypotension	Information included in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC	None proposed
Hyperkalaemia	Information included in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC	None proposed
Angioedema / hypersensitivity	Information included in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC	None proposed
Neutropenia/Agranulocytosis/Thrombocytopenia	Information included in sections 4.4 and 4.8 of the SmPC	None proposed
Foetotoxicity/ Embryotoxicity/ Use during	Information included in sections 4.3 and	None proposed

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
pregnancy	4.6 of the SmPC	
Myopathy/Rhabdomyolysis	Information included in sections 4.4, 4.5 4.8 and 5.2 of the SmPC	None proposed
Drug-induced hepatitis	Information included in sections 4.2, 4.3 and 4.4 of the SmPC	None proposed
New onset of diabetes in patients with increased risk of diabetes	Information included in sections 4.4 and 4.8 of the SmPC	None proposed
Important potential risk		
Interstitial lung disease	Information included in sections 4.4 and 4.8 of the SmPC	None proposed
Missing information		
Children and adolescents (<18 years old)	Information included in sections 4.2 and 5.1 of the SmPC	None proposed
Lactating women	Information included in sections 4.3 and 4.6 of the SmPC	None proposed
Patients with severe renal impairment	Information included in sections 4.2, 4.4, 4.5 and 5.2 of the SmPC	None proposed
Patients with severe hepatic impairment	Information included in 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

High blood pressure and increased lipid (known as cholesterol and triglycerides) levels are very common co-existing conditions, reaching up to 1 in 5 people in high-income countries. These two conditions are often concomitant to existing coronary heart disease, the most common cause of death in the world. People are at increased risk if they are aged over 55, are overweight, have a family history of cardiovascular disease, are of African descent, have a lack of physical activity, eat a lot of salt, consume excessive amounts of alcohol, are smoking, and/or have high blood sugar levels. The coexistence of high blood pressure and/or existing coronary heart disease with increased blood lipid levels can be associated with wide-ranging complications including angina, stroke, heart failure, heart attack, sudden death and kidney disease. Treatment of all risk factors will generally include lifestyle modifications and medicines to decrease blood pressure and lipid levels, and options depend on the risk of developing complications.

VI.2.2 Summary of treatment benefits

Triveram/ Stapressial provides a combination of well-known medicinal substances, which are used for treatment of high blood pressure, preventin of CV diseases and increased lipid (cholesterol and triglycerides) levels, in a single tablet. The benefit of a single tablet compared to taking each of these products separately (in other words, taking three tablets) is to simplify treatment.

Triveram/ Stapressial contains atorvastatin, a product used to regulate your lipid levels, and two blood-pressure lowering medicines, perindopril and amlodipine. Triveram/ Stapressial is used for

treatment of patients with high blood pressure and/or stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) which also suffer from either elevated cholesterol levels; or elevated cholesterol and triglycerides levels at the same time.

VI.2.3 Unknowns relating to treatment benefits

The populations where experience is limited such as children and adolescents (< 18 years old), lactating women, patients with severe kidney problems, patients with severe hepatic 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**
Low blood pressure (hypotension)	Low blood pressure is a common side effect with perindopril (seen between 1 and 10 patients in 100) and uncommon with amlodipine (seen between 1 and 100 patients in 1000). This may lead to light-headedness, dizziness, fainting. This side effect may also occur with Triveram/ Stapressial.	Yes by following the special warnings and precautions for use and the interactions with other medicinal products.
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 Triveram/ Stapressial.	Yes by following the special warnings and precautions for use and the interactions with other medicinal products.
Swelling of eyelids, face, lips, tongue or throat, which can cause great difficulty in breathing (Angioedema) / hypersensitivity	Swelling of eyelids, face, lips, tongue or throat are uncommon side effects with perindopril (seen between 1 and 10 patients in 1000), which are rarely observed with atorvastatin (seen up to 1 patient in 1000) and very rarely with amlodipine (seen up to 1 patient in 10000). This side effect may also occur with Triveram/ Stapressial.	Yes by monitoring for early symptoms and by following the contraindication for patients with history of angioedema with previous ACE inhibitor therapy and in patients with hereditary or idiopathic angioedema to use Triveram/ Stapressial. In case of swelling, treatment must be immediately discontinued and patient should seek urgent advice from a doctor. Triveram/ Stapressial must not be re-started at any time in patients who

Risk	What is known	Preventability
		have developed swelling.
Changes in blood values such as a lower number of white cells or blood platelets (Neutropenia/Agranulocytosis/ Thrombocytopenia)	Disorders of the blood are very rare side effects with perindopril and amlodipine (seen up to 1 patient in 10000) and are rarely observed with atorvastatin (seen up to 1 patient in 1000). These side effects may also occur with Triveram/ Stapressial.	Yes by following the special warnings and precautions for use. Triveram/ Stapressial 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.
Foetotoxicity/Embryotoxicity of Triveram/ Stapressial used during pregnancy	Triveram/ Stapressial may cause serious harm to baby if used during pregnancy.	Yes by following the contra-indication of Triveram/ Stapressial during pregnancy. You must tell your doctor if you think you are pregnant or if you plan to have a baby.
Pain or weakness in muscles (Myopathy); abnormal muscle breakdown which can lead to kidney problems (Rhabdomyolysis)	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 Triveram/ Stapressial. Concomitant use of medicines increases the risk.	Yes by following the 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.
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 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.	Yes by following the contraindication for patients with history of active liver disease or unexplained persistent abnormal blood tests for liver function, 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

Risk	What is known	Preventability
	Liver disease (hepatitis) is an uncommon side effect of atorvastatin (seen between 1 and 10 patients in 1000), and has been very rarely observed with perindopril and amlodipine (seen up to 1 patient in 10000). Yellowing of the skin and/or eyes (jaundice) is a very rare side effect of amlodipine (seen up to 1 patient in 10000). 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 liver failure (hepatic failure) is a very rare side effect (seen up to 1 patient in 10000) of atorvastatin. Rarely (seen up to 1 patient in 1000), ACE inhibitors have been associated with a syndrome that starts with jaundice and progresses to fulminant death of liver tissue (hepatic necrosis) and (sometimes) death. The mechanism of this syndrome is not understood. These side effects may also occur with Triveram/ Stapressial.	if they have a liver problem and if they regularly drink a large amount of alcohol.
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 Triveram/ Stapressial. 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.

Important potential risks

Risk	What is known	Preventability
Injury to the lung tissue that leads to	Breathing problems including	Yes by following the special

Risk	What is known	Preventability
breathing problems (interstitial lung disease)	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 Triveram/ Stapressial.	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).

Missing information

Risk	What is known
Limited information on use in children and adolescents < 18 years	The efficacy and safety of Triveram/ Stapressial has not been studied in this population.
Limited information on use in lactating women	The efficacy and safety of Triveram/ Stapressial has not been studied in this population.
Limited information on use in patients with severe renal impairment	The efficacy and safety of Triveram/ Stapressial has not been studied in this population.
Limited information on use in patients with severe hepatic impairment	The efficacy and safety of Triveram/ Stapressial 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 Triveram/ Stapressial 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 the 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 Triveram/ Stapressial Risk Management Plan.