PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

VALSARTAN ORION 80, 160, 320 MG FILM-COATED TABLETS

ORION CORPORATION

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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 sustainly 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.

In heart attack (myocardial infarction) blood flow to the heart is blocked. This is most often caused by a build-up of a plaque in the arteries that feed the heart (coronary arteries). When the blood flow is diminished the heart muscle or part of it is suffering from lack of oxygen and may be damaged. Heart attack can be fatal, but the treatment has improved over the years.

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

Valsartan Orion is used for:

- *High blood pressure in adults and in children and adolescents 6 to18 years of age*. In most patients, the antihypertensive activity occurs within 2 hours after administration of a single oral dose. The antihypertensive effect persists over 24 hours after dosing and is substantially present within 2 weeks during repeated dosing. Maximal effects of valsartan are attained within 4 weeks.
- *Recent (12 hours – 10 days) heart attack (myocardial infarction).* VALIANT (The VAlsartan In Acute myocardial iNfarcTion trial) was a study of 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction. Valsartan, captopril, or the combination of both were used to study the mortality in different patient gropus. The study showed that valsartan was as effective as captopril in reducing all-cause mortality (time to death) after myocardial infarction. Allcause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan+captopril (19.3%) groups. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalisation for heart failure, and recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke.
- *Symptomatic heart failure in adult patients.* Val-HeFT was a clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 heart failure patients. In the overall Val-HeFT population, valsartan treated patients showed significant improvement in heart failure signs and symptoms, including distress in breathing (dyspnea), fatigue, the presence of excessive amount of fluid in/around cells, tissues or serous cavities of the body (oedema) and rales compared to placebo. Patients treated with valsartan had also a better quality of life.

VI.2.3 Unknowns relating to treatment benefits

Two clinical studies have been conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. Children below the age of 1 year were not enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater blood pressure reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Low blood pressure	Low blood pressure is a known adverse effect of this therapy. Symptoms of low blood pressure include e.g. dizziness, weakness and fainting. Especially, patients who have impaired function of the heart, have had diarrhoea or have been vomiting are at	Valsartan Orion therapy is 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 Valsartan Orion may be reduced or the treatment discontinued. Patients with low blood sodium- and/or volume should be corrected before

Risk	What is known	Preventability
	increased risk for this adverse effect.	starting treatment with Valsartan Orion. Patients with diabetes or impaired kidney function should not take concomitantly blood pressure lowering medicine containing aliskiren.
Increased concentration of potassium in the blood (hyperkalemia)	Electrolytes such as potassium play a vital role in maintaining body homeostasis. Valsartan may increase potassium concentration in serum. Patients with impaired function of the heart or kidneys are at higher risk for hyperkalemia.	Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels is not recommended. Monitoring of potassium should be undertaken as appropriate. Patients with diabetes or impaired kidney function should not take concomitantly blood pressure lowering medicine containing aliskiren.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Elevation of liver function values	The use of Valsartan Orion may cause elevation of liver function values. The effect of valsartan increases when used in patients with mild to moderately impaired function of the liver. Valsartan Orion should not be used in patients with severely impaired function of the liver and in patients with certain conditions affecting the liver.
Renal impairment	Valsartan Orion should be used with caution in patients with severely impaired function of the kidney, in patients undergoing dialysis, in patients suffering narrowing of the kidney artery and/or in patients who have recently undergone kidney transplantation.
Allergic reactions including swelling of the tongue and face (Hypersensitivity including angioedema and serum sickness)	Allergic conditions have been reported to occur with the use of valsartan. Angioedema, a condition including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Also signs of a type of delayed allergic reaction (serum sickness), like muscle pain, flu-like symptoms and rash, may occur with the use of valsartan.
Medication error including overdose	A Summary of Product Characteristics (SmPC) of valsartan tablets has been prepared as a guidance to physicians to help them with correct use. Similarly a Patient Information Leaflet is available in layman's language to educate the patients regarding correct use of the product. However, as with any medicine, medication error including overdose due to incorrect use can happen.

Missing information

Risk	What is known
Use in heart failure in children	Valsartan Orion is not recommended for the treatment of heart failure in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.
Use in recent heart attack in children	Valsartan Orion is not recommended for the treatment of recent heart attack in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.
Use in high blood pressure in children with impaired function of the kidney	Use in children with severely impaired function of the kidney or in children undergoing dialysis has not been studied and therefore valsartan is not recommended in these patients. In these patients kidney function and potassium levels in the blood should be closely monitored.
Use in high blood pressure in children with mild to moderately impaired function of the liver	As in adults, Valsartan Orion should not be used in children with severely impaired function of the liver and in children with certain conditions affecting the liver. The dose of Valsartan Orion should not exceed 80 mg/day in these patients.
Appropriateness of use for high blood pressure in children less than 6 years of age	Valsartan Orion is not recommended in children under 6 years of age, since the safety and efficacy of valsartan in these hypertensive children has not been established.

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.