VI.2 Elements for a public summary

VI.2.1Overview of disease epidemiology[1]

Losartan is indicated for:

- Treatment of essential hypertension in adults and in children and adolescent 6 – 18 years of age.
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria > 0.5 g/day as part of an antihypertensive treatment.
- Treatment of chronic heart failure (in patients > 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction < 40% and should be stabilised under the treatment of the chronic heart failure.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

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]

[1]Very brief overview of the natural history of the disease.

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]

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VI.2.2 Summary of treatment benefits2

Pharmacotherapeutic group: Angiotensin II Receptor Antagonists, ATC code: C09CA01

Losartan is a synthetic 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 gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

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

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykininmediated effects.

During administration of Losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of Losartan, PRA and angiotensin II values fell within three days to the baseline values.

Both Losartan and its principal active metabolite have a far greater affinity for the AT1-receptor than for the AT2-receptor. The active metabolite is 10- to 40- times more active than Losartan on a weight for weight basis.

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
Hypotension	The use of losartan may decrease your blood pressure	Treatment with losartan especially after the first dose and after increasing of the dose, may cause hypotension. Be aware that other antihypertensive agents may increase the hypotensive action of Losartan. Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.
Hyperkalemia	The use of losartan may	Losartan should not be taken if

[2] The summary of treatment benefits (one page maximum per indication/population) should be in lay language and the following should be considered for inclusion:

Risk	What is known	Preventability
	increase the potassium levels in your blood.	the patients having high levels of potassium in blood (hyperkalemia) or patients taking groups of drugs which help to excrete excessive body fluid, (potassium sparing diuretics) or "salt tablets" (potassium supplements). Losartan must not be taken with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) together (which are used to treat high blood pressure, heart disease or particular kidney conditions) as these drugs may increase the risk of high potassium levels in blood.
Renal function impairment	As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported.	Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Use in pediatric patients with renal function impairment Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m2as no data are available Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function. Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.
Primary aldosteronism	Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system.	The use of Losartan tablets is not recommended.
Pregnancy	The use of losartan is not recommended during the first trimester of pregnancy. The use	AIIRAs should not be initiated during pregnancy. Unless continued AIIRA therapy is

Risk	What is known	Preventability
	of losartan is contra-indicated during the 2nd and 3rd trimester of pregnancy	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
Interaction with lithium	Concomitant use with lithium may increases serum lithium concentrations and toxicity.	Very rare cases have also been reported with antiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Important potential risks

Risk	What is known
Coronary heart disease and cerebrovascular disease	As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.
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
Interaction with other antihypertensive agents	Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

Important missing information

Risk	What is known
Severe hepatic impairment	There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.
Renal transplantation	There is no experience in patients with recent kidney transplantation.
Heart failure	There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups.

VI.2.5 Summary of risk minimization measures by safety concern

Summary of Product Characteristics (SmPC) of losartan 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). All these risk minimization measures are given in SmPC and PL of losartan.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

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

Not applicable