EU RISK MANAGEMENT PLAN (EU – RMP)

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Enalapril/lercanidipine is a fixed combination of an ACE inhibitor (enalapril) and a calcium channel blocker (lercanidipine), two medicines that lower blood pressure.

High blood pressure (hypertension)

Overall, approximately 20% of the world's adults are estimated to have high blood pressure. The frequency of people with high blood pressure dramatically increases in patients older than 60 years. In many countries, 50% of the population older than 60 years have high blood pressure. Until age 45 years, a higher percentage of men than women have high blood pressure; from age 45 years onward, the percentages are nearly equal between men and women. In women, those who use oral contraceptives, particularly obese and older women, have a 2- to 3-fold higher risk of developing high blood pressure than women not using this medication. Globally, black adults have among the highest rates of high blood pressure.

VI.2.2 Summary of treatment benefits

Enalapril/lercanidipine has been tested in several clinical trials worldwide to be effective for the treatment of high blood pressure.

The main measure of effectiveness in all the studies was the number of patients who had a complete or partial response to treatment.

In one study lercanidipine/enalapril 10mg/10mg once daily significantly reduced sitting blood pressure in patients with mild to moderate high blood pressure who had previously not responded to 4 weeks' treatment with lercanidipine. In a similarly designed trial, lercanidipine/enalapril 10mg/20mg once daily was significantly more effective than enalapril 20mg once daily in high blood pressure patients who had previously not responded to enalapril treatment on its own. Lercanidipine/enalapril was generally well tolerated, any unfavourable reactions were similar to that of either the individual drugs alone or the dummy pill (placebo). Cough was reported in ≤5.2% of patients and swelling of the limbs (peripheral oedema) in <or=1.5% of lercanidipine/enalapril recipients.

Another study was conducted in 100 centres across seven countries. The aim was to look at patients blood pressures at home and at work whilst they were being treated with different combinations of lercanidipine and enalapril. Patients were given a 10-week treatment with a dummy pill (placebo), lercanidipine (10 or 20mg), enalapril (10 or 20mg) or the lercanidipine/enalapril combination. A marked 'placebo effect' was observed on office but not on home blood pressure. Combination therapy was superior to the dummy pill (placebo) at all doses for both office and home blood pressure. The greatest positive effect was observed in the lercanidipine 20mg/enalapril 20mg group. This combination was associated with less cough, abnormal heart beat (palpitations) and leg swelling (oedema) than enalapril or lercanidipine alone (monotherapies), with no increased rate of dizziness or low blood pressure.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, enalapril/lercanidipine can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

However as stated in the proposed SmPC, safety in patients who have recently undergone renal transplantation and use during breast feeding has not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions (Severe Hypersensitivity Reactions (anaphylaxis or anaphylactoid reactions) and / angioedema	Patients taking this medicine may experience an allergic reaction in the form of swelling of the face, lips, tongue, and throat.	Patients should not take this medicine if they are allergic to enalapril or lercanidipine or any of the other ingredients of this medicine. Or if they are allergic to medicines closely related to enalapril/lercanidipine (e.g. amlodipine, felodipine, nifedipine, captopril, fosinopril, lisinopril, ramipril). Patients should not take this medicine if they have ever developed swelling of the face, lips, tongue, and/or throat, hands, and feet), either hereditary in type or after previous treatment with this type of medicine (ACE-inhibitor). Or if they have a hereditary tendency to tissue swelling or if you develop tissue swelling of unknown cause (hereditary or idiopathic angioedema). If patients experience any of the symptoms of an allergic reaction they should stop taking the medicinal product at once and tell their doctor immediately.
Kidney damage (Acute renal impairment)	This medicine can cause kidney problems. This is an uncommon side effect (may effect up to 1 in 100 people).	Patients should not take this medication if they have severe liver or kidney problems, or if they are undergoing dialysis.
Low blood pressure (Symptomatic 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.	If patients 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.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
High blood potassium levels	Increased potassium levels in the blood is a common side effect with this medicine (it may affect up to 1 in 10 people). This is more likely

(Hyperkalaemia)	if patients use potassium-sparing diuretics (spironolactone) or potassium supplements. Patients should talk to their doctor before taking enalapril/lercanidipine if they are at risk of an elevation of the potassium level in their blood. The doctor may check the amount of electrolytes (e.g. potassium) in the patient's blood at regular intervals.
Liver damage (Hepatotoxicity)	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. If patients experience any symptoms of liver problems they should stop taking the medicinal product at once and tell their doctor immediately.
Reduction in white blood cells, platelets and red blood cells (Neutropenia/agranulocytosis/ thrombocytopenia/anaemia)	Use of this medicine can cause reduction in the number of certain blood cells. This occurs rarely (may effect up to 1 in 1000 people). Patients should talk to their doctor before taking enalapril/lercanidipine if their white blood cells are reduced to various degrees (leucopenia, agranulocytosis), possibly resulting in susceptibility to infection and severe general symptoms.
Use with certain other medications and food/drink (Drug-drug interactions)	Use with certain other medicines can either increase or decrease the effects of enalapril/lercanidipine. Patients should not take this medicine if they are simultaneously using a medicine known as cyclosporin or ciclosporin or together with grapefruit or grapefruit juice.
Use during pregnancy	Studies have not been conclusive regarding the risk of birth defects when this medicine is taken during the first trimester of pregnancy, however a small risk cannot be excluded. Treatment should not be initiated during pregnancy. Unless continued treatment is considered essential, 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 should be stopped immediately, and, if appropriate, alternative therapy should be started.
Increased risk of heart problems in patients with certain type of heart disease (Increased cardiovascular toxicity in patients with 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). Patients should talk to their doctor before taking this medicine if they suffer from heart disease involving interruption of blood flow (ischaemia).

Missing information

Risk	**What is known**
Use in patients who have recently undergone kidney (renal) transplantation	The safety of this product when used in patients who have recently undergone a kidney transplant has not been established. Talk to your doctor or pharmacist if you have a kidney problem including kidney transplantation.
Use during breast feeding	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. Tell your doctor if you are breast feeding or about to start breast feeding.

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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

There are no studies in the post authorisation development plan.

VI.2.7 Summary of changes to the risk management plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	**Date**	**Safety Concerns**	**Comment**
Version 1	Under Review	Important Identified Risks: • Renal impairment • Hepatic impairment • Hypersensitivity/ angioedema and anaphylactoid reactions • Left ventricular dysfunction and ischaemic heart disease • Co administration with: strong CYP3A4 inhibitors/inducers, ciclosporin, grapefruit juice. • Dual blockade of the renin-angiotensin-aldosterone system (RAAS) • Concomitant use with lithium • Symptomatic hypotension • Sick sinus syndrome • Renovascular hypertension • Neutropenia/agranulocytosis/thrombocytopenia/anaemia • Cough • Hyperkalaemia • Pregnancy and lactation • Use in diabetic patients • Steven-Johnson syndrome and Toxic Epidermal Necrolysis Important potential risks: • Ethnic differences Missing information • Use in patients < 18 years old • Use in patients who have recently undergone renal transplantation	N/A

Version	Date	Safety Concerns	Comment
Version 1.1	Under review	Important Identified Risks: • Renal impairment • Hepatic impairment • Hypersensitivity/ angioedema and anaphylactoid reactions • Left ventricular dysfunction and ischaemic heart disease • Co administration with: strong CYP3A4 inhibitors/inducers, ciclosporin, grapefruit juice. • Symptomatic hypotension • Neutropenia/agranulocytosis /thrombocytopenia/anaemia • Hyperkalaemia • Foetotoxicity and neonatal toxicity Important potential risks: • Teratogenicity Missing information: • Use in patients < 18 years old • Use in patients who have recently undergone renal transplantation • Use during breast feeding	Amended following RMS day 70 preliminary assessment report
Version 1.2	Under review	Important Identified Risks: -Acute Renal impairment -Severe Hypersensitivity Reactions (anaphylaxis or anaphylactoid reactions) and angioedema -Symptomatic hypotension Important potential risks: -Hyperkalaemia -Hepatotoxicity - Neutropenia/agranulocytosis /thrombocytopenia/anaemia	Amended following RMS day 120 preliminary assessment report

Version	Date	Safety Concerns	Comment
		-Drug-drug interactions -Use during pregnancy -Increased cardiovascular toxicity in patients with ischaemic heart disease Missing information: -Use in patients who have recently undergone renal transplantation -Use during pregnancy	