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## **PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)**

### **LOSARTAN 50 MG AND 100 MG FILM-COATED TABLETS**

#### **ORION CORPORATION**

**DATE: 21-04-2017, VERSION 1.1**

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## **VI.2 Elements for a Public Summary**

### ***VI.2.1 Overview of disease epidemiology***

Hypertension is a chronic disease in which the blood pressure is sustainably elevated. Systolic blood pressure means the pressure inside the arteries (blood vessels that carry blood from heart into the tissues) during the contraction of the heart, whereas diastolic blood pressure can be described as the pressure inside the arteries during the relaxation and filling of the heart. Blood pressure is considered elevated, when systolic blood pressure in repeated blood pressure measurements exceeds 140 mmHg and/or diastolic blood pressure is over 90 mmHg. Hypertension has been estimated to affect approximately 26 % of the adult population and this proportion is considered to be increasing. Untreated hypertension increases risk of other diseases, such as stroke, heart attack (myocardial infarction), heart failure and impaired function of the kidneys. High blood pressure is also associated with a shortened life expectancy. Thus, treatment of hypertension is essential in terms of public health. Reduction of the systolic blood pressure by 10 mmHg and diastolic blood pressure by 5 mmHg in hypertensive patients has been shown to decrease incidence of stroke by 35-40% and events of severe coronary artery disease by 20-25%, respectively. Similarly, reduction of isolated systolic blood pressure (meaning that the diastolic blood pressure is normal while the systolic blood pressure is high) leads to reduction on incidence of stroke and events of severe coronary artery disease by 30% and 23%, respectively.

Heart failure, also known as congestive heart failure, occurs when heart muscle doesn't pump blood as well as it should. Certain conditions, like narrowed arteries in the heart (coronary artery disease) or high blood pressure in long term, gradually cause a state where heart is too weak or stiff to fill and pump efficiently. Like hypertension, heart failure is a major public health issue, with a prevalence of over 23 million worldwide. The lifetime risk of developing heart failure is one in five. Heart failure carries substantial morbidity and mortality. A number of risk factors, such as ischemic heart disease, hypertension, smoking, obesity, and diabetes, among others, have been identified that predict not only the incidence of heart failure but as well its severity.

### ***VI.2.2 Summary of treatment benefits***

Losartan is an angiotensin-II receptor blocker (angiotensin-II receptor antagonist); losartan blocks the effect of a substance called angiotensin II, the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II narrows the blood vessels and also leads to production of aldosterone, which increases the amount of fluid in the blood. By preventing the action of angiotensin II, losartan reduces the work of the heart and lowers the blood pressure. It also has a protective effect on kidneys.

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### High blood pressure

In controlled clinical studies, once daily administration of losartan to patients with mild to moderate essential hypertension showed that losartan significantly reduced blood pressure. In a study in children 6 to 16 years of age, comparing several losartan dose strengths, the higher doses consistently reduced blood pressure compared with placebo.

### Kidney disease in patients with diabetes

In a study of 1513 type 2 diabetic patients with proteinuria, with or without hypertension comparing losartan or placebo added to patients' regular blood pressure medication, found that patients receiving losartan were 16.1% less likely to have worsening of kidney problems.

### Chronic heart failure who cannot take angiotensin converting enzyme (ACE) inhibitors

A study of 3834 patients aged 18 to 98 compared two different doses of losartan added to patients' existing blood pressure medications found that patients receiving losartan 150 mg were 10.1% less likely to die from any cause or be hospitalized for heart failure than patients receiving losartan 50 mg.

### Reduction in stroke in patients with high blood pressure and enlarged heart

A study of 9193 hypertensive patients aged 55 to 80 years with enlargement and thickening of the walls of heart's main pumping chamber (left-ventricular hypertrophy) compared losartan to atenolol (a beta-blocker for high blood pressure) when added to other high blood pressure drugs if needed, which found that patients receiving losartan were 13% less likely to die or become sick due to heart-related events (e.g. heart attack) or stroke than those receiving atenolol.

#### VI.2.3 Unknowns relating to treatment benefits

There are limited data on the efficacy and safety of losartan in children and adolescents aged 6 -18 years old for the treatment of hypertension. Limited pharmacokinetic data are available in hypertensive children above one month of age.

No information is available regarding the use of losartan during breast-feeding. Losartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

#### VI.2.4 Summary of safety concerns

##### Important identified risks

Risk	What is known	Preventability
Allergic reactions (Hypersensitivity)	Losartan may cause allergic reactions. A serious adverse event called angioedema, may cause swelling of the face, lips, tongue, and throat, and may make breathing difficult. This risk is increased in patients with a history of these types of reactions.	Patients should not take losartan if they are allergic to any ingredient. Losartan should be used carefully in patients who have had angioedema reactions with other drugs, such as angiotensin converting enzyme (ACE) inhibitors, which are also used to treat high blood pressure.
Low blood pressure	Low blood pressure may occur	Losartan therapy is

Risk	What is known	Preventability
(Hypotension)	with losartan, most commonly after the first dose, and also in patients who are dehydrated (e.g., due to vomiting or diarrhea, or certain drugs, such as diuretics or "water tablets"). Patients taking blood pressure medications that work in a similar manner to losartan may increase the likelihood of low blood pressure. These drugs include ACE inhibitors and direct renin inhibitors (e.g., aliskiren).	started under medical supervision. Whenever the dose is adjusted, the patients should be followed closely. In case of too low blood pressure, the dose of losartan may be reduced or the treatment discontinued. If the patient is dehydrated the condition should be corrected before taking losartan and/or a lower dose of losartan should be used. Blood pressure should be closely monitored in patients taking losartan in conjunction with ACE inhibitors or aliskiren (blood pressure lowering medicine). Patients with diabetes or impaired kidney function should not take concomitantly aliskiren.
High potassium levels (Hyperkalaemia)	High levels of potassium may occur with losartan, particularly in patients with kidney problems and/or diabetes. In addition, high potassium levels may occur in patients also taking potassium supplements, potassium-sparing diuretics ("water tablets"), and nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, which are used to treat pain. Patients taking blood pressure medications that work in a similar manner to losartan may increase the likelihood of high potassium levels. These drugs include ACE inhibitors and direct renin inhibitors (e.g., aliskiren).	Patients should not take both losartan and potassium supplements or potassium-sparing diuretics. Patients should tell their doctors or pharmacists if they are taking NSAIDs, ACE inhibitors, or aliskiren. Potassium levels should be closely monitored in patients taking losartan in conjunction with an ACE inhibitor or aliskiren, and in patients with kidney problems.
Impaired kidney function (Renal impairment)	Losartan may impair kidney function, particularly in patients with pre-existing kidney problems and patients with heart failure. Use of losartan together with ACE inhibitors and/or aliskiren may worsen kidney function.	Losartan should be used with caution in patients with narrowed arteries to the kidney (bilateral renal artery stenosis) and in patients who have only one kidney, which also has a narrowed artery. In patients receiving losartan with an ACE

Risk	What is known	Preventability
		inhibitor and/or aliskiren, kidney function should be monitored carefully. Losartan should not be used with aliskiren in patients with existing kidney problems.
Use during pregnancy	Losartan has not been studied specifically in pregnant women. However, use of drugs similar to losartan during the 2nd and 3rd trimesters of pregnancy have been associated with impaired kidney function, impaired skull formation in the fetus and decreased amniotic fluid in the mother.	Losartan is not recommended during the first trimester of pregnancy, and should not be used in the second and third trimesters of pregnancy. When possible, patients planning for pregnancy should be changed to another blood pressure medication with an established safety profile in pregnancy. In patients taking losartan who become pregnant, losartan should be stopped and an alternative therapy should be started if appropriate.

### Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Impaired function of the liver (Hepatic impairment)	Although losartan has not been studied specifically in patients with severe liver problems, increased concentrations of losartan have been seen in cirrhotic patients (in patients with impaired function of the liver).
Cough	Losartan may cause cough as an adverse event. ACE inhibitors, which have a somewhat similar mechanism as losartan, are associated with increased rates of cough, though more than that seen with losartan. Patients who have had cough with ACE inhibitors may be at greater risk of cough with losartan. Other risk factors include female gender, overweight, asthma or rhinitis (hay fever), and smoking/and exposure to tobacco smoke.

### Missing information

Risk	What is known
Use during breast feeding	Because no information is available regarding the use of losartan during breastfeeding, losartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.
Use in children < 6 years	The safety and efficacy of children aged 6 months to less than 6 years has not been established and losartan is not recommended for use in children under 6 years old. Limited pharmacokinetic

Risk	What is known
	data are available in hypertensive children above one month of age.

#### ***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. The Summary of Product Characteristics and the Package leaflet for this medicinal product can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

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

Not applicable.

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

Not applicable.