VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Product therapeutic indications:

Myocardial infarction is the medical term for an event commonly known as a heart attack. It happens when blood stops flowing properly to part of the heart and the heart muscle is injured due to not receiving enough oxygen. In the other hand, ***systolic dysfunction*** occurs when the heart muscle doesn't contract with enough force, so there is less oxygen-rich blood that is pumped throughout the body.

Myocardial infarction is a common presentation of ischemic heart disease/coronary artery disease. The World Health Organization estimated in 2004, that 12.2% of worldwide deaths were from ischemic heart disease; with it being the leading cause of death in high- or middle-income countries. More than 20 million people have heart failure worldwide. The number of cases occurred heart failure as well as the number of new cases each year, are increasing, mostly because of increasing life span, but also because of increased prevalence of risk factors (hypertension, diabetes, dyslipidemia, and obesity) and improved survival rates from other types of cardiovascular disease (myocardial infarction, valvular disease, and arrhythmias).

In the United States, heart failure affects 5.8 million people, and each year 550,000 new cases are diagnosed. In 2011, congestive heart failure was the most common reason for hospitalization for adults aged 85 years and older, and the second most common for adults aged 65–84 years. Heart failure is much higher in African Americans, Hispanics, Native Americans and recent immigrants from the eastern bloc countries like Russia. This high prevalence in these ethnic minority populations has been linked to high incidence of diabetes and hypertension.
Men have a higher incidence of heart failure, but the overall prevalence rate is similar in both sexes, since women survive longer after the onset of heart failure

VI.2.2 Summary of treatment benefits

Eplerenone lowers blood pressure by blocking the body's receptors for the hormone aldosterone. Aldosterone is produced by the adrenal glands, and it makes the body hold on to sodium and water. As a result, the amount of fluid in your body increases, and blood pressure increases too. By keeping body tissue from receiving aldosterone, eplerenone lowers blood pressure and helps the heart pump blood more effectively with less effort.

Eplerenone effectively reduces blood pressure compared with agents such as spironolactone, enalapr il, losartan, and amlodipine. Different studies between eplerenone and spironolactone revealed that b oth medicines are safe and effective. However, spironolactone is usually used in combination with o ther drugs, than eplerenone may be used alone or in combination regimens. Spironolactone is associ ated with a well-established risk of sexual side effects that are dose and duration dependent. In contr ast, eplerenone is associated with no or very low incidence of sexual side effects. Sexual side effects of drugs are of particular concern because patients are typically unwilling to tolerate these effects, a nd sexual dysfunction is a major reason for noncompliance among hypertensive patients. Moreover, the most important adverse event been occurred with eplerenone is hyperkalemia (concentration of t he electrolyte potassium (K+) in the blood is elevated) that is dose dependent. The same adverse eve

nt occurred also with spironolactone. However, available evidence suggests that the risk is lower wit h eplerenone than spironolactone when the drugs are administered at recommended doses

VI.2.3 Unknowns relating to treatment benefits

The treatment remains unknown for children and adolescents due to lack of data in this age group.

There are no adequate data on the use of eplerenone in pregnant women. Moreover, it is unknown if eplerenone is excreted in human breast milk after oral administration.

The use of eplerenone in patients with severe hepatic impairment has not been evaluated and its use is therefore contraindicated.

VI.2.4 Summary of safety concerns

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Patients known to be allergic to eplerenone or excipients of the medicinal product *(Hypersensitivity)*	Some patients may have the side effects such as swollen face, tongue or throat, difficulty of swallowing hives and difficulties breathing	Yes, by discontinuation of the treatment and immediate medical consultation.
Heart attack *(Myocardial infarction)*	Heart attack may be occurred with a frequency >1/100 of patients been treated with eplerenone. In a clinical study has been found that myocardial infarction such as adverse event had an incidence of 2.6% of subjects in the eprelerone treatment and was more frequent than in placebo treated group of subjects. (EMPHASIS-HF study: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)	Yes, by discontinuation of the treatment following physician advice
Elevated concentration of the electrolyte potassium (K+) in the blood *(Hyperkalemia (furthermore increased by co-administration with potassium-sparing diuretics, potassium-supplements or strong inhibitors of CYP 3A4 as well as combination with an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB))*	Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage. Thereafter, periodic monitoring is recommended especially in patients at risk for the development of hyperkalaemia, such as (elderly) patients, patients with renal insufficiency and patients with diabetes. The use of potassium supplements after	Yes, by reduction of dosage. Physician should be aware on the other medicinal products administered to the patient

	initiation of eplerenone therapy is not recommended, due to an increased risk of hyperkalaemia The risk of hyperkalaemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB). The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone should not be used.	
Patients with severe kidney disease *(Renal impairment)*	Potassium levels should be monitored regularly in patients with severe kidney disease, including diabetic microalbuminuria (urine albumin). The risk of increased concentration of potassium (K+) in the blood rises with decreasing renal function. There is no experience in patients with creatinine clearance (CrCl0 <50 ml/min with post myocardial infarction heart failure. The use of eplerenone in these patients should be done cautiously. In patients with severe renal impairment (CrCl <30 ml/min) the use of eplerenone is contraindicated. Eplerenone is not removed by haemodialysis.	Yes, by closely monitoring of potassium level in the blood. Physician, based on creatinine clearance values will decide if eplerenone may be administered
Itching *(Pruritus)*	Pruritus may be occurred with a frequency >1/100 of patients been treated with eplerenone.	Yes, by discontinuation of the treatment following physician advice

	In a clinical study has been found that myocardial infarction such as adverse event had an incidence of 2.1% of subjects in the eprelerone treatment and was more frequent than in placebo treated group of subjects (EMPHASIS-HF study: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)	

Important potential risks	
Risk	**What is known (Including reason why it is considered a pote ntial risk)**
Rash	Rash is an adverse event occurring with an incidence <2% of subjects treated with eplerenone and was found more frequent that in the placebo group of patients in two studies, the EMPHASIS-HF Study and the EPHESUS Study (EMPHASIS-HF Study: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS Study: Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study
Decreased efficacy if co-administered with CYP3A4 inducers (such as rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort)	St John's Wort (herbal medicinal product), rifampicin (used to treat bacterial infections), carbamazepine, phenytoin, and phenobarbital (used, among others, to treat epilepsy) may increase the break-down of [Eplerenone] and thus decrease its effect.
Increased hypotensive effect and/or postular hypotension if combined with alpha 1-blockers (e.g prazosin, alfuzosine), tricyclic anti-depressants, neuroleptics, amifostine and baclofen	Combined administration of enalapril with drugs such as those mention below, may lead to a fall in blood pressure and dizziness upon standing. • Alpha I blockers, like prazosin or alfuzosin (used to treat high blood pressure and particular prostate conditions). • Tricyclic antidepressants like amitryptyline or amoxapine (for treatment of depressions), antipsychotics (also known as neuroleptics) such as chlorpromazine or haloperidol (for the treatment of psychiatric disorders), amifostine (used during cancer chemotherapy) and baclofen (used to treat muscle spasm). • Glucocorticoids, such as hydrocortisone or prednisone (used to treat inflammation and certain skin conditions) and tetracosactide (mainly used for diagnosing and treating disorders of the adrenal cortex).

Important missing information	
Risk	**What is known**
Use in paediatric population	There are no data to recommend the use of eplerenone in the paediatric population, and therefore, use in this age group is not recommended.
Use in pregnancy and lactation	Preclinical studies on safety pharmacology, genotoxicity, carcinogenic potential and toxicity to reproduction revealed no special hazard for humans. In repeated dose toxicity studies, prostate atrophy was observed in rats and dogs at exposure levels slightly above clinical exposure levels. The prostatic changes were not associated with adverse functional consequences. The clinical relevance of these findings is unknown. However, caution should be exercised prescribing eplerenone to pregnant women It is unknown if eplerenone is excreted in human breast milk after oral administration. However, preclinical data show that eplerenone and/or metabolites are present in rat breast milk and that rat pups exposed by this route developed normally. Because of the unknown potential for adverse effects on the breast fed infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.
Patients with severe liver disease *(Severe hepatic insufficiency)*	In patients with mild to moderate hepatic impairment (Child Pugh class A and B), no elevations of serum potassium above 5.5 mmol/L were observed However, potassium levels should be monitored in patients with mild to moderate hepatic impairment. The use of eplerenone in patients with severe hepatic impairment has not been evaluated and its use is therefore contraindicated.

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

Not applicable