PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

CANDESARTAN/HYDROCHLOROTHIAZIDE ORION 8 MG/12.5 MG, 16 MG/12.5 MG, 32 MG/12.5 MG, 32 MG/25 MG

ORION CORPORATION

DATE: 17-04-2015, VERSION 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 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 (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

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).

In patients with increased blood pressure Candesartan and hydrochlorothiazide have additive blood pressure lowering effects and this effect is dose-dependent and long-lasting (lasting over 24 hours). In two clinical studies including 275 and 1524 patients, the candesartan hydrochlorothiazide combinations 32 mg/12.5 mg and 32 mg/25 mg resulted in blood pressure reduction of 22/15 mmHg and 21/14 mmHg, respectively, and were significantly more effective than candesartan or hydrochlorothiazide alone. In another study including 1975 patients not optimally controlled on 32 mg candesartan alone, the addition of 12.5 mg or 25 mg hydrochlorothiazide resulted in additional decrease in blood pressure. The overall mean blood pressure reduction were 16/10 mmHg and 13/9 mmHg, respectively (4).

VI.2.3 Unknowns relating to treatment benefits

Combination treatment with candesartan and hydrochlorothiazide is similarly effective in patients irrespective of age and gender. Currently, there are no data on the use of candesartan and hydrochlorothiazide combination in patients with renal disease or congestive heart failure or in patients who have previously had myocardial infarction (heart attack). (4)

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity	Hypersensitivity to candesartan or hydrochlorothiazide exists and is a contraindication for use of Candesartan/ Hydrochlorothiazide Orion. In addition, hypersensitivity to substances having a similar chemical structure with hydrochlorothiazide (so called	In cases of hypersensitivity reaction, Candesartan/ Hydrochlorothiazide Orion should be discontinued and appropriate medical care and monitoring should be instituted.

Risk	What is known	Preventability
	sulfonamide –derived active substances) is a contraindication for use of Candesartan/ Hydrochlorothiazide Orion.	
Low blood pressure, which causes symptoms to the patient	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 increased risk for this adverse effect.	Candesartan/ Hydrochlorothiazide Orion therapy is started under medical supervision. Additionally, the patients should be followed closely whenever the dose is adjusted. In case of too low blood pressure, the dose of Candesartan/ 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 electrolyte (*e.g.* potassium or sodium) balance	Electrolytes (such as potassium and sodium) play a vital role in maintaining body homeostasis. 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 that may lead to decreased potassium concentration in serum, so called hypokalaemia. However, this effect seems to be less evident when combined with candesartan, which may increase potassium concentration in serum. Patients with impaired function of the heart or kidneys are at higher risk for disturbances of electrolyte balance.	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.
Impaired function of the kidneys	Dose titration of candesartan is recommended in patients with mild to moderate renal	A periodic monitoring of kidney tests and electrolytes is recommended. Patients

Risk	What is known	Preventability
	impairment before the treatment with Candesartan/ Hydrochlorothiazide Orion is started. The use of Candesartan/ Hydrochlorothiazide Orion is contraindicated in patients with severe renal impairment. Concomitant use of anti-inflammatory painkillers may lead to increased risk for worsening of kidney function.	with diabetes or impaired kidney function should not take concomitantly blood pressure lowering medicine containing aliskiren.
Use during pregnancy and lactation	The use of angiotensin receptor antagonists, such as candesartan, is not recommended during the first trimester of pregnancy. The use of angiotensin receptor antagonists is contraindicated during the second and third trimester of pregnancy. Currently, there is no information on use of angiotensin receptor antagonists 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).	Candesartan/ 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 Candesartan/ Hydrochlorothiazide Orion should be discontinued, and, if appropriate, alternative therapy started. Should exposure to Candesartan/ 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 Candesartan/ Hydrochlorothiazide Orion should be closely observed for decreased blood pressure.

Important potential risks

Risk	What is known
Impaired function of the liver	Candesartan/ Hydrochlorothiazide Orion should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alteration of water and electrolyte balance may precipitate a condition called hepatic coma. Dose titration of candesartan is recommended in patients with mild to moderate hepatic impairment before treatment with Candesartan/

Risk	What is known
	Hydrochlorothiazide Orion is started. The use of Candesartan/ Hydrochlorothiazide Orion is contraindicated in patients with severe hepatic impairment and /or cholestasis (obstruction of biliary system).
Concomitant use of antidiabetic medicines with Candesartan/ Hydrochlorothiazide Orion Orion	Treatment with hydrochlorothiazide may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required during Candesartan/ Hydrochlorothiazide Orion treatment.
Concomitant use of Candesartan/ Hydrochlorothiazide Orion with medicines which increase the blood levels of potassium	There is risk for elevated potassium levels in concomitant use of Candesartan/ 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.

Missing information

Risk	What is known
Limited information on use in children.	The safety and efficacy of Candesartan/ Hydrochlorothiazide Orion in children aged between birth and 18 years have not been established.
Use in patients with kidney transplantation	There is no experience regarding the administration of Candesartan/ Hydrochlorothiazide Orion in patients with a recent kidney transplantation.

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 Candesartan/Hydrochlorothiazide Orion 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

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 1	13.06.2013	<u>Important identified risks</u> Hypersensitivity	First approved version

Version	Date	Safety Concerns	Comment
		Symptomatic hypotension Disturbance of electrolyte balance Renal impairment Use during pregnancy and lactation <u>Important potential risks</u> Hepatic impairment Concomitant use of potassium-sparing diuretics and potassium supplements <u>Missing information</u> Paediatric use Kidney transplantation	
Version 2	17.04.2015	No changes in defined risks	Information concerning lower strength of Candesartan Comp Orion and the text regarding the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren which causes an increase in the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure) was added based on the SPC.