Risk Management Plan

Active substance: Enalapril/Lercanidipine

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Hypertension is generally defined as blood pressure higher than 140/90 mmHg.
Hypertension may be classified as primary or secondary. Primary hypertension is also called essential and does not have an identifiable cause that may be treated in order to control blood pressure. Primary hypertension accounts for the great majority of cases (over 90 percent) and develops as a combination of environmental and genetic factors.
Overall, around the world, one in every five persons suffers from hypertension. The numbers increase with age so that over 60 years, almost a half of the world's population may be classified as hypertensive.

Before the age of 45, more men than women suffer from hypertension. However, from 45 years onward, the proportions become nearly equal between sexes.
Globally, black adults have among the highest rates of hypertension and on average, develop the condition earlier in life than white persons. (Madhur, 2014)

VI.2.2 Summary of treatment benefits

The efficacy of the fixed combination of enalapril and lercanidipine was evaluated in two clinical trials, in patients with hypertension who did not respond to treatment with lercanidipine alone or enalapril alone. Patients treated with monotherapy were divided into two groups in each of the two trials. One group was switched to the fixed-combination while the other group was treated with the same monotherapy agent they did not respond to.
In the first trial, the fixed combination was more effective than lercanidipine monotherapy in decreasing blood pressure. Significant decreases in blood pressure occurred after two weeks of treatment and were maintained through the 12 weeks of study. Also, a significant greater proportion of patients treated with the fixed combination had normalized blood pressure as compared to those treated with lercanidipine alone.
Similar results were obtained in the second trial that compared the fixed combination with enalapril alone. In a separate analysis of a subgroup of elderly patients (older than 60 years), it was observed that the fixed combination significantly decreased diastolic blood pressure at 12 weeks but the changes in systolic blood pressure were not significant.

VI.2.3 Unknowns relating to treatment benefits

According to the SmPC, there is limited information regarding enalapril/lercanidipine use in children and in patients who have recently undergone renal transplant. Based on the current knowledge, renal impairment increases the exposure to enalapril and enalaprilat in a degree correlated with the severity of the impairment. For this reason enalapril/lercanidipine is contraindicated in patients with severe renal impairment and caution is indicated when administering it to patients with mild to moderate renal dysfunction. These data would indicate that in

case of impaired renal function after transplant, the efficacy of the combination would in- crease to toxicity and not decrease. Treatment in this subpopulation is not recommended.
The prevalence of hypertension increases with age and is thus low in children. This is why this subpopulation is considered to represent a small part of the target population. However, before more data are collected and evaluated, treatment is not recommended in children.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reactions (Anaphylaxis, Anaphylactoid Reactions) and Angioedema (a swelling similar to hives but that is located in deeper layers of the skin or of mucous membranes such as that of the throat or gut)	In rare instances some patients have had severe allergic reactions after taking ACE inhibitors including enalapril. One kind of such allergic reaction is called angioedema and involves the swelling of tissue under the skin. If this reaction involves swelling in the throat area it may be fatal and it is regarded a medical emergency. The reaction may resolve without treatment or in some cases anti-allergic medication may help relieve the symptoms. Black patients are more frequently affected by angioedema.	Severe allergic reactions may be prevented by avoiding enalapril/lercanidipine in patients at risk (several risk factors are described in the product information). The product is contraindicated for patients with a history of angioedema or hypersensitivity to the active substances.

Risk	What is known	Preventability
	Other severe allergic reactions may occur when enalapril containing medicines are administered to patients who are under treatment for the relief of effects of allergy to insect bites or are under dialysis or LDL apheresis (removal of certain toxins from the blood with the help of a machine).	
Kidney disease (acute renal impairment)	There are reports of patients whose kidneys have failed during treatment with ACE inhibitors including enalapril. This may happen especially in patients with risk factors such as: severe heart failure (the heart cannot pump enough blood), renal artery stenosis (narrowing of the vessel supplying the kidney with blood) or concomitant treatment with diuretics (drugs that stimulate urination). Kidney failure has rarely been observed when drugs related to enalapril (ACE inhibitors) are administered in combination with NSAIDS (pain medication such as ibuprofen). A functional kidney is important for the elimination of enalapril.	If kidney function is monitored and kidney failure is promptly diagnosed and treated it is usually reversible.
Severe drops in blood pressure (symptomatic hypotension)	In certain patients, blood pressure may drop excessively. Such patients are those with a low blood volume, those with heart failure or those taking a combination of several antihypertensive drugs. Patients who have ischemic heart or cerebrovascular disease (a build-up of material on the inside walls of blood vessels that feed the heart or the brain with blood) may suffer heart attack or stroke if their blood pressure falls too steeply.	Blood pressure should be monitored especially in patients at risk in order to be able to modify doses and avoid severe drops in blood pressure. Enalapril/lercanidipine is also contraindicated in patients suffering from untreated heart failure or unstable angina pectoris (a sensation of chest pain or pressure that is the result of ischemic heart disease and may happen even when the patient is at rest).

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Abnormally high levels of po-	An increase in serum potassium levels has been observed in

Risk	What is known (Including reason why it is considered a potential risk)
tassium in the blood (Hyperkalaemia)	patients treated with ACE inhibitors. Patients with impaired kidney function, those with diabetes or those who take drugs or eat food that may increase potassium levels (some diuretics, salt substitutes etc.) are at increased risk. An increase in blood potassium levels has also been observed in some patients treated with a combination of two or more anti-hypertensive drugs with related mechanism of action known as renin-angiotensin-aldosterone system blockers (enalapril is one such drug).
Liver toxicity (Hepatotoxicity)	In rare cases ACE inhibitors (such as enalapril) have been reported to cause severe diseases of the liver. The first signs are the development of jaundice (a yellow discoloration of the skin and whites of the eyes) but the condition evolves rapidly with the death of hepatic cells and in severe cases it ends with the death of the patient.
Changes in the number of blood components (Blood dyscrasias)	Decreases in the number of certain blood cells have been observed during treatment with ACE inhibitors. The activities of these cells include protecting the body against infections, blood coagulation and carrying oxygen to tissues. The risk may be increased in some situations such as: treatment with certain medications (drugs that inhibit the immune system, a drug used for heart rhythm disorders named procainamide etc.), impaired kidney function or certain diseases where the immune system attacks other cells of the body (these are called autoimmune disorders).
Interactions with other drugs that can modify the way enalapril/lercanidipine is eliminated from the body (drug-drug interactions)	Medicines such as oral antifungals, a certain kind of antibiotics (macrolides) and antivirals may decrease the rate at which the body modifies and eliminates lercanidipine and thus may increase its quantity inside the body and induce toxicity. When used together with another drug called cyclosporine (also called ciclosporin, a drug used for preventing the rejection of transplanted organs) lercanidipine may increase the levels of this substance in the body while cyclosporine may increase the quantity of lercanidipine. On the other hand, other drugs (such as anticonvulsants) may increase the elimination of lercanidipine and decrease the effect of the product.
Use under pregnancy	Evidence from studies including cases of pregnant women who have taken medicines containing ACE inhibitors (drugs related to enalapril) during their first 3 months of pregnancy is not conclusive. However, harmful effects cannot be completely excluded. Use of ACE inhibitors (drugs related to enalapril) by pregnant women from the third month of pregnancy onward, is known to have harmful effects on the unborn baby (the foetus). Such effects that have been described are: a decreased kidney function, a decreased quantity of amniotic fluid (a liquid that surrounds the unborn baby and helps it develop), problems with the formation of the skull. Toxic effects can also be apparent later in the life of the newborn. These are kidney failure, low blood pressure or increased plasma potassium

Risk	What is known (Including reason why it is considered a potential risk)
	levels.
Increased risk of heart attack in patients suffering from heart disease involving an interruption of blood flow.(increased cardiovascular toxicity in patients with ischaemic heart disease)	In patients suffering from heart disease involving an interruption of blood flow, an excessive fall in blood pressure may trigger a heart attack. Such adverse events have been reported for enalapril and thus are expected for the combination of enalapril and lercanidipine.

Missing information

Risk	What is known
Use during breastfeeding	Limited pharmacokinetic data demonstrate very low concentrations of enalapril and enalaprilat in breast milk. These concentrations seem to be clinically irrelevant. The excretion of lercanidipine in human milk is unknown.

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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for enalapril/lercanidipine.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	16-12-2014	<u>Identified</u> Severe Hypersensitivity Reactions (Anaphylaxis or Anaphylactoid reactions) and Angioedema Acute renal impairment Hyperkalaemia Blood Dyscrasias Symptomatic hypotension Hepatotoxicity Risks related to the use during the second and third trimesters of pregnancy <u>Potential</u> Risks related to the use during the first trimester of pregnancy	First version

Version	Date	Safety Concerns	Comment
		Missing information Use in children Use during breastfeeding	
2.0	15-05-2015	Identified Severe Hypersensitivity Reactions (Anaphylaxis or Anaphylactoid reactions) and Angioedema Acute renal impairment Hyperkalaemia Blood Dyscrasias Symptomatic hypotension Hepatotoxicity Foetotoxicity and neonatal toxicity following exposure during the second and third trimesters of pregnancy Drug/drug interactions with CYP3A4 inducers and inhibitors and cyclosporine Potential Teratogenicity following exposure during the first trimester of pregnancy Increased cardiovascular risk in patients with ischemic heart disease Missing information Use during breastfeeding	Updated version in response to Day 70 AR for procedure DK/H/2472/001-002/DC. The safety concern: “risks related to the use during the second and third trimesters of pregnancy” was renamed “foetotoxicity and neonatal toxicity”. The safety concern: “risks related to the use during the first trimester of pregnancy” was renamed “teratogenicity”. The identified important safety concern “drug/drug interactions with CYP3A4 inducers and inhibitors and cyclosporine was added. The potential important safety concern “increased cardiovascular risk in patients with ischaemic heart disease” was added. The missing information regarding the use of enapril/lercanidipine in children has been excluded as the use in this subpopulation for hypertension is considered irrelevant.
3.0	21-10-2015	Identified Severe Hypersensitivity Reactions (Anaphylaxis or Anaphylactoid reactions) and Angioedema Acute renal impairment Symptomatic hypotension Potential Hyperkalaemia Hepatotoxicity Blood dyscrasias	The summary of safety concerns was updated in accordance with Day 120 RMS AR (DK/H/2472/001-002/DC).

Version	Date	Safety Concerns	Comment
		Drug-drug interactions Use under pregnancy Increased cardiovascular toxicity in patients with ischaemic heart disease Missing information Use during breastfeeding	