Elements for a public summary

VI.2.1 Overview of disease epidemiology

High blood pressure increases the risk of developing diseases affecting the heart or blood vessels, including coronary heart disease, heart failure, stroke and kidney failure.
Fixed-dose combination of enalapril/lercanidipine is used for the treatment of high blood pressure, a serious and common disorder. In the US, data from the National Health and Nutrition Survey (NHANES) collected in 2003–2004 showed that the proportion of a population found to have high blood pressure was 29.3%. In a sample of large population, the proportion of a population with high blood pressure during the 1990s was 27.6% in the US and Canada and 44.2% in Europe. On average, only 8% of Europeans had controlled high blood pressure, compared with 23% of those in the US. Importantly, high blood pressure is a significant factor in the development of diseases affecting the heart or blood vessels and kidney failure. 26,4% of the adult population in year 2000 had high blood pressure (26,6% of men and 26,1% of women). At young ages the number of cases with high blood pressure is higher in male then in female population. High blood pressure is more common in economically developed countries (37,3%) than in economically developing ones (22,9%).
Blood pressure control is important for improving the negative effect high blood pressure has on the heart and blood vessels. However, according to NHANES data from 1999–2004, only 35.1% of patients had evidence of sufficient controlled high blood pressure. Treatment guidelines show that in addition to lifestyle changes, most patients will need at least two antihypertensive drugs to achieve blood pressure goals. Combination therapy may increase the lowering of high blood pressure and may also result in fewer adverse effects. In addition to these benefits, fixed-dose combinations also make the treatment schedule easier and may be the best option for achieving blood pressure goals in many patients.

VI.2.2 Summary of treatment benefits

The goal of the treatment in patients with high blood pressure is to decrease the long-term risk of diseases affecting the heart or blood vessels and mortality. This is achieved by lowering raised blood pressure and reducing the effects of other diseases affecting the heart and blood vessels, such as diabetes and high levels of lipids in blood (cholesterol). There is strong evidence that control of blood pressure has many benefits, including reductions in the risk of stroke and heart attack, and reduction of kidney impairment in patients with kidney disease.

VI.2.3 Unknowns relating to treatment benefits

Not applicable. This is a generic application. Our SmPC comply with the innovator product regarding indications and adverse events.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions including swelling of the face, lips,	Patients taking this medicine may experience an allergic	Please inform your doctor if you have ever experienced allergic reaction to any

Risk	What is known	Preventability
tongue, throat, hands **(Hypersensitivity reactions, including angioedema)**	reaction, which could be also in the form of swelling of the face, lips, tongue, and throat.	medicine or developed angioedema (oedema of the face, lips, tongue, and/or larynx, hands, and feet). Immediately stop taking the medication if you have any of the following signs or symptoms: swelling of the face, limbs, lips, mucous membranes, tongue, and/or larynx, or shortness of breath and inform your doctor about it.
Increased potassium level in blood **(Hyperkalaemia)**	Increased potassium level was observed in patients on ACE-inhibitors, including enalapril. Risk factors for developing Increased potassium level in blood are kidney failure, diabetes, treatment with potassium-sparing diuretics (for example spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes.	Please inform your doctor if you take potassium-sparing diuretics (for example spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes or if you have history of diabetes, kidney failure. If you do not know if you are taking the above medications, please ask your doctor.
Low blood pressure **(Hypotension)**	This medicine is given to people in order to lower their blood pressure. In some cases it can lower the blood pressure too much.	Please inform your doctor if you experience excessive reduction in blood pressure including excessive fall in blood pressure when standing up, they should stop taking the medicinal product at once and tell the doctor immediately. Alcohol can increase the effect of enalapril/lercanidipine. Patients are therefore advised either to consume no alcohol or to strictly limit their alcohol intake.

Risk	What is known	Preventability
Co-administration of 2 different drugs which affect renin-angiotensin-aldosteron system **(Dual blockade of the renin-angiotensin-aldosterone system (RAAS))**	Changes in kidney function, low blood pressure and high potassium levels have been reported in some individuals who were treated with another medicine which affect renin-angiotensin-aldosteron system.	Yes, by monitoring of biochemical laboratory tests.
Liver damage **(Hepatic impairment)**	Patients taking this medicine may develop fever, chills, tiredness, loss of appetite, stomach pain, feeling sick, yellowing of your skin or eyes (jaundice). These can be signs of liver problems such as hepatitis (inflammation of the liver) or liver damage. Patients should not take this medication if they have severe liver or kidney problems, or if they are undergoing dialysis.	Tell your doctor if you experience any symptoms of liver problems they should stop taking the medicinal product at once and tell their doctor immediately.
Use in patients with renal impairment	Treatment with angiotensin converting enzyme inhibitors, such as enalapril, in some patients with kidney problems has been associated with possible degradation of kidney function. These medications may cause a decrease in kidney function, especially in people who are elderly, have kidney disease, have severe congestive heart failure (CHF), or are taking nonsteroidal anti-inflammatory drugs (NSAIDs) diuretics (water pills), or other medicines affecting the same system as enalapril component of the drug (renin-angiotensin-aldosteron system)	Yes, by monitoring for early symptoms. Tell your doctor if you have any heart problems or problems with your kidneys. Your doctor may need to give you urine tests to monitor your condition (Renal impairment). Also tell your doctor if you are taking any other medicines, including non-prescription or food-supplements.
Drug interactions	Use with certain other medicines can either increase or decrease the effects of enalapril/lercanidipine.	Tell your doctor if you are taking, have recently taken or might take any other medicines. Your doctor may

Risk	What is known	Preventability
	Medicines such as oral antifungals, a certain kind of antibiotics (macrolides) and antivirals may decrease the rate at which the body modifies and eliminates enalapril/lercanidipine and thus may increase its quantity inside the body and induce toxicity. When used together with another drug called cyclosporine (a drug used for preventing the rejec- tion of transplanted organs) enalapril/lercanidipine may increase the levels of this substance in the body and its toxicity and additionally, cyclosporine may increase the quantity of enalapril/lercanidipine. On the other hand, other drugs (such as anticonvulsants) may increase the elimination of enalapril/lercanidipine and decrease the effect of the product.	need to change the dose or take other precautions. In some cases you may have to stop taking one of the medicines.
Risk of damage to your baby after 3rd month of pregnancy **(Fetotoxicity with use in 2nd or 3rd trimester of pregnancy)**	This product is not recommended in early 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 enalapril/lercanidipine before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead if really necessary.

Important potential risks

Risk	What is known
Risk of damage to your baby in first months of pregnancy **(Teratogenicity with use during 1st trimester of**	Enalapril/lercanidipin is not recommended in early pregnancy. The risk of malformations of newborn can not be excluded.

Risk	What is known
pregnancy)	
Increased risk of heart problems in patients with certain type of heart disease **(Increased cardiovascular risk in patient with left ventricular dysfunction and ischaemic heart disease)**	This medicine can cause an increased risk of heart attack in patients who already have a certain type of heart disease. If patients suffer from certain heart diseases they should not take this medicine: - Obstruction to the flow of blood from the left ventricle of the heart, including a narrowing of the main artery of the heart (aortic stenosis). - Chest pain. - Within one month after suffering a heart attack (myocardial infarction).

Missing information

Risk	What is known
Use in children **(Use in paediatric patients)**	The safety and efficacy of this product (containing enalapril and lercanidipine) in children under the age of 18 has not been demonstrated in controlled studies therefore the use of the product in children under 18 years is not recommended.
Use during breastfeeding	Breastfeeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking enalapril/lercanidipine. In the case of an older baby your doctor should advise you on the benefits and risks of taking enalapril/lercanidipine whilst breast feeding, compared with other treatments.
Use in patients with certain type of heart disease **(Use in patients with left ventricular outflow obstruction, untreated congestive heart failure, unstable angina pectoris and within one month of a myocardial infarction)**	There is not enough information about use of enalapril/lercanidipine in patients with certain type of heart disease, including narrowing the aorta(the vessel which goes from the heart), untreated heart failure or chest pain originating from the heart(angina pectoris). There is also not enough information for patients one month after a heart attack.

VI.2.5 Summary of additional 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 (if applicable)

Not applicable. No postauthorisation studies are planned.

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

Table: Major changes to the Risk Management Plan over time

Version	*Date*	*Safety concerns*	*Comment*
2.0	24.9.2014 At time of variation According to Article 31 referrals (Renin-angiotensin-system (RAAS)-acting agents)	The previous term »renal dysfunction as consequence of dual RAAS blockade" was updated to »renal dysfunction, hypotension and hyperkalaemia as consequence of dual RAAS blockade"	Risk Management System (version number 2, date of final sign off: 24.9.2014) was not evaluated and is therefore not accepted.
2.1	5.10.2016	Following risks were **added** as IMPORTANT IDENTIFIED RISKS: - Hypotension - Hepatic impairment - Drug interactions - Fetotoxicity Following were **removed** from important identified risks: - Intestional oedema Following were **changed**: - Hypersensitivity was added to angioedema - Renal dysfunction, hypotension and hyperkalaemia as consequence of dual RAAS blockade was rephrased to Dual blockade of the renin-angiotensin-aldosterone system (RAAS) - Renal failure was rephrased to Use in patients with renal impairment Following risks were **added** as IMPORTANT POTENTIAL RISKS: - Teratogenicity - Increased cardiovascular risk in patient with left ventricular dysfunction and ischaemic heart disease Following risks were **added** in	The risks have been harmonized with reference product.

		MISSING INFORMATION: - Use during breastfeeding - Use in patients with left ventricular outflow obstruction, untreated congestive heart failure, unstable angina pectoris and within one month of a myocardial infarction Following risks were **changed**: - Use in children and adolescents was rephrased to Use in paediatric patient	