Module 1- Administrative and product information

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

1.3.1 Summary of Product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium Tablets USP 50 mg, 50 mg per Tablets, Film coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains
Losartan Potassium USP 50 mg
Excipients Q.S.
Colour: Titanium dioxide BP

Kindly refer section 6.1 for full list of Excipients.

3 PHARMACEUTICAL FORM

Film coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age.
- Treatment of renal disease in adult 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 adult patients, when treatment with Angiotensin converting enzyme (ACE)inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilized with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
- Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

4.2 Posology and method of administration

Special populations

Use in patients with intravascular volume depletion:

For patients with intravascular volume-depletion (e.g. those treated with high dose diuretics), a starting dose of 25 mg once daily should be considered.

Use in patients with renal impairment and haemodialysis patients:

No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment:
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.

Paediatric population
6 months − less than 6 years
The safety and efficacy of children aged 6 months to less than 6 years has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on posology can be made.
6 years to 18 years
For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients > 20 to < 50 kg. (In exceptional cases the dose can be increased to a maximum of 50 mg once daily). Dosage should be adjusted according to blood pressure response.
In patients > 50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/ kg (or in excess of 100 mg) daily have not been studied in paediatric patients.
Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
Losartan is also not recommended in children with hepatic impairment.

Use in Elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.
Losartan potassium tablets are available in 25 mg, 50 mg and 100 mg.

Method of administration
Losartan tablets should be swallowed with a glass of water.
Losartan potassium may be administered with or without food.

4.3 Contraindications

2^{nd} and 3^{rd} trimester of pregnancy.
Severe hepatic impairment.
The concomitant use of Losartan potassium with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

4.4 Special warnings and precautions for use

Hypersensitivity
Angio-oedema.
Patients with a history of angio-oedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored.
Hypotension and electrolyte/fluid imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used. This also applies to children 6 to 18 years of age.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group. Therefore, the plasma concentrations of potassium as well as 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.

Use in paediatric patients with renal impairment

Losartan is not recommended in children with glomerular filtration rate <30 ml/ min/ 1.73 m^2.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with Fluvastatin (weak inhibitor of CYP2C9).

As with other medicinal products that block angiotensin II or its effects, concomitant use of other medicinal products which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin, trimethoprim-containing products), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin 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.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of

worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

4.6 Pregnancy and lactation

Pregnancy

The use of losartan is not recommended during the first trimester of pregnancy. The use of losartan is contra-indicated during the 2nd and 3rd trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of medicinal products. Unless continued AIIRA 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 losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Breastfeeding

Because no information is available regarding the use of losartan during breastfeeding, losartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

Losartan has been evaluated in clinical studies as follows:

- In controlled clinical trials in >3,000 adult patients 18 years of age and older for essential hypertension
- In a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age
- In a controlled clinical trial in > 9,000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
- In a controlled clinical trials in > 7,700 adult patients with chronic heart failure

- In a controlled clinical trial in > 1,500 type 2 diabetic patients 31 years of age and older with proteinuria
- In these clinical trials, the most common adverse reaction was dizziness.

4.9 Overdose

Symptoms of intoxication:
Limited data are available with regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.
Treatment of intoxication
If symptomatic hypotension should occur, supportive treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Losartan is a synthetic oral angiotensin-II receptor (type AT_1) 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 AT_1 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 bradykinin mediated 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 AT_1 receptor than for the AT_2 receptor. The active metabolite is 10 to 40 times more active than losartan on a weight for weight basis.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, losartan is well absorbed and undergoes first pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic

bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4hours, respectively.

Distribution

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously or orally administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.

In addition to the active metabolite, inactive metabolites are formed.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively.

When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially, with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of ^{14}C labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

5.3 Preclinical safety data

No inhouse preclinical safety data has been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline Cellulose
Maize Starch
Povidone K-30
Magnesium Stearate
Purified Talc
Colloidal Anhydrous Silica
Sodium Lauryl Sulphate
Hydroxypropylmethylcellulose
Polyethylene Glycol 4000
Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store protected from light, at a temperature not exceeding 30°C.
keep out of the reach and sight of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

4 tablets are packed in one blister pack. Such 7 blister pack is packed in Carton along with Insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/ MANUFACTURER

APPLICANT:
M/s. WINGS PHARM AFRICAN. LIMITED
Chellarams PLC. 110/114, WH3, First floor Oshodi apapa Exp.way, opp.five star Bus stand, Isolo,Lagos.

MANUFACTURED BY:
SPENSUS PHARMA PVT LTD
Unit No.1, Survey No.284,
Ganeshpura -382 705, Dist.
Mehsana, Gujarat, India