2.0 ELEMENTS FOR A PUBLIC SUMMARY

2.1 Overview of disease epidemiology

High blood pressure, also known as hypertension, occurs in a large percentage of the adult population. From 25 to 50% of adults in various European and North American countries have high blood pressure. The rate of high blood pressure increases with age. High blood pressure is associated with a higher risk of cardiovascular disease and kidney disease. According to the World Health Organization, more than half of strokes and heart attacks are caused by high blood pressure. Because it is associated with strokes, heart attacks, and kidney failure, high blood pressure is estimated to cause almost 13% of deaths worldwide.

There is limited information on the rate of high blood pressure in children in Europe. One study showed that approximately 25% of 11 year old children in one Greek community had high blood pressure. The rate of high blood pressure in children in the US ranges from 5 to approximately 20% depending on gender and ethnicity.

2.2 Summary of Treatment Benefits

The main studies of losartan included more than 10,000 adult patients, and are described below by the population and/or the disease treated.

<u>High blood pressure</u>

Losartan was evaluated in 11 trials in which a total of 1679 patients received losartan, 471 patients received placebo (“sugar pill”), and 488 received other medications for high blood pressure. These studies showed that losartan significantly reduced blood pressure.

There were several studies in children. In a study in 177 children age 6 to 16 years comparing several losartan dose strengths, the higher doses consistently reduced blood pressure compared with placebo.

<u>Kidney disease in patients with diabetes</u>

A study comparing losartan (715 patients) or placebo (726 patients) added to patients’ regular blood pressure medication found that patients receiving losartan were 16.1% less likely to have worsening of kidney problems.

<u>Chronic heart failure who cannot take angiotensin converting enzyme (ACE) inhibitors</u>

A study of 3834 patients 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 compared losartan (4605 patients) to atenolol (a beta-blocker for high blood pressure; 4588 patients) 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.

2.3 Unknowns Relating to Treatment Benefits

Losartan has not been studied and should not be used in patients who:

- Are allergic to any of the ingredients of the medication (listed in the product label);
- Are In the 2nd or 3rd trimester of pregnancy;
- Have severe liver impairment.

2.4 Summary of safety concerns

Important Identified Risks

Table 3 Summary of Important Identified Risks

Risk	What is Known	Preventability
Hypersensitivity (allergic reactions)	Losartan may cause allergic reactions. A serious type 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. In clinical trials, up to 2.7% of patients experienced any type of allergic reactions, but fewer than 0.1% experienced a serious allergic reaction. Most reactions were mild to moderately severe and went away after stopping losartan treatment.	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.
Hypotension (low blood pressure)	Low blood pressure may occur 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 pills”). Patients taking blood pressure medications that work in a similar manner to losartan may increase the likelihood	Dehydration should be corrected before taking losartan and/or a lower dose of losartan should be used. Blood pressure should be closely monitored in paitents taking losartan in conjunction with ACE inhibitors or aliskiren.

Table 3 Summary of Important Identified Risks

Risk	What is Known	Preventability
	of low blood pressure. These drugs include ACE inhibitors and direct renin inhibitors (e.g., aliskiren) . In clinical trials, approximately 12% of patients experienced dizziness (a symptom of hypotension), but less than 3% had hypotension or low blood pressure measurements. Serious low blood pressure effects were found in less than 0.7% of patients. Overall, most cases were mild to moderate in severity.	
Hyperkalemia (high potassium levels)	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 pills”), 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) . In clinical trials, approximately 1% of patients experienced elevated potassium levels, and less than 0.2% of these were serious.	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 renal (kidney) function	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. In clinical trials, up to 4.7% of patients experienced some type of impaired kidney function with losartan, and occurred mostly in patients with diabetes, existing kidney disease, and in elderly patients.Less than 0.2% of cases were considered serious.	Losartan should be used with caution in patients with narrowed arteries to the kidney (bilateral renal artery stenosis) and in patients who have only 1 kidney, which also has a narrowed artery. In patients receiving losartan plus an ACE inhibitor and/or aliskiren, kidney function should be monitored carefully. Losartan should not be used with aliskiren in patients with existing kidney problems.

Table 3 Summary of Important Identified Risks

Risk	What is Known	Preventability
Exposure (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 and impaired skull formation in the fetus, and decreased amniotic fluid in the mother. In clinical studies, 2 patients became pregnant while taking losartan in drug trials. The pregnancies were terminated by elective abortion.	Losartan is not recommended during the 1st trimester of pregnancy, and should not be used in the 2nd and 3rd 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

Table 4 Summary of Important Potential Risks

Risk	What is Known
Abnormal liver function	Although losartan has not been studied specifically in patients with severe liver problems, abnormal liver function was seen in less than 1.8% of patients. Of these, 0.04% were considered serious. However, based on findings in patients with less severe problems, a lower dose should be used in patients with abnormal liver function. In addition, losartan should not be used in people with severe liver problems.
Cough	In clinical trials, 6.2% of patients experienced cough; 0.01% of these were considered serious. 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, overweigh, asthma or rhinitis (hay fever), and smoking/and exposure to tobacco smoke.

Important Missing Information

Table 5 Summary of Important Missing Information

Missing Information	What is Known
Use in nursing mothers	Use of losartan has not been specifically studied in nursing mothers. Some drugs can be present in breast milk in nursing mothers. Although this is not known for losartan, the use of losartan in nursing mothers is not recommended. In nursing mothers requiring blood pressure medications, other treatments with established safety profiles during breastfeeding should be sought.
Treatment of proteinuria (protein in the urine) in children under 1 year of age, and treatment of hypertension in children under 6 months of age	Losartan has not been studied in children younger than 1 year of age with proteinuria, or in children younger than 6 months with high blood pressure. Therefore, losartan use in these populations is not recommended.

2.5 Summary of Additional Risk Minimization Measures by Safety Concern

This medicine has no additional risk minimization measures.

2.6 Planned Post-authorization Development Plan

2.6.1 List of Studies in Post-authorization Development Plan

There are no studies in the post-authorization development plan for this medicine.

2.6.2 Studies Which are a Condition of the Marketing Authorization

There are no studies in the post-authorization development plan for this medicine.

2.7 Summary of Changes to the Risk Management Plan Over Time

Table 6 Major Changes to the Risk Management Plan

RMP Version	Date	Safety Concerns	Comment
1.0	18-JAN-2010	**Summary—Ongoing Safety Concerns** **Important Identified Risks** Allergic Reactions Low Blood Pressure Too much potassium in the blood Impaired kidney function Use during Pregnancy **Important Potential Risks** Abnormal liver function Cough **Important Missing Information** Use in nursing mothers Missing Information in Pediatric Populations: • Long-term treatment of children over 1 year of age with protein in their urine • Use in children between 6 months and 6 years of age with high blood pressure • Treatment of protein in urine in children under 1 year of age, and treatment of high blood pressure in children under 6 months of age	
2.0	03-NOV-2010	No changes were made to the safety concerns with this RMP update.	Completion of a study to evaluate the effects of two doses of losartan (50 mg and 150 mg) on disease and death in patients with symptomatic congestive heart failure and who cannot take ACE inhibitors.
3.0	20-APR-2012	Long-term treatment of children over 1 year of age with protein in their urine was removed from the list of important missing safety information	Completion of a study of losartan in children with protein in their urine.

Table 6 Major Changes to the Risk Management Plan

RMP Version	Date	Safety Concerns	Comment
4.0		Use in children between 6 months and 6 years of age with high blood pressure was removed from the list of important missing safety information Since the previous RMP (v 3.0) there have been 2 new important additions to the losartan Company label and proposed additions to the European label regarding simultaneous use of 2 or more drugs that work similar to losartan: 1) A new contraindication stating that patients with diabetes (high blood sugar) receiving aliskiren (a medicine to treat high blood pressure) should not take losartan, and 2) updated wording in the drug interactions section text regarding use of ACE inhibitors, angiotensin receptor blockers (such as losartan), and/or aliskiren (medicines used to lower high blood pressure). As stated in the Company label and proposed European label, the side effects associated with simultaneous use of 2 or more of these drug are low blood pressure, fainting, too much potassium in the blood, and changes in kidney function.	Completion of a study of children between 6 months and 6 years of age with high blood pressure.