Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the EPAR

According to module V of the Guideline on Good Pharmacovigilance Practices the RMP summary of a generic application should be based on the public RMP summary of the reference medicinal product. To the best of the applicant´s knowledge, there is no public RMP summary of the reference medicinal product available.

VI.1.1 Summary table of Safety concerns

Table 4: *Summary of* Safety concerns

Summary of safety concerns	
Important identified risks	• Hyperkalemia • Hypotension • Hypersensitivity • Renal dysfunction as a consequence of dual renin-angiotensin-aldosterone system (RAAS) blockade • Foetotoxicity
Important potential risks	• Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with cardiac/cardiovascular disorders • Rhabdomyolysis • Drug-drug interaction with NSAIDs and lithium
Missing information	• Safety in the first trimester of pregnancy • Use during breastfeeding • Use in patients with severe hepatic impairment • Use in patients with recent kidney transplantation • Use in paediatric population: - Children <6 years of age - Paediatric patients with renal impairment (GFR <30 mL/min/1.73 m^2) - Paediatric patients with hepatic impairment

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Table 5: *Summary table of risk minimization measures*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hyperkalemia	Warnings and precautions for use in the section 4.4 “Special warnings and precautions for use”. Listed in the Section 4.8 “Undesirable effects”. Prescription only medicine.	Not applicable.
Hypotension	Warnings in sections 4.4 “Special warnings and precautions for use”, 4.5 “Interaction with other medicinal products and other forms of interaction”, and 4.9 “Overdose”. Listed in the Section 4.8 “Undesirable effects”. Prescription only medicine.	Not applicable.
Hypersensitivity	Hypersensitivity to the active substance or excipients contraindication in section 4.3 “Contraindications”. Warning for patients with a history of angioedema in the section 4.4 “Special warnings and precautions for use”. Listed in the Section 4.8 “Undesirable effects”. Prescription only medicine.	Not applicable.
Renal dysfunction as a consequence of dual renin-angiotensin-aldosterone system (RAAS) blockade	Contraindication for concomitant use of losartan with aliskiren-containing products is in patients with diabetes mellitus or renal impairment is given in the section 4.3 “Contraindication”. Warnings in sections 4.4 “Special warnings and precautions for use”, and 4.5 “Interaction with other medicinal products and other forms of interaction” that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of decreased renal function. Observations from clinical trials are given in the section 5.1 “Pharmacodynamic properties”. Prescription only medicine.	Not applicable.
Foetotoxicity	Contraindication in 2nd and 3rd trimester of pregnancy is given in the section 4.3 “Contraindications”. Warnings are given in the sections 4.4 “Special warnings and precautions for use”, and 4.6 “Fertility, pregnancy and lactation”. Prescription only medicine.	Not applicable.
Important potential risks		
Use in patients with hepatic	Instructions for use in patients with hepatic impairment is given in the section 4.2 “Posology and method of	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
impairment	administration". Contraindication for use in Severe hepatic impairment is given in the section 4.3 "Contraindications". Warning in the sections 4.4 "Special warnings and precautions for use". Pharmacokinetic properties of losartan in patients with mild to moderate alcohol-induced hepatic cirrhosis is given in section 5.2 "Pharmacokinetic properties". Prescription only medicine.	
Use in patients with renal impairment	Warnings in the sections 4.4 "Special warnings and precautions for use", and 4.5 "Interaction with other medicinal products and other forms of interaction". Listed in the section 4.8 "Undesirable effects" Pharmacokinetic properties of losartan are listed in the section 5.2 "Pharmacokinetic properties". Prescription only medicine.	Not applicable.
Use in patients with cardiac/cardiovascular disorders	Precautions for use are given in the section 4.4 "Special warnings and precautions for use". Prescription only medicine.	Not applicable.
Rhabdomyolysis	Listed in the section 4.8 "Undesirable effects" Prescription only medicine.	Not applicable.
Drug-drug interaction with NSAIDs and lithium	Warnings for potential interactions are given in the section 4.5 "Interaction with other medicinal products and other forms of interaction". Prescription only medicine.	Not applicable.
Missing information		
Safety in the first trimester of pregnancy	Warnings are given in the sections 4.4 "Special warnings and precautions for use", and 4.6 "Fertility, pregnancy and lactation". Prescription only medicine.	Not applicable.
Use during breastfeeding	Warning that losartan is not recommended during breastfeeding is given in the section 4.6 "Fertility, pregnancy and lactation" Prescription only medicine.	Not applicable.
Use in patients with severe hepatic impairment	Instructions for use in patients with hepatic impairment is given in the section 4.2 "Posology and method of administration". Contraindication for use in Severe hepatic impairment is given in the section 4.3 "Contraindications". Warning in the sections 4.4 "Special warnings and precautions for use". Prescription only medicine.	Not applicable.
Use in patients with recent kidney transplantation	Warning in the sections 4.4 "Special warnings and precautions for use". Prescription only medicine.	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in paediatric population: - Children <6 years of age - Paediatric patients with renal impairment (GFR <30 mL/min/1.73 m^2) - Paediatric patients with hepatic impairment	Instructions for use in paediatric patients is given in the section 4.2 “Posology and method of administration”. Warning in the sections 4.4 “Special warnings and precautions for use”. Prescription only medicine.	Not applicable.

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Hypertension or high blood pressure affects at least 1 billion people worldwide. Diseases caused by high blood pressure include ischemic heart disease, heart failure stroke and renal disease. Hypertension increases the risk of heart failure by two or three-fold and probably accounts for about 25% of all cases of heart failure. In addition, hypertension precedes heart failure in 90% of cases and the majority of heart failure in the elderly may be attributable to hypertension. Chronic heart failure is associated with an increased risk of thrombus formation and is accompanied by a 2- to 3-fold increased risk of stroke.

VI.2.2 Summary of treatment benefits

The benefits of losartan have been established in the treatment of essential hypertension in adults and in children and adolescents 6-18 years of age; treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment; treatment of chronic heart failure in adult patients when treatment with angiotensin-converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication; reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

In randomized controlled clinical studies (LIFE /9193 patients/, RENAAL /1513 patients/, HEAAL /3834 patients/, ELITE /722 patients/and ELITE-II /3152 patients/, once-daily administration of losartan potassium to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5-6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood-pressure reduction at the end of the dosing interval was 70-80% of the effect seen 5-6 hours post-dose.

Losartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.
The antihypertensive effect of losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age.

VI.2.3 Unknowns relating to treatment benefits

Since only limited data are available losartan is not recommended for use in

- children <6 years of age
- paediatric patients with kidney impairment (GFR <30 mL/min/1.73 m^2)
- paediatric patients with liver impairment

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VI.2.4 Summary of safety concerns

Table 6: *Summary table of safety concerns – Important identified risks*

Risk	**What is known**	**Preventability**
Hyperkalemia	Losartan may induce high blood potassium levels (hyperkalaemia), which may impair the functioning of the heart.	The plasma levels of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored. The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended.
Hypotension	Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Other antihypertensive agents may increase the hypotensive effects of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension. The most likely manifestation of overdose would be hypotension and tachycardia.	These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used. This also applies to children 6 to 18 years of age. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. If symptomatic hypotension should occur, supportive treatment should be instituted by your doctor.
Hypersensitivity	Rarely, hypersensitivity reactions may occur to losartan-containing preparations.	Do not use this medicine if you are allergic to losartan or to any of the other ingredients of this medicine. Patients with a history of angiooedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored by their doctor. If you experience a severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing) stop taking losartan tablets and tell your doctor immediately or go to the casualty department of your nearest hospital.
Kidney impairment due to concomitant use of RAS-acting agents (medicines used to treat high blood pressure): - an ACE-inhibitor for	RAS-acting agents are medicines acting on a hormone system that helps to control blood pressure and the amount of fluid in the body. These medicines can be of	Do not take losartan if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Risk	What is known	Preventability
example enalapril, lisinopril, ramipril - aliskiren.	three different classes known as ARBs, ACE inhibitors and direct renin inhibitors (the last represented by the medicine aliskiren). RAS-acting agents from two different classes have sometimes been combined for an increased effect. However, a review of the latest evidence has suggested that in most patients such combination does not increase the benefits, and may increase the risks of low blood pressure, increased potassium in the blood and possible damage to the kidney.	Tell your doctor before taking losartan if you are taking any of the following medicines used to treat high blood pressure: - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems. - aliskiren. If you are taking an ACE-inhibitor or aliskiren your doctor may need to change your dose and/or to take other precautions.
Toxicity to the foetus	Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Exposure to this class of medicines during the second and third trimesters is known to induce serious harm to foetus and neonatal toxicity.	You must tell your doctor if you think you are (or might become) pregnant. Losartan is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at this stage. Your doctor will normally advise you to stop taking losartan before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of losartan.

Table 7: *Summary table of safety concerns - Important potential risks*

Risk	What is known (Including reason why it is considered a potential risk)
Use in patients with hepatic impairment	Blood levels of losartan may be increased in liver impairment. A lower dose should be considered for patients with a history of liver impairment. There is no therapeutic experience in patients with severe liver impairment. Therefore, losartan is contraindicated in patients with severe liver impairment. Losartan is also not recommended in children with liver impairment.
Use in patients with renal impairment	Changes in kidney function including kidney failure have been reported (in particular, in patients pre-existing kidney dysfunction). Losartan should be used with caution in patients with bilateral renal artery stenosis (narrowing or blockage of the blood vessels leading to kidneys) or stenosis of the artery to a solitary kidney. If your kidney function is impaired the concomitant use of these medicines may lead to a worsening of the kidney function: other blood pressure lowering medicines in particular ACE-inhibitor (for example enalapril, lisinopril, ramipril) and aliskiren, medicines which retain potassium or may increase potassium levels (e.g. potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamteren, spironolactone] or heparin), and non-steroidal anti-inflammatory drugs such as indomethacin, including COX-2 inhibitors (medicines that reduce inflammation, and can be used to help relieve pain).

Risk	What is known (Including reason why it is considered a potential risk)
Use in patients with cardiac/cardiovascular disorders	Losartan should be used with caution in the following conditions: Coronary heart disease (caused by a reduced blood flow in the blood vessels of the heart) and cerebrovascular disease (caused by a reduced blood circulation in the brain): As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in myocardial infarction or stroke. Heart failure: In patients with heart failure, with or without kidney impairment, there is - as with other medicinal products acting on the renin-angiotensin system (hormone system that regulates blood pressure and water (fluid) balance)- a risk of severe arterial hypotension, and (often acute) kidney impairment. The combination of losartan with a beta-blocker should be used with caution. Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.
Rhabdomyolysis – an unexplained muscle pain with dark (tea-coloured) urine	Rhabdomyolysis has been reported for losartan. Rhabdomyolysis is the breakdown of muscle tissue that leads to the release of muscle fiber contents into the blood. These substances are harmful to the kidney and often cause kidney damage.
Drug interactions with non-steroidal anti-inflammatory drugs and lithium	Blood lowering effect of losartan may be reduced when concomitantly used with non-steroidal anti-inflammatory drugs such as indomethacin, including COX-2 inhibitors (medicines that reduce inflammation, and can be used to help relieve pain). Concomitant use with non-steroidal anti-inflammatory drugs may also lead to an increased risk of worsening of kidney function especially in patients with poor pre-existing kidney function. Lithium-containing medicines should not be taken in combination with losartan without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

Table 8: *Summary table of safety concerns - missing information*

Risk	What is known
Use in the first 3 months of pregnancy	The use of losartan is not recommended during the first three months of pregnancy. While exposure to this class of medicines during the second and third trimesters is known to induce serious harm to foetus, there is no controlled epidemiological data on the risk in the first 3 months of pregnancy.
Use during breastfeeding	No information is available regarding the use of losartan during breastfeeding, therefore losartan is not recommended for mothers who are breastfeeding,
Use in patients with severe liver impairment	There is no therapeutic experience in patients with severe liver impairment. Therefore, losartan is contraindicated in patients with severe liver impairment.
Use in patients with recent kidney transplantation	There is no experience in patients with recent kidney transplantation.
Use in paediatric population: - Children <6 years of age - Paediatric patients with renal impairment (GFR <30 mL/min/1.73 m^2) - Paediatric patients with	Losartan is not recommended for use in children suffering from kidney or liver impairment, or children under 6 years old, as only limited data are available in these patient groups.

Risk	What is known
hepatic impairment	

VI.2.5 Summary of risk minimisation measures by safety concern

No additional risk minimisation measures are proposed.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Not applicable. This is the first RMP version.