Elements for a public summary

VI.2.1 Overview of disease epidemiology

This product is prescribed for the treatment of high blood pressure (hypertension) and/or treatment of stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).
Hypertension or high blood pressure is the disease that affects approximately 1 billion individuals worldwide. As the population ages, the frequency of hypertension is increasing. In the industrialized world approximately 25% of the people has hypertension. This disease and its consequences have been identified as the leading cause of death.
The factors that increase the risk of high bood pressure are smoking, overweight, dietary habits such as increased salt, fat and alcohol intake, if someone in the family had high blood pressure. problems with heart or vessels, diabetes or elevated lipids in blood.

VI.2.2 Summary of treatment benefits

Patients already taking perindopril and amlodipine separately may instead receive only one tablet of this product which contains both ingredients.

It is a combination of two active ingredients, perindopril and amlodipine. Perindopril is an ACE (angiotensin converting enzyme) inhibitor and amlodipine is a calcium antagonist (which belongs to medicines called dihydropyridines). Together they work more easily and makes it easier for your heart to maintain a good blood flow.

VI.2.3 Unknowns relating to treatment benefits

The substances perindopril and amlodipine have been in use for many years. When switching the therapy in patients treated with these two drugs in the form of two pills to one pill with both substances, the expected benefit and safety is expected to be the same. The patients with special conditions, such as kidney disease, heart disease, liver disease, elderly, pregnancy are considered to be well evaluated. There is a lack of studies in children and adolescents however this product is not intended for children and adolescents therefore they should not be treated with it.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Swelling of eyelids, face, lips, tongue or throat, which can cause great difficulty in breathing **(Angioedema)**	Swelling of eyelids, face, lips, tongue or throat are uncommon side effects with perindopril (seen between 1 and 10 patients in 1000) and very rare with amlodipine (seen up to 1 patient in 10000). This side effect may also occur with perindopril/ amlodipine combination medicine. Also patients, concomitantly taking some anticancer medicines	Yes by monitoring for early symptoms. Tell your doctor if you previously experienced angioedema with ACE inhibitor therapy and if you have a diagnosis of hereditary or idiopathic angioedema. In case of swelling, treatment must be immediately discontinued and you should seek urgent advice from a

Risk	What is known	Preventability
	(mTOR inhibitors) may be at increased risk for angioedema.	doctor. Perindopril/amlodipine combination medicine must not be re-started at any time in patients who have developed swelling.
High level of potassium in the blood **(Hyperkalaemia)**	For the function of the body it is important that minerals such as kalium are in appropriate amounts. Usually the body regulates this balance however when we use some drugs that influence the elimination of the minerals (for example non-steroidal anti-inflammatory drugs-NSAIDs), potassium sparing diuretics) or the input of minerals is too high (for example with potassium supplements or potassium-containing salt substitutes), this can cause serious conditions. Especially elderly, diabetic patients or patients with lower function of kidneys are more prone to developing elevated kalium levels in the blood.	Tell your doctor if you are on a salt restricted diet or use salt substitutes which contain potassium. Also tell your doctor if you are taking any other medicines, including non-prescription or food-supplements.
Low blood pressure **(Hypotension)**	In patients with high blood pressure perindopril and amlodipine works by relaxing blood vessels, so that blood passes through them more easily. Each of the active ingredients reduces blood pressure and they work together to control your blood pressure.	Yes, by monitoring for early symptoms. Talk to your doctor or pharmacist if you have severe decrease in blood pressure. Make sure to tell your doctor if you are taking also other medicines for treating high blood pressure.
Changes in blood values **(Decreased blood cell count)**	Decreased count of blood cells have been reported in patients receiving ACE inhibitors. Perindopril should be used with extreme caution in patients with connective tissue disease, immunosuppressant therapy, or treatment with some other medicines (such as allopurinol and procainamide), or a combination of these complicating factors, especially if patients already have kidney problems.	Yes by following the special warnings and precautions for use. You should tell your doctor if you are taking any medicines and if you have connective tissue disorder and/or kidney problems.

Risk	What is known	Preventability
Risk of damage to your baby after 3rd month of pregnancy **(Teratogenicity following exposure during the 2nd and 3rd trimester of pregnancy)**	Treatment with this product should not be started in pregnancy and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.	You must tell your doctor if you think that you are (or might become) pregnant. Your doctor will normally advise you to stop taking perindopril/amlodipine before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of perindopril/amlodipine.
Co-administration with lithium, and NSAIDs	Use of lithium (used to treat mania or depression) with ACE inhibitors is not recommended because reversible increases in serum lithium concentrations have been observed and therefore more toxicity due to lithium (severe nerve damage). Concomitant use of ACE-inhibitors and NSAIDs may result in reduced antihypertensive effect. It can also lead to an increased risk of worsening of kidney function, including possible kidney failure, and an increase in serum potassium, especially in patients with already poor kidney function. The combination should be administered with caution, especially in the elderly.	You should tell your doctor if you are taking lithium or NSAIDs. Concomitant use of lithium and perindopril/amlodipine should be avoided. The doctor will give you the advice how much fluid you must consume in order to be adequately hydrated and maybe he will also consider monitoring of kidney function during the treatment with perindopril/amlodipine.
Kidney problems **(Renal impairment)**	Kidney problems have been seen with perindopril use in between 1 and 10 patients in 1000. Patients with already existing kidney problems and the ones taking some medicines (such as NSAIDs or aliskiren) are at more risk. Additionally, also patients with normal kidney function who are dehydrated and with low blood pressure are more prone to this risk.	Tell your doctor if you have kidney problems or if you are taking any other medicines. The doctor will give you the advice how much fluid you must consume in order to be adequately hydrated and maybe he will also consider monitoring of kidney function during the treatment with perindopril/amlodipine.
Liver problems **(Hepatic impairment)**	Liver problems have been seen with both, perindopril and amlodipine use in in less than 1 patient in 10.000. Rarely, ACE inhibitors have been associated with a syndrome that starts with yellowing of the skin and progresses to severe	You should tell your doctor if you experience yellowing of the skin. Patients receiving ACE inhibitors who develop yellowing of the skin or marked elevations of liver enzymes should discontinue

Risk	What is known	Preventability
	inflammation of the liver and sometimes death. The mechanism of this syndrome is not understood.	the ACE inhibitor and tests for evaluation of liver function is recommended.
Serious skin disorders (e.g. Stevens-Johnson Syndrome)	Severe skin reactions may occur during treatment with perindopril, 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). They have been seen with both amlodipine use in less than 1 patient in 10.000.	Tell your doctor if you ever experienced serious skin reaction due to medicines before. If you experience 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, stop taking the medicine and tell your doctor immediately

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Risk of damage to your baby in first 3 months of pregnancy **(Teratogenicity following exposure during the 1st trimester of pregnancy)**	The safety of perindopril/amlodipine has not been established during the first 3 months. Evidence regarding the risk of exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. You must tell your doctor if you think that you are (or might become) pregnant. Your doctor will normally advise you to stop taking perindopril/amlodipine before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of perindopril/amlodipine.
Co-administration with CYP3A4 inhibitors	Concomitant use of amlodipine with medicines that influence the metabolic pathway of some medicines and their elimination from the body may increase the levels of amlodipine and therefore its effects and side effects.
Excess fluid in the lungs in patients with poor heart function (**Pulmonary oedema in patients with heart failure)**	Pulmonary edema is a condition caused by excess fluid in the lungs. In most cases, heart problems cause pulmonary edema. But fluid can accumulate for other reasons, including pneumonia, exposure to certain medications, trauma to the chest wall, and exercising or living at high elevations. In a study evaluating patients with poor heart function more patients, treated with amlodipine, developed pulmonary oedema than other, who did not receive amlodipine. Consult a doctor immediately if you experience sudden

	wheeziness, chest pain, shortness of breath or difficulty in breathing.

Missing information

Risk	What is known (Including reason why it is considered a potential risk)
Exposure during breastfeeding	Because no information is available regarding the use of perindopril during breastfeeding perindopril/amlodipine is not recommended for mothers who are breastfeeding. Tell your doctor if you are breast-feeding or about to start breast-feeding perindopril/amlodipine is contra-indicated for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.
Use in children and adolescents	Perindopril/amlodipine should not be used in children and adolescents as the efficacy and safety of perindopril and amlodipine, in combination, have not been established in children and adolescents.

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 this product can be found at the agency's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

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

Not applicable, this is the first Risk management plan.