## VI.2 Elements for a public summary

### *VI.2.1 Overview of disease epidemiology*

Losartan/Hydrohlorothiazide tablets is indicated for the:

- hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy (50 mg/12.5 mg film-coated tablets)
- For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled by losartan 50 mg/ hydrochlorothiazide 12.5 mg once daily (100 mg/25 mg film-coated tablets)

**Hypertension / Essential hypertension**

Cardiovascular disease is the most common cause of death in Western countries and arterial hypertension is a major predisposing factor for this outcome. The prevalence of age-adjusted hypertension for persons 35 to 64 years is high in European countries according to current estimates (Sweden [38%], Italy [38%], England [42%], Spain [47%], and Germany [55%])[Wolf-Maier, 2004]. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) show a continuous graded independent relationship with risk of stroke and coronary events.[ESH-ESC,2003]

Hypertension is a worldwide epidemic. Data from National Health and Nutrition Examination Survey (NHANES) spanning 1999-2002 in the United States found that in the population aged 20 years or older, an estimated 41.9 million men and 27.8 million women had prehypertension, 12.8 million men and 12.2 million women had stage 1 hypertension, and 4.1 million men and 6.9 million women had stage 2 hypertension.[Qureshi, 2005] Data from NHANES spanning 2003–2006 showed that 33.6% of US adults 20 years of age have hypertension, resulting in an estimated 74.5 million US adults with hypertension.

In many countries, 50% of the population older than 60 years have hypertension. Overall, approximately 20% of the world's adults are estimated to have hypertension. The 20% prevalence is for hypertension defined as blood pressure (BP) in excess of 140/90 mm Hg. The prevalence dramatically increases in patients older than 60 years.

In a large Spanish epidemiologic study over a 10-year period, investigators found that despite an increase in the intensity of hypertensive therapy, the prevalence of uncontrolled hypertension (systolic BP [SBP] $\leq$140 mm Hg and/or diastolic BP [DBP] $\leq$90 mm Hg) did not change significantly over time.[Catalá-López, 2012] In addition, there appeared to be worsecontrol in at-risk individuals (SBP $\leq$130 mm Hg and/or DBP $\leq$80-85 mm Hg) who had comorbidities.

As of 2000, nearly one billion people or $\sim$26% of the adult population of the world had hypertension.It was common in both developed (333 million) and undeveloped (639 million) countries.[Kearney, 2005] However rates vary markedly in different regions with rates as low as 3.4% (men) and 6.8% (women) in rural India and as high as 68.9% (men) and 72.5% (women) in Poland.[Kearney, 2004]

In 1995 it was estimated that 43 million people in the United States had hypertension or were taking antihypertensive medication, almost 24% of the adult United States population.[Burt, 1995] The prevalence of hypertension in the United States is increasing and reached 29% in 2004.[Burt, 1995] [Ostchega, 2007] As of 2006 hypertension affects 76 million US adults (34% of the population) and African American adults have among the highest rates of hypertension in the world at 44%.[Lloyd-Jones, 2010] It is more common in blacks and native Americans and less in whites and Mexican Americans, rates increase with age, and is greater in the southeastern United States. Hypertension is more prevalent in men (though menopause tends to decrease this difference) and in those of low socioeconomic status.[Carretero, 2000]

Essential hypertension, also called primary hypertension or idiopathic hypertension, is the form of hypertension that by definition, has no identifiable cause. It is the most common type of hypertension, affecting 95% of hypertensive patients,it tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. Prevalence of essential hypertension increases with age, and individuals with relatively high blood pressure at younger ages are at increased risk for the subsequent development of hypertension. Hypertension can increase the risk of cerebral, cardiac, and renal events.[Messerli, 2007] [Carretero, 2000] [Oparil, 2003]

### *VI.2.2 Summary of treatment benefits*

Pharmacotherapeutic group: Angiotensin II antagonists + diuretics, ATC code: C09DA06

Within the ATC system, candesartan cilexetil is classified as an agent acting on the reninangiotensin system (RAS), specifically a plain angiotensin II receptor antagonist, and coded C09CA06; when combined with a diuretic, the code is C09DA06. Hydrochlorothiazide is a low-ceiling, thiazide-type diuretic coded C03AA03 or C03AX01when referring to a hydrochlorothiazide combination product.
Losartan potassium/hydrochlorothiazide is a combination of an angiotensin II receptor antagonist, losartan potassium, and a thiazide diuretic; hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
The antihypertensive effect of the losartan/hydrochlorothiazide combination is sustained for a 24-hour period.

Losartan

Losartan potassium is a synthetically produced oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gl and, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates the proliferation of smooth-muscle cells proliferation.

Losartan potassium selectively blocks the AT1 receptor. In vitro and in vivo, both losartan potassium and its pharmacologically active carboxylic acid metabolite E-3174 block inhibit all physiologically relevant actions of angiotensin II, regardless of its the source or route of its synthesis.

Losartan potassium does not possess an agonist action and there is also no blockade, nor does it block of other hormone receptors or ion channels that are important in cardiovascular regulation. Furthermore, losartan potassium does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, thereThere is thus is no potentiation increaseof undesirable in bradykinin-mediated undesirable effects.

During the administration of losartan potassium, the removal of the angiotensin II negative feedback on renin secretion leads to increased plasma-renin activity (PRA). An iIncrease in the PRA leads to an increases in angiotensin II in plasma. Despite these increases, the antihypertensive activity action and suppression of the plasma aldosterone concentration are maintained, indicating which indicates effective angiotensin II receptor blockade. After the discontinuation of losartan potassium, the PRA and angiotensin II values fell to the baseline values within three days.
Both losartan potassium and also its principal active mainactive metabolite have a far much greater affinity for the AT1 receptor than for the AT2 receptor. On a weight basis tThe active metabolite is 10 to 40 times more effective active than losartan.

### *VI.2.3 Unknowns relating to treatment benefits*

No other evidence of efficacy has been detected.

### *VI.2.4 Summary of safety concerns*

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Electrolyte imbalance | Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. | Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored<br><br>The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan/ hydrochlorothiazide is not recommended.<br>(section 4.4 of the SmPC, Annex II) |
| Hypotension | As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. | The labeling describes the appearance "hypotension". SmPC section 4.8, Annex II. |
| Changes in renal function including renal failure | Some studies have shown that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the rennin-angiotensin-aldosterone system, is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) as compared to use of a single rennin-angiotensin-aldosterone system agent. | The labeling describes the appearance of changes in renal function. SmPC section 4.4, Annex II. |
| Serious allergic reaction which causes swelling of the face or throat (angioedema) | Patients with a history of angiooedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored | The labeling warning of the closely monitored of patients with history of angioedema "angioedema". SmPC section 4.4, Annex II.<br>The labeling describes the appearance of "angioedema". SmPC section 4.8, Annex II. |

**Important potential risks**

| Risk | What is known | Preventability |
|---|---|---|
| Severe low blood pressure in patients with narrowing of the renal artery that can impede blood flow to the kidney<br>(Severe hypotension in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney) | Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. | The labeling describes the severe hypotension in patients with bilateral renal artery stenosis. SmPC section 4.4, Annex II. |
| Special caution in patients with abnormal narrowing of the aortic and mitral valve in the heart, disease in which the heart muscle (myocardium) becomes abnormally thick<br><br>(Special caution in patients with aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy) | As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. | The labeling describes the special caution in patients with aortic and mitral valve stenosis. SmPC section 4.4, Annex II. |
| Toxic to the foetus (Foetotoxicity) | AIIRAs should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. | The labeling describes the special caution in pregnancy. SmPC section 4.4, Annex II. |
| Increased risk of adverse events in patients with hepatic impairment | Hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.<br><br>Losartan potassium and Hydrochlorothiazide tablets is contraindicated for patients with severe hepatic impairment | The labeling describes the increased risk of adverse events in patients with hepatic impairment. SmPC 4.4, Annex II.<br><br>The labeling describes the contraindication use of Losartan SmPC section 4.3, Annex II. |

| Risk | What is known | Preventability |
|---|---|---|
| Thiazide-related impaired glucose tolerance in diabetic patients | Thiazide therapy may impair glucose tolerance. In diabetic patients, dosage adjustments of insulin or oral hypoglycaemia agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy. | The labeling describes thiazide-related impaired glucose tolerance in diabetic patients. SmPC 4.4, Annex II. |
| Thiazide-related increases in cholesterol and triglyceride levels | Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. | The labeling describes thiazide-related increases in cholesterol and triglyceride levels. SmPC 4.4, Annex II. |
| High level of blood uric acid (Hyperuricaemia) | Hyperuricaemia or frank gout may be precipitated in some patients receiving thiazide therapy. | The labeling describes the precaution of hyperucaemia. SmPC 4.4, Annex II.<br><br>The labeling describes the appearance "hyperuricaemia". SmPC section 4.8, Annex II |
| Thiazide-related aggravation of chronic autoimmune disease (Thiazide-related exacerbation or activation of systemic lupus erythematosus) | Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides. | The labeling describes the thiazide-related exacerbation or activation of systemic lupus SmPC 4.4, Annex II. |
| Less efficacious in black patients | As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black patients than in non-blacks, possibly because of higher prevalence or low-renin states in the black hypertensive population. | The labeling describes the less efficacious in black patients SmPC 4.4, Annex II. |

**Important missing information**

Not applicable.

### VI.2.5 Summary of additional 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 Losartan + hydrochlorothiazide can be found in the Losartan + hydrochlorothiazide EPAR page.

This medicine has no additional risk minimisation measures.

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

It is not necessary.

### VI.2.7 Summary of changes to the risk management plan over time

Notaplicable.