VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

An elevated blood pressure is probably the most important public health problem in developed countries. It is readily detectable, usually easily treatable, but often leads to lethal complications if left untreated. Although the precise cause of hypertension remains unclear, the following risk factors increase the chance of its development: history of raised blood pressure among first-degree relatives, African race, male gender, older age (men > 55 years, women > 65 years), obesity, high alcohol consumption, and sedentary or inactive lifestyle.

Hypertension is more prevalent and severe in urban black populations compared to whites, and is associated with a greater degree of -organ damage for any given blood pressure level. Compared with whites, blacks develop hypertension at an earlier age, their average blood pressures are much higher and they experience worse disease severity. Consequently, blacks have a 1.3 times greater rate of nonfatal stroke, 1.8 times greater rate of fatal stroke, 1.5 times greater rate of heart disease death, 4.2 times greater rate of end-stage kidney disease, and a 50% higher frequency of heart failure; overall, mortality due to hypertension and its consequences is 4-5 times more likely in African Americans than in whites (Lindhorst et al. 2007, Ferdinand & Armani 2007).

VI.2.2 Summary of treatment benefits

Valsartan/Hydrochlorothiazide tablets of the Marketing Authorization Applicant (MAA) are generic versions of Co-Diovan® tablets of Novartis. Valsartan/Hydrochlorothiazide has been marketed in the European Community for more than 10 years, and the efficacy of the same is well established in the approved indications.

The MAA has conducted two bioequivalence studies aimed at comparing blood levels of the MAA's Valsartan/Hydrochlorothiazide 160/25 mg, and 320/25 mg Film-coated Tablets with Reference Products [Co Diovan®] of Novartis of the corresponding strengths in healthy adult, human subjects, under fasting conditions. Based on the results of these studies, the valsartan/hydrochlorothiazide formulation of the MAA and Novartis (Co Diovan®) were found to be bioequivalent under fasting conditions.

In such bioequivalence studies the same doses of generic medicine (Test) are compared with the reference (Reference) medicine of the innovator. The volunteers take the test drug and the reference drug sequentially separated by a reasonable period known as washout period. They receive either test drug first followed by the reference drug or the reference drug first followed by the test drug in a random order. Blood concentrations of the drug are measured at several predefined time points for each volunteer. If the blood concentration and time curve known as the Area Under the Curve (AUC) up to a certain predefined time point and the maximum concentration of the drug known as Cmax are found to be similar

based on a predefined statistical criterion, the Test and Reference are concluded to be bioequivalent.

VI.2.3 Unknowns relating to treatment benefits

None

VI.2.4 Summary of safety concerns

Table 18. Important identified risks

Risk	What is known	Preventability
Hyperkalemia (increased blood potassium levels)	Treatment with valsartan may cause increased potassium levels especially in the presence of kidney damage and concomitant administration of certain other medicines. Increased potassium in blood has been reported in post marketing experience.	It can be prevented by physician awareness, proper patient selection and periodic monitoring in patients of kidney damage and when used with other medicines or in other conditions that can cause or increase potassium levels in the blood.
Hypotension (low blood pressure)	Low blood pressure has been commonly reported in post marketing experience with valsartan/hydrochlorothiazide.	Special precautions are advised in conditions predisposing to low blood pressure such as in patients with sodium of fluid derangements, heart failure etc.
Foetotoxicity (harm to unborn babies)	Exposure during pregnancy to medicines of the same class as valsartan component of valsartan/hydrochlorothiazide tablets is known to induce harm to human unborn babies such as kidney damage, slow bone formation of the head etc.	The use of valsartan is not recommended during the first trimester of pregnancy and forbidden during the second and third trimester of pregnancy
Elevation of liver function values	Elevation of liver function values such as liver enzymes has been reported has been reported especially with the	Valsartan/hydrochlorothiazide should not be used in case of known severe liver damage and certain conditions affecting the liver. In mild to

Risk	What is known	Preventability
	use of valsartan component. Thiazides such as hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.	moderate liver damage valsartan/hydrochlorothiazide should be used with caution.
Renal impairment (kidney damage)	Kidney damage involving use of valsartan/hydrochlorothiazide has been seen reported with unknown frequency.	In conditions affecting kidney valsartan/hydrochlorothiazide should be used with caution.
Hypersensitivity including angioedema and serum sickness	Allergic conditions have been reported to occur with the use of both valsartan and hydrochlorothiazide. 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	In the presence of known allergy to valsartan or hydrochlorothiazide, this product should not be used. However, this condition is not entirely preventable.

Table 19. Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Medication error including overdose	As guidance to the physicians a Summary of Product Characteristics (SmPC) for valsartan tablets has been prepared to help them with correct use. Similarly a Patient Information Leaflet is available in layman's language to educate the patients regarding do's and don'ts. However, as

	with any medicine, medication error including overdose due to incorrect use can happen.

Table 20. Missing information

Risk	What is known
Clinical management and use of pharmacotherapy in pediatric heart failure (Use for treatment of heart failure in children)	Valsartan/Hydrochlorothiazide Jubilant is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.
Clinical management and use of pharmacotherapy in pediatric recent myocardial infarction (Use for recent heart attack in children)	Valsartan/Hydrochlorothiazide Jubilant is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.
Clinical management and use of pharmacotherapy in pediatric hypertension with renal impairment (Use for treatment of high blood pressure in children with kidney damage)	Valsartan/Hydrochlorothiazide Jubilant is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.
Clinical management and use of pharmacotherapy in pediatric hypertension with mild to moderate hepatic impairment (Use for treatment of high blood pressure in children with liver damage)	Valsartan/Hydrochlorothiazide Jubilant is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy. There is limited clinical experience with valsartan monosubstance product in children with mild to moderate liver damage. The dose of valsartan should not exceed 80 mg in these patients. In case of severe liver damage, valsartan should not be used either in children or adults.
Established benefit-risk ratio of pharmacotherapy in hypertensive children <5 years of age (Appropriateness of use for treatment of high blood pressure in children less than	Valsartan/Hydrochlorothiazide Jubilant is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy. There is some experience with the use of valsartan monosubstance product in children less than 6 years of age. However, safety and efficacy of such use has not yet been established.

5 years of age)	

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 valsartan/hydrochlorothiazide can be found in the MAA's EPAR 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

Table 21. Major changes to the Risk Management Plan over time:

Version	Date	Safety Concerns	Comment
v.1.0	23 May 2014	Important identified risks • Hyperkalemia • Hypotension • Foetotoxicity • Elevation of liver function values • Renal impairment • Hypersensitivity including angioedema and serum sickness Important potential risks • Rhabdomyolysis • Interstitial lung disease • Malignancies Missing Information	None

		• None	
v. 2.0	27 Jan 2015	Important identified risks • Hyperkalemia • Hypotension • Foetotoxicity • Elevation of liver function values • Renal impairment • Hypersensitivity including angioedema and serum sickness Important potential risks • Medication error including overdose Missing information • Clinical management and use of pharmacotherapy in paediatric heart failure • Clinical management and use of pharmacotherapy in paediatric recent myocardial infarction • Clinical management and use of pharmacotherapy in paediatric hypertension with renal impairment • Clinical management and use of pharmacotherapy in paediatric hypertension with mild to moderate hepatic impairment • Benefit-risk ratio of pharmacotherapy in hypertensive children <5 years of age	Updated Important potential risks and Missing information in line with the current version of RMP for the Reference Product as per RMS Day 70 Preliminary Assessment Report dated 25 Aug 2014 (NL/H/3221/001-002/DC)