PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

VI.1 Summary of activities in the risk management plan

The summary below was prepared based on the information included in Part II, IV and V of the present document.

Summary of safety concerns	
Important identified risks	• Hyperkalemia Renal impairment
Important potential risks	N/A
Missing information	• Use in children and adolescents • Use in patients who are pregnant or breast-feeding

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Hyperkalemia	Warning concerning hyperkalemia may be occurred with eplerenone, is already included in *sections 4.2, 4.3, 4.4* and *4.8* of the SmPC. Warning on the increased risk of hyperkalemia when eplerenone is co-administered 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), is also included in *sections 4.4* and *4.5* of the SmPC. In addition it is listed in *section 2* of the	None proposed

	PL (risk communication to reduce the incidence of it) *Other routine risk minimisation measures:* Prescription only medicine	
Renal impairment	Warning concerning use of eplerenone in patients with severe renal insufficiency (eGFR <30 mL per minute per 1.73 m2), is already included in *sections 4.2, 4.3, 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *3* of the PL (risk communication to reduce the incidence of it) *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Use in children and adolescents	Information on the lack of data of eplerenone use in children and adolescents is already included in *section 4.2* of the SPC. In addition, referred to under *sections 2* and *3* of PL (risk communication to reduce the incidence of) *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Use in patients who are pregnant or breast-feeding	Information on the lack of data on the use of eplerenone during pregnancy and breast-feeding, already included in *section 4.6* of the SPC. In addition, referred to under *section 3* of PL (risk communication to reduce the incidence of) *Other routine risk minimisation measures*: Prescription only medicine	None proposed

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 heart attack /coronary artery disease. The World Health Organization estimated in 2004, that 12.2% of worldwide deaths were from heart attack; 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, elevation of plasma cholesterol, triglycerides, 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, enalapril, losartan, and amlodipine.
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**
Elevated concentration of the electrolyte potassium (K+) in the blood *(Hyperkalemia*	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 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.	Yes, by reduction of dosage. Physician should be aware on the other medicinal products administered to the patient
Patients with severe kidney disease	Potassium levels should be monitored regularly in	Yes, by closely monitoring of potassium level in the

(Renal impairment)	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.	blood. Physician, based on creatinine clearance values will decide if eplerenone may be administered

Important missing information	
Risk	**What is known**
Use in children and adolescents	There are no data to recommend the use of eplerenone in children and adolescents, and therefore, use in this age group is not recommended.
Use in patients who are pregnant or breast-feeding	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.

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

VI.2.A Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	27.01.2014	**Important identified risks** • Hypersensitivity to the active substance or to any of the excipients • Myocardial infarction • 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)) • Renal impairment • Severe hepatic insufficiency • Pruritus **Important potential risks** • Rash • Decreased efficacy if co-administered with CYP3A4 inducers (such as rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) • Increased hypotensive effect and/or postular hypotension if combined with alpha 1- blockers (e.g prazosin, alfuzosine), tricyclic anti-depressants, neuroleptics,	Initial version

		amifostine and baclofen **Missing information** • Use in paediatric population • Use in pregnancy and lactation	
2.0	14.05.2014	**Important identified risks** • Hypersensitivity • Myocardial infarction • 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)) • Renal impairment • Pruritus **Important potential risks** • Rash • Decreased efficacy if co-administered with CYP3A4 inducers (such as rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) • Increased hypotensive effect and/or postular hypotension if combined with alpha 1- blockers (e.g prazosin, alfuzosine), tricyclic anti-depressants, neuroleptics, amifostine and baclofen **Missing information** • Use in paediatric population • Use in pregnancy and lactation • Severe hepatic insufficiency	Day 40 – Deficiency letter answers
3.0	07.11.2017	**Important identified risks** • Hyperkalemia • Renal impairment **Important potential risks** • N/A **Missing information** • Use in patients who are pregnant or breast-feeding	Renewal

		• Use in children and adolescents	

PART VII: ANNEXES

Table of contents