Risk Management Plan

Version: 3.0

Candesartan/hydrochlorothiazide

VI.2 Elements for a public summary

V/.2.1 Overview of disease epidemiology [1 2 7]

More than a billion people throughout the world are affected by this disease. It can be found widely affecting people in both developed as well as underdeveloped countries. However, the rate of occurrence might vary significantly from one region to another. In India, only 3.4% of men and 6.8% of women are affected by this disorder, whereas in Poland, the figures read 68.9% for men and 72.5% for women. By 2004, the incidence rate for essential hypertension (high blood pressure with an unknown cause) in the US reached to 29%. It further went on to reach 34% by 2006, while African American adults had a peak incidence of 44% at the same time. The condition is more prevalently seen in Native American and black population and less frequently observed in Mexican Americans and whites. It generally affects more men or people belonging to the lower socioeconomic group.

Essential hypertension is also common in young children, pre-teens and teenagers.

By definition, essential hypertension has no definite cause. However, genetic and a number of environmental factors are believed to be responsible for the cause of this disorder. A wide array of factors can lead to the development of essential hypertension. The cause of this condition can differ greatly amongst individuals within a wider population. Although no definite cause has been identified that can give rise to this condition, a number of risk factors that increases the tendency of essential hypertension have been identified.

Genetic factors can greatly increase the risk of development of this disorder. More than fifty genes that might contribute to hypertension have been identified, and it is believed that numerous genetic defects exhibit raised blood pressure as an essential feature. Another opinion is that essential hypertension might occur as a result of single gene mutations that can be passed on from parent to child.

Hypertension can be caused by increasing age, and in such cases it is most likely caused by multiple factors. One mechanism involves stiffening of the arteries; it can be caused by increased arterial blood pressure. There is a relation between increased age and reduced ability for the kidneys to efficiently eliminate sodium from the body. Certain diseases involving small blood vessels of the kidney might also lead to increased blood sodium levels that can potentially increase blood pressure.

Obesity can greatly increase the chances of hypertension. More than 85% cases of essential hypertension are caused by Body Mass Index (BMI) greater than 25.

Other important risk factors include:

•Potassium
•Alcoholism
•Renin elevation
•Diabetes Mellitus
•Sodium sensitivity
•Cigarette smoking
•Vitamin D deficiency
•Stress or anxiousness
•Hyperinsulinemia and/or insulin resistance

V/.2.2 Summary of treatment benefits[3,4]

Various types of medications, collectively known as antihypertensive drugs can be used for treating hypertension. Candesartan/hydrochlorothiazide belong to a group of medicines which lower the blood pressure.
Reduction of blood pressure by around 5 mmHg can minimize the risks of stroke by nearly 34%, of an ischemic heart disease by around 21% as well as reduce the propensity of conditions such as of heart failure, dementia, and the death rate from cardiovascular diseases. The main goal of treatment must be to reduce the blood pressure lower than the level of 140/90 mmHg for the majority of patients, and even lower for patients of diabetes and/or kidney disease.

V/.2.3 Unknowns relating to treatment benefits

Based on the information currently available, no further studies are needed on how well candesartan/hydrochlorothiazide works. There is also no evidence to suggest that factors such as age, sex, race or organ disease affect how well candesartan/hydrochlorothiazide works in the people most likely to take it. However it is not known if candesartan/hydrochlorothiazide are safe and effective to use in children under 18 years of age.

V/.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Kidney and urinary disorders	Candesartan (AIlRA) plus the use of other AIlRAs and anti-inflammatory medicines (NSAIDs) may lead to an increased risk of worsening of kidney function, including possible kidney failure, and an increase in blood potassium levels, especially in patients with poor pre-existing kidney function. Hydrochlorothiazide may increase the risk of kidney insufficiency especially with high doses of iodinated contrast media.	The combination (ACE inhibitors (e.g. Captopril)), with the use of AIIRAs and NSAIDs) should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitaring kidney function after beginning combination therapy, and periodically thereafter.
Hypotension	In patients with decreased blood volume and/or decreased sodium levels hypotension may occur. Hypotension may occur during anaesthesia and surgery. Very	Treatment to reduce the symptoms should be started and vital signs monitored. The patient should be placed on there back with the legs elevated. If this is not sufficient, intravenous fluids

	rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or medications that will increase the blood pressure.	should be given. Blood electrolyte and acid balance should be checked and corrected, if needed. Other medicines that increase the function of the heart may be administered if the above-mentioned measures are not sufficient.
Electrolyte imbalance	Thiazide diuretics (hydrochlorothiazide) may decrease the output of calcium in the urine and may causes lightly increased blood calcium concentrations. Marked hypercalcaemia may be a sign of hidden hyperparathyroidism (over active parathyroid gland). The potassium losing effect of hydrochlorothiazide could be expected to be increased by other medicinal products associated with potassium loss and hypokalaemia. Candesartan/hydrochlorothiazide and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) used together, may lead to increases in blood potassium. Diuretic-induced hypokalaemia and hypomagnesaemia (decreased magnesium) predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics medication used to treat the heart.	Periodic determination of blood electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypercalcaemia, hypokalaemia, hyponatraemia, hypomagnesaemia and hypochloraemic alkalosis). Periodic monitoring of serum potassium is recommended when candesartan/hydrochlorothiazide is administered with such medicinal products.
Toxic effects to the unborn (foetus) and newborn baby in case of late pregnancy exposure	Evidence from studies regarding the risk of birth defects following exposure to medicines known as angiotensin converting enzyme inhibitors (ACE inhibitors) during the first trimester (12 weeks) of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled data on the risk with medicines known as Angiotensin II Receptor antagonists (AIIRAs), similar risks may exist for this class of drugs. Exposure to AIIRA therapy during the second and third trimesters is	Unless continued AIIRA therapy is considered necessary, patients planning pregnancy should be changed to other blood pressure lowering medicines that are safe to use during pregnancy. When pregnancy is first discovered, treatment with AIIRAs should be stopped immediately and, if appropriate, other therapy should be started. Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of kidney function and skull is recommended.

	known to induce human toxic effects on the foetus (decreased kidney function, deficiency of amniotic fluid, decreased bone formation of the skull) and newborn (kidney failure, low blood pressure, increased potassium levels). There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta and enters the foetal blood circulation. Based on the way hydrochlorothiazide works, its use during the second and third trimesters may compromise foetal blood circulation and may cause unwanted foetal effects on the newborn like jaundice, disturbance of electrolyte balance and decreased amounts of blood platelets. Hydrochlorothiazide should not be used during pregnancy for oedema, high blood pressure or preeclampsia (high blood pressure with protein in the urine) due to the risk of decreased blood volume which leads to a decreased flow of nutrients and oxygen to the foetus, without a beneficial effect on the course of the disease.	Infants whose mothers have taken AIIRAs should be closely observed for low blood pressure. Hydrochlorothiazide should not be used for high blood pressure in pregnant women except in rare situations where no other treatment could be used.

Important potential risks

Risk	What is known	Preventability
Glucose intolerance	Treatment with a thiazide diuretic may effect glucose tolerance	Dose adjustment of antidiabetic medicinal products, including insulin, may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide
Lithium toxicity	Reversible increases in blood lithium concentrations and toxicity have been reported during administration of lithium with Angiotensin Convert-	Use of candesartan and hydrochlorothiazide with lithium is not recommended. If the combination proves necessary, careful monitoring of

	ing Enzyme (ACE) inhibitors or hydrochlorothiazide.	serum lithium levels is recommended.

Important missing information

Risk	What is known
Use in children under 18 years of age	The safety and efficacy of candesartan/hydrochlorothiazide in children aged between birth and 18 years have not been established. No data is available.
Breastfeeding	Angiotensin II Rece(;)tor Antagonists (AIIRAs}: Because no information is available regarding the use of candesartan/hydrochlorothiazide during breastfeeding, candesartan/hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant. Hydrochlorothiazide: Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can stop the milk production. The use of candesartan/hydrochlorothiazide during breast-feeding is not recommended.

VI.2.5 Summary of additional risk minimisation measures by safety concern

This medicine has no additional risk minimisation measures.

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

No post-authorisation safety or efficacy studies are on-going or are planned to be conducted for candesartan/hydrochlorothiazide.

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
1.0	21-09-2012	Initial version	Initial version
2.0	20-03-2013	**Important identified risks:** ▪ Renal and urinary disorders ▪ Hypotension ▪ Electrolyte imbalance • Foetotoxicity and neonatal toxicity in case of late pregnancy exposure **Important potential risks:** ▪ Glucose intolerance	Update of RMP with additional risks.

Version	Date	Safety Concerns	Comment
		▪ Lithium toxicity	
3.0	07-08-2013	Important missing informations: ,, Use in children under 18 years of age. • Breastfeeding	Additon of more sections (section V1.2) Addition of more risks