PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

VALSARTAN/HYDROCHLOROTHIAZIDE ORION 80 MG/12.5 MG FILM-COATED TABLETS

VALSARTAN/HYDROCHLOROTHIAZIDE ORION 160 MG/12.5 MG FILM-COATED TABLETS

VALSARTAN/HYDROCHLOROTHIAZIDE ORION 160 MG/25 MG FILM-COATED TABLETS

ORION OYJ

DATE: 18-01-2016, VERSION 1.2

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 (1). Untreated hypertension increases risk of other diseases, such as stroke, heart attack, 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.

VI.2.2 Summary of treatment benefits

In patients with increased blood pressure, valsartan and hydrochlorothiazide have additive blood pressure lowering effects.

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 (2). 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 (3).

VI.2.3 Unknowns relating to treatment benefits

The use of Valsartan/Hydrochlorothiazide Orion in patients with severe chronic heart failure has not been established. There is currently no experience on the safe use of Valsartan/Hydrochlorothiazide Orion in patients who have recently undergone kidney transplantation.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions	Allergic reactions to valsartan or hydrochlorothiazide exists and is a contraindication for use of Valsartan/Hydrochlorothiazide Orion. In addition, allergic reactions to substances having a similar chemical structure with hydrochlorothiazide (so called sulfonamide–derived active substances) is a contraindication for use of Valsartan/Hydrochlorothiazide Orion.	Valsartan/Hydrochlorothiazide Orion should not be used in patients with known allergic reactions to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients. In cases of allergic reactions, Valsartan/Hydrochlorothiazide Orion should be discontinued and appropriate medical care and monitoring should be instituted.
Low blood pressure, which causes symptoms to the patient	Low blood pressure is a known adverse effect of therapy with Valsartan/Hydrochlorothiazide Orion. 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 increased risk for this adverse effect.	Valsartan/Hydrochlorothiazide Orion therapy is started under medical supervision. The patient should be followed when the dose is adjusted. In case of too low blood pressure, the dose of Valsartan/Hydrochlorothiazide Orion may be reduced or the treatment discontinued. Patients with diabetes or impaired kidney function should not take concomitantly blood pressure lowering medicine containing aliskiren.
Disturbances of mineral (electrolytes, e.g. potassium or sodium) balance in the blood	Electrolytes (such as potassium and sodium) play a vital role in the body. They help to regulate, e.g., function of the heart and nerves, water balance, oxygen delivery to the tissues and acid-base balance of the body. Hydrochlorothiazide can cause disturbances in water and electrolyte balance, since it increases excretion of potassium into the urine, which may lead to decreased potassium concentration in serum (so called hypokalaemia). However, this effect seems to be less evident when combined with valsartan which may increase potassium concentration in serum. Patients with impaired function of the heart or kidneys	Periodic determination of serum electrolytes should be performed at appropriate intervals. Patients with diabetes or impaired kidney function should not take concomitantly blood pressure lowering medicine containing aliskiren.

Risk	What is known	Preventability
	are at higher risk for disturbances of electrolyte balance.	
Impaired function of the kidneys	Impairment of the function of the kidneys has been reported during the use of Valsartan/Hydrochlorothiazide Orion, especially in patients with previous renal failure.	Valsartan/Hydrochlorothiazide Orion is contraindicated in patients with severe renal impairment. A periodic monitoring of kidney tests and electrolytes is recommended in patients with mild to moderate renal impairment. Patients with diabetes or impaired kidney function should not take concomitantly blood pressure lowering medicine containing aliskiren.
Use during pregnancy and lactation	Currently, there is no information on use of angiotensin receptor blockers during the first trimester of pregnancy and there may be increased risk for abnormalities of the embryo. The use during second and third trimester of pregnancy is known to induce harmful effects to the development of the fetus (decreased renal function, retardation of development of bone structures of the skull) and to the development of the newborn infant (renal impairment, decreased blood pressure, increased serum potassium levels).	The use of angiotensin receptor blockers, such as valsartan, is not recommended during the first trimester of pregnancy. The use of angiotensin receptor blockers is contraindicated during the second and third trimester of pregnancy. Valsartan/Hydrochlorothiazide Orion therapy should not be initiated during pregnancy. Unless continued therapy is considered essential, patient planning pregnancy should be changed to alternative anti-hypertensive treatment. When pregnancy is diagnosed, the treatment with Valsartan/Hydrochlorothiazide Orion should be discontinued, and, if appropriate, alternative therapy started. Should exposure to Valsartan/Hydrochlorothiazide Orion have occurred from the second trimester of pregnancy, the ultrasound check of renal function and the formation of bone structure of the skull is recommended. Infants whose mother has taken Valsartan/Hydrochlorothiazide Orion should be closely observed for decreased blood pressure.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Impaired function of the liver	Valsartan/Hydrochlorothiazide Orion should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alteration of water and blood minerals balance may precipitate a condition called hepatic coma. In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg. Valsartan/Hydrochlorothiazide Orion is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and cholestasis (obstruction of biliary system).
Concomitant use of medicines which increase the blood levels of potassium	There is a risk for elevated potassium levels in concomitant use of Valsartan/Hydrochlorothiazide Orion and other medications which increase the serum levels of potassium. These medications include certain diuretics (so called potassium-sparing diuretics), potassium supplements or potassium-containing salt substitutes. Monitoring of potassium should be undertaken as appropriate.
Concomitant use of antidiabetic medicines	Treatment with hydrochlorothiazide may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required during Valsartan/Hydrochlorothiazide Orion treatment.

Missing information

Risk	What is known
Use in patients with kidney transplantation	There is currently no experience regarding the administration of Valsartan/Hydrochlorothiazide Orion in patients with recent kidney transplantation.
Use in children	Valsartan/Hydrochlorothiazide Orion is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

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 product can be found in the national authority's web page www.fimea.fi.

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.