Public Assessment Report

Decentralised Procedure

LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE
50 MG/12.5 MG, 100 MG/12.5 MG AND 100 MG/25 MG
FILM-COATED TABLETS

LOSARTAN POTASSIUM
HYDROCHLOROTHIAZIDE

UK/H/1685/001-3/DC

UK Licence No: PL 32256/0069, 0095-6

AUROBINDO PHARMA (MALTA) LIMITED
LAY SUMMARY

On 16th September 2011, the UK granted Aurobindo Pharma (Malta) Limited Marketing Authorisations (licences) for Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets (PL 32256/0069, 0095-6; UK/H/1685/001-3/DC).

Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets contain a combination of an angiotensin II receptor antagonist (losartan potassium) and a diuretic (hydrochlorothiazide).

Losartan potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension (high blood pressure).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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# Module 1

| **Product Name** | Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets  
| Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg film-coated tablets  
| Losartan potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets |
| **Type of Application** | Generic application, Article 10.1 |
| **Active Substance** | Losartan potassium  
| Hydrochlorothiazide |
| **Form** | Film-coated tablets |
| **Strength** | 50/12.5 mg  
| 100/12.5 mg  
| 100/25 mg |
| **MA Holder** | Aurobindo Pharma (Malta) Limited  
| Vault 14, Level 2, Valletta Waterfront  
| Floriana FRN 1913  
| Malta |
| **Reference Member State (RMS)** | United Kingdom (UK) |
| **Concerned Member States (CMS)** | Germany (DE), France (FR), Italy (IT), the Netherlands (NL), Portugal (PT) |
| **Procedure Number** | UK/H/1658/001-3/DC |
| **End of Procedure** | Day 210: 18th August 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Excipients Each tablet contains 222 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet
White, Oval shaped, beveled edge, biconvex film-coated tablets debossed with ‘F’ on one side and ‘74’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Losartan potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

4.2 Posology and method of administration
Losartan potassium/Hydrochlorothiazide may be administered with other antihypertensive agents.
Losartan potassium/Hydrochlorothiazide tablets should be swallowed with a glass of water
Losartan potassium/Hydrochlorothiazide may be administered with or without food.

Hypertension
Losartan potassium and Hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of Losartan potassium/Hydrochlorothiazide is one tablet of Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, the dosage may be increased to one tablet of Losartan potassium/Hydrochlorothiazide 100 mg/25 mg (losartan 100 mg/HCTZ 25 mg) once daily. The maximum dose is one tablet of Losartan potassium/Hydrochlorothiazide 100 mg/25 mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy. Losartan potassium/Hydrochlorothiazide 100/12.5 (losartan 100 mg/HCTZ 12.5 mg) is available for those patients titrated to 100 mg of Losartan potassium who require additional blood pressure control.

Use in patients with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan potassium/ Hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan potassium/Hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

Use in patients with intravascular volume depletion
Volume and/or sodium depletion should be corrected prior to administration of Losartan potassium/Hydrochlorothiazide tablets.
Use in patients with hepatic impairment
Losartan potassium/Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see section 4.3.).

Use in the elderly
Dosage adjustment is not usually necessary for the elderly.

Use in children and adolescents (< 18 years)
There is no experience in children and adolescents. Therefore, Losartan potassium/Hydrochlorothiazide should not be administered to children and adolescents.

4.3 Contraindications
• Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients
• Therapy resistant hypokalaemia or hypercalcaemia
• Severe hepatic impairment; Cholestasis and biliary obstructive disorders
• Refractory hyponatraemia
• Symptomatic hyperuricaemia/gout
• 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
• Severe renal impairment (i.e. creatinine clearance <30 ml/min)
• Anuria

4.4 Special warnings and precautions for use
Losartan
Angioedema
Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hypotension and Intravascular volume depletion
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Losartan potassium/Hydrochlorothiazide tablets (see sections 4.2. and 4.3.).

Electrolyte imbalances
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.

The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with Losartan potassium/ Hydrochlorothiazide is not recommended (see section 4.5).

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan potassium/ Hydrochlorothiazide should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore Losartan potassium/Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or preexisting renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.
Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan potassium/Hydrochlorothiazide tablets is not recommended.

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.

Heart failure:
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

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.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy
Losartan/Hydrochlorothiazide should not be initiated during pregnancy. Unless continued Losartan/HTCZ 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/Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hydrochlorothiazide
Hypotension and electrolyte/fluid imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic induced hyperuricemia.

Hepatic impairment
Thiazides 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.
Losartan potassium/Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).

Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 6.1).

4.5 Interaction with other medicinal products and other forms of interaction

Losartan
Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be coadministered with angiotensin II receptor antagonists.

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.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

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.

Hydrochlorothiazide
When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug 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.

Other antihypertensive drugs
Additive effect.

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (eg cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates
In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa
There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Losartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulthiame, amisulpride, tiapride, pimozone, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).
Calcium salts
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Laboratory Test Interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine
Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine Contrast Media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Losartan:
The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

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 drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 'Preclinical safety data'). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation
Losartan:
Because no information is available regarding the use of Losartan potassium/ Hydrochlorothiazide
during breastfeeding, Losartan potassium/ Hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding 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 inhibit the milk production. The use of Losartan potassium/Hydrochlorothiazide during breast feeding is not recommended. If Losartan potassium/Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

### 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

The adverse reactions below are classified where appropriate by system organ class and frequency according to the following convention:

- **Very common**: ≥ 1/10
- **Common**: ≥ 1/100 to < 1/10
- **Uncommon**: ≥ 1/1,000 to ≤ 1/100
- **Rare**: ≥ 1/10,000 to ≤ 1/1,000
- **Very rare**: ≤ 1/10,000
- **Not known**: (cannot be estimated from the available data)

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse reactions peculiar to this combination of substances were observed. The adverse reactions were restricted to those which were formerly observed with losartan potassium salt and/or hydrochlorothiazide.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as substance-related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan and hydrochlorothiazide.

Next to these effects, there are further adverse reactions reported after the introduction of the product to the market as follows:

**Hepato-biliary disorders**
- Rare: Hepatitis

**Investigations**
- Rare: Hyperkalaemia, elevation of ALT

Additional adverse reactions that have been seen with one of the individual components and may be potential adverse reactions with losartan potassium/ hydrochlorothiazide are the following:

**Losartan**

**Blood and lymphatic system disorders**
- Uncommon: Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

**Immune system disorders**
- Rare: Anaphylactic reactions, angioedema, urticaria

**Metabolism and nutrition disorders**
- Uncommon: Anorexia, gout

**Psychiatric disorders**
- Common: Insomnia
- Uncommon: Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment
Nervous system disorders
Common: Headache, dizziness
Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

Eye disorders
Uncommon: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus

Cardiac disorders
Uncommon: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Vascular disorders
Uncommon: Vasculitis

Respiratory, thoracic and mediastinal disorders
Common: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder
Uncommon: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Gastrointestinal disorders
Common: Abdominal pain, nausea, diarrhoea, dyspepsia
Uncommon: Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting

Hepato-biliary disorders
Not known: Liver function abnormalities

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

Musculoskeletal and connective tissue disorders
Common: Muscle cramp, back pain, leg pain, myalgia
Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness
Not known: Rhabdomyolysis

Renal and urinary disorders
Uncommon: Nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders
Uncommon: Decreased libido, impotence

General disorders and administration site conditions
Common: Asthenia, fatigue, chest pain
Uncommon: Facial oedema, fever

Investigations
Common: Hyperkalaemia, mild reduction of haematocrit and haemoglobin
Uncommon: Mild increase in urea and creatinine serum levels
Very rare: Increase in hepatic enzymes and bilirubin.

Hydrochlorothiazide
Blood and lymphatic system disorders
Uncommon: Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia
Immune system disorders
Rare: Anaphylactic reaction

Metabolism and nutrition disorders
Uncommon: Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Psychiatric disorders
Uncommon: Insomnia

Nervous system disorders
Common: Cephalalgia

Eye disorders
Uncommon: Transient blurred vision, xanthopsia

Vascular disorders
Uncommon: Necrotizing angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
Uncommon: Respiratory distress including pneumonitis and pulmonary oedema

Gastrointestinal disorders
Uncommon: Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

Hepato-biliary disorders
Uncommon: Icterus (intrahepatic cholestatis), pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

Renal and urinary disorders
Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administration site conditions
Uncommon: Fever, dizziness

4.9 Overdose

No specific information is available on the treatment of overdose with Losartan potassium/Hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Losartan potassium/Hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan
Limited data are available in regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.
5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA01

Losartan-Hydrochlorothiazide
The components of Losartan/Hydrochlorothiazide have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

The antihypertensive effect of Losartan/Hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year’s duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Losartan/Hydrochlorothiazide had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/ hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

Losartan/Hydrochlorothiazide is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Losartan
Losartan 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 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 thus no increase in bradykinin-mediated undesirable effects.

During the administration of losartan the removal of the angiotensin II negative feedback on rennin 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 the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II values fell within 3 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.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that
of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.

Hypertension Studies
In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80 % of the effect seen 5-6 hours postdose.

Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effects on heart rate.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

LIFE Study
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.
After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.

5.2 Pharmacokinetic properties

Absorption

Losartan
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 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labeled 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 one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan
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 excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan-Hydrochlorothiazide
The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.
Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

Losartan

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Neither losartan nor the active metabolite can be removed by hemodialysis.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse fetal and neonatal effects, including renal toxicity and fetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
- Cellulose Microcrystalline
- Lactose Monohydrate
- Starch, Pregelatinised (maize)
- Silica Colloidal Anhydrous
- Magnesium stearate

Tablet coat:
- Hydroxypropyl Cellulose (E463)
- Hypromellose 6cP (E464)
- Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Losartan potassium/Hydrochlorothiazide is available in packs of PVC/Aclar – Aluminium foil blisters and HDPE bottle packs.

Pack sizes:
- Blister pack: 14, 28, 30, 50, 56, 60, 90, 98, 100, 280 and 500 film-coated tablets
- Bottle pack: 14 and 500 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma (Malta) Limited
PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta

8 MARKETING AUTHORISATION NUMBER(S)
PL 32256/0069

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/09/2011

10 DATE OF REVISION OF THE TEXT
16/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Excipients Each tablet contains 111 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet
Yellow coloured, oval shaped, beveled edge, biconvex film-coated tablets debossed with ‘E’ on one side and ‘48’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Losartan potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

4.2 Posology and method of administration
Losartan potassium/Hydrochlorothiazide may be administered with other antihypertensive agents.
Losartan potassium/Hydrochlorothiazide tablets should be swallowed with a glass of water
Losartan potassium/Hydrochlorothiazide may be administered with or without food.

Hypertension
Losartan potassium and Hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of Losartan potassium/Hydrochlorothiazide is one tablet of Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, the dosage may be increased to one tablet of Losartan potassium/Hydrochlorothiazide 100 mg/25 mg (losartan 100 mg/ HCTZ 25 mg) once daily. The maximum dose is one tablet of Losartan potassium/Hydrochlorothiazide 100 mg/25 mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy. Losartan potassium/Hydrochlorothiazide 100/12.5 (losartan 100 mg/ HCTZ 12.5 mg) is available for those patients titrated to 100 mg of Losartan potassium who require additional blood pressure control.

Use in patients with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan potassium/ Hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan potassium/Hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

Use in patients with intravascular volume depletion
Volume and/or sodium depletion should be corrected prior to administration of Losartan potassium/Hydrochlorothiazide tablets.

Use in patients with hepatic impairment
Losartan potassium/Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see section 4.3.).

Use in the elderly
Dosage adjustment is not usually necessary for the elderly.
Use in children and adolescents (< 18 years)
There is no experience in children and adolescents. Therefore, Losartan potassium/Hydrochlorothiazide should not be administered to children and adolescents.

4.3 Contraindications
- Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; Cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)
- Anuria

4.4 Special warnings and precautions for use

Losartan
Angioedema
Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hypotension and Intravascular volume depletion
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Losartan potassium/Hydrochlorothiazide tablets (see sections 4.2 and 4.3).

Electrolyte imbalances
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.

The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with Losartan potassium/ Hydrochlorothiazide is not recommended (see section 4.5).

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan potassium/ Hydrochlorothiazide should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore Losartan potassium/Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or preexisting renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation
There is no experience in patients with recent kidney transplantation.
Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan potassium/Hydrochlorothiazide tablets is not recommended.

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.

Heart failure:
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

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.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy
Losartan/Hydrochlorothiazide should not be initiated during pregnancy. Unless continued Losartan/HTCZ 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/Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hydrochlorothiazide
Hypotension and electrolyte/fluid imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic induced hyperuricemia.

Hepatic impairment
Thiazides 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. Losartan potassium/Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).
**Other**

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 6.1).

**4.5 Interaction with other medicinal products and other forms of interaction**

**Losartan**

Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be coadministered with angiotensin II receptor antagonists.

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.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

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.

**Hydrochlorothiazide**

When given concurrently, the following drugs may interact with thiazide diuretics:

- **Alcohol, barbiturates, narcotics or antidepressants:**
  Potentiation of orthostatic hypotension may occur.

- **Antidiabetic drugs (oral agents and insulin):**
  The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug 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.

- **Other antihypertensive drugs**
  Additive effect.

- **Cholestyramine and colestipol resins:**
  Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

- **Corticosteroids, ACTH**
  Intensified electrolyte depletion, particularly hypokalemia.
Pressor amines (e.g., adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity;
concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may
raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be
necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to
allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and
stomach emptying rate.

Cytotoxic agents (eg cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their
myelosuppressive effects.

Salicylates
In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the
salicylates on the central nervous system.

Methyldopa
There have been isolated reports of haemolytic anaemia occurring with concomitant use of
hydrochlorothiazide and methyldopa.

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type
complications.

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced
cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Losartan/
hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances
(e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular
tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a
predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine,
cyamemazine, sulpiride, sulthiopride, amisulpride, pimozide, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphenamid, erythromycin IV, halofantrin, mizolastin, pentamidine,
terfenadine, vircamine IV).

Calcium salts
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium
supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should
be adjusted accordingly.
Laboratory Test Interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine
Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine Contrast Media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product.
Patients should be rehydrated before the administration.

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Losartan:
The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4).
The use of AIIRAs is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

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 drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 'Preclinical safety data').
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation
Losartan:
Because no information is available regarding the use of Losartan potassium/ Hydrochlorothiazide during breastfeeding, Losartan potassium/ Hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding 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 inhibit the milk production. The use of Losartan potassium/Hydrochlorothiazide during breast feeding is not recommended. If Losartan potassium/Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

### 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

The adverse reactions below are classified where appropriate by system organ class and frequency according to the following convention:

- **Very common**: $\geq 1/10$
- **Common**: $\geq 1/100$ to $< 1/10$
- **Uncommon**: $\geq 1/1,000$ to $\leq 1/100$
- **Rare**: $\geq 1/10,000$ to $\leq 1/1,000$
- **Very rare**: $\leq 1/10,000$
- **Not known**: (cannot be estimated from the available data)

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse reactions peculiar to this combination of substances were observed. The adverse reactions were restricted to those which were formerly observed with losartan potassium salt and/or hydrochlorothiazide.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as substance-related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan and hydrochlorothiazide.

Next to these effects, there are further adverse reactions reported after the introduction of the product to the market as follows:

**Hepato-biliary disorders**

- **Rare**: Hepatitis

**Investigations**

- **Rare**: Hyperkalaemia, elevation of ALT

Additional adverse reactions that have been seen with one of the individual components and may be potential adverse reactions with losartan potassium/ hydrochlorothiazide are the following:

**Losartan**

**Blood and lymphatic system disorders**

- **Uncommon**: Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

**Immune system disorders**

- **Rare**: Anaphylactic reactions, angioedema, urticaria

**Metabolism and nutrition disorders**

- **Uncommon**: Anorexia, gout

**Psychiatric disorders**

- **Common**: Insomnia

**Nervous system disorders**

- **Common**: Headache, dizziness

- **Uncommon**: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope
**Eye disorders**
Uncommon: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity

**Ear and labyrinth disorders**
Uncommon: Vertigo, tinnitus

**Cardiac disorders**
Uncommon: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

**Vascular disorders**
Uncommon: Vasculitis

**Respiratory, thoracic and mediastinal disorders**
Common: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder
Uncommon: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

**Gastrointestinal disorders**
Common: Abdominal pain, nausea, diarrhoea, dyspepsia
Uncommon: Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting

**Hepato-biliary disorders**
Not known: Liver function abnormalities

**Skin and subcutaneous tissue disorders**
Uncommon: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

**Musculoskeletal and connective tissue disorders**
Common: Muscle cramp, back pain, leg pain, myalgia
Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness
Not known: Rhabdomyolysis

**Renal and urinary disorders**
Uncommon: Nocturia, urinary frequency, urinary tract infection

**Reproductive system and breast disorders**
Uncommon: Decreased libido, impotence

**General disorders and administration site conditions**
Common: Asthenia, fatigue, chest pain
Uncommon: Facial oedema, fever

**Investigations**
Common: Hyperkalaemia, mild reduction of haematocrit and haemoglobin
Uncommon: Mild increase in urea and creatinine serum levels
Very rare: Increase in hepatic enzymes and bilirubin.

**Hydrochlorothiazide**

**Blood and lymphatic system disorders**
Uncommon: Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia

**Immune system disorders**
Rare: Anaphylactic reaction
**Metabolism and nutrition disorders**  
Uncommon: Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

**Psychiatric disorders**  
Uncommon: Insomnia

**Nervous system disorders**  
Common: Cephalalgia

**Eye disorders**  
Uncommon: Transient blurred vision, xanthopsia

**Vascular disorders**  
Uncommon: Necrotizing angiitis (vasculitis, cutaneous vasculitis)

**Respiratory, thoracic and mediastinal disorders**  
Uncommon: Respiratory distress including pneumonitis and pulmonary oedema

**Gastrointestinal disorders**  
Uncommon: Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

**Hepato-biliary disorders**  
Uncommon: Icterus (intrahepatic cholestatis), pancreatitis

**Skin and subcutaneous tissue disorders**  
Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

**Musculoskeletal and connective tissue disorders**  
Uncommon: Muscle cramps

**Renal and urinary disorders**  
Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

**General disorders and administration site conditions**  
Uncommon: Fever, dizziness

### 4.9 Overdose

No specific information is available on the treatment of overdose with Losartan potassium/Hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Losartan potassium/Hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

**Losartan**

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

Neither losartan nor the active metabolite can be removed by hemodialysis.

**Hydrochlorothiazide**

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA01
Losartan-Hydrochlorothiazide
The components of Losartan/Hydrochlorothiazide have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

The antihypertensive effect of Losartan/Hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Losartan/Hydrochlorothiazide had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

Losartan/Hydrochlorothiazide is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Losartan
Losartan 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 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 thus no increase in bradykinin-mediated undesirable effects.

During the administration of losartan the removal of the angiotensin II negative feedback on rennin 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 the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II values fell within 3 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.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains...
glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.

**Hypertension Studies**

In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80 % of the effect seen 5-6 hours postdose.

Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effects on heart rate.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

**LIFE Study**

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

**Hydrochlorothiazide**

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.
5.2 Pharmacokinetic properties

Absorption

Losartan
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 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labeled 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 one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan
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 excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan-Hydrochlorothiazide
The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Neither losartan nor the active metabolite can be removed by hemodialysis.
5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse fetal and neonatal effects, including renal toxicity and fetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core:
- Cellulose Microcrystalline
- Lactose Monohydrate
- Starch, Pregelatinised (maize)
- Silica Colloidal Anhydrous
- Magnesium stearate

Tablet coat:
- Hydroxypropyl Cellulose (E463)
- Hypromellose 6cP (E464)
- Titanium Dioxide (E171)
- Quinoline Yellow Aluminium lake (E104)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Losartan potassium/Hydrochlorothiazide is available in packs of PVC/Aclar – Aluminium foil blisters and HDPE bottle packs.

Pack sizes:
- Blister pack: 14, 28, 30, 56, 60, 90, 98, 100, 280 and 500 film-coated tablets
- Bottle pack: 14 and 500 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta
PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

8 MARKETING AUTHORISATION NUMBER(S)
   PL 32256/0095

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   16/09/2011

10 DATE OF REVISION OF THE TEXT
    16/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Excipients Each tablet contains 222 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet

Yellow coloured, oval shaped, beveled edge, biconvex film-coated tablets debossed with ‘E’ on one side and ‘49’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Losartan potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

4.2 Posology and method of administration
Losartan potassium/Hydrochlorothiazide may be administered with other antihypertensive agents.
Losartan potassium/Hydrochlorothiazide tablets should be swallowed with a glass of water
Losartan potassium/Hydrochlorothiazide may be administered with or without food.

Hypertension
Losartan potassium and Hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of Losartan potassium/Hydrochlorothiazide is one tablet of Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, the dosage may be increased to one tablet of Losartan potassium/Hydrochlorothiazide 100 mg/25 mg (losartan 100 mg/ HCTZ 25 mg) once daily. The maximum dose is one tablet of Losartan potassium/Hydrochlorothiazide 100 mg/25 mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy. Losartan potassium/Hydrochlorothiazide 100/12.5 (losartan 100 mg/ HCTZ 12.5 mg) is available for those patients titrated to 100 mg of Losartan potassium who require additional blood pressure control.

Use in patients with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan potassium/ Hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan potassium/Hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

Use in patients with intravascular volume depletion
Volume and /or sodium depletion should be corrected prior to administration of Losartan potassium/Hydrochlorothiazide tablets.

Use in patients with hepatic impairment
Losartan potassium/Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see section 4.3.).
Use in the elderly
Dosage adjustment is not usually necessary for the elderly.

Use in children and adolescents (< 18 years)
There is no experience in children and adolescents. Therefore, Losartan potassium/Hydrochlorothiazide should not be administered to children and adolescents.

4.3 Contraindications

- Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; Cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester of pregnancy (see section 4.4 and 4.6)
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)
- Anuria

4.4 Special warnings and precautions for use

Losartan

Angioedema
Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hypotension and Intravascular volume depletion
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Losartan potassium/Hydrochlorothiazide tablets (see sections 4.2 and 4.3).

Electrolyte imbalances
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. The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with Losartan potassium/Hydrochlorothiazide is not recommended (see section 4.5).

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan potassium/Hydrochlorothiazide should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore Losartan potassium/Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or preexisting renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation
There is no experience in patients with recent kidney transplantation.
**Primary hyperaldosteronism**
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan potassium/Hydrochlorothiazide tablets is not recommended.

**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.

**Heart failure:**
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

**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.

**Ethnic differences**
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

**Pregnancy**
Losartan/Hydrochlorothiazide should not be initiated during pregnancy. Unless continued Losartan/HTCZ 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/Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

**Hydrochlorothiazide**

**Hypotension and electrolyte/fluid imbalance**
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

**Metabolic and endocrine effects**
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic induced hyperuricemia.

**Hepatic impairment**
Thiazides 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. Losartan potassium/Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).
Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 6.1).

4.5 Interaction with other medicinal products and other forms of interaction

Losartan
Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be coadministered with angiotensin II receptor antagonists.

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.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

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.

Hydrochlorothiazide
When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug 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.

Other antihypertensive drugs
Additive effect.

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.
Pressor amines (e.g., adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates
In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa
There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Losartan/ hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulotropride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphenamid, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vancamine IV).

Calcium salts
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.
Laboratory Test Interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine
Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine Contrast Media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product.
Patients should be rehydrated before the administration.

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Losartan:
The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4).
The use of AIIRAs is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

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 drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 'Preclinical safety data').
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation
Losartan:
Because no information is available regarding the use of Losartan potassium/ Hydrochlorothiazide during breastfeeding, Losartan potassium/ Hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding 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 inhibit the milk production. The use of Losartan potassium/Hydrochlorothiazide during breast feeding is not recommended. If Losartan potassium/Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

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
The adverse reactions below are classified where appropriate by system organ class and frequency according to the following convention:

| Very common | ≥ 1/10 |
| Common      | ≥ 1/100 to < 1/10 |
| Uncommon    | ≥ 1/1,000 to ≤ 1/100 |
| Rare        | ≥ 1/10,000 to ≤ 1/1,000 |
| Very rare   | ≤ 1/10,000 |
| Not known   | (cannot be estimated from the available data) |

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse reactions peculiar to this combination of substances were observed. The adverse reactions were restricted to those which were formerly observed with losartan potassium salt and/or hydrochlorothiazide.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as substance-related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan and hydrochlorothiazide.

Next to these effects, there are further adverse reactions reported after the introduction of the product to the market as follows:

Hepato-biliary disorders
Rare: Hepatitis

Investigations
Rare: Hyperkalaemia, elevation of ALT

Additional adverse reactions that have been seen with one of the individual components and may be potential adverse reactions with losartan potassium/hydrochlorothiazide are the following:

Losartan
Blood and lymphatic system disorders
Uncommon: Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

Immune system disorders
Rare: Anaphylactic reactions, angioedema, urticaria

Metabolism and nutrition disorders
Uncommon: Anorexia, gout

Psychiatric disorders
Common: Insomnia
Uncommon: Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment

Nervous system disorders
Common: Headache, dizziness
Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope
Eye disorders
Uncommon: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus

Cardiac disorders
Uncommon: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitations, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Vascular disorders
Uncommon: Vasculitis

Respiratory, thoracic and mediastinal disorders
Common: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder
Uncommon: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Gastrointestinal disorders
Common: Abdominal pain, nausea, diarrhoea, dyspepsia
Uncommon: Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting

Hepato-biliary disorders
Not known: Liver function abnormalities

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

Musculoskeletal and connective tissue disorders
Common: Muscle cramp, back pain, leg pain, myalgia
Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness
Not known: Rhabdomyolysis

Renal and urinary disorders
Uncommon: Nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders
Uncommon: Decreased libido, impotence

General disorders and administration site conditions
Common: Asthenia, fatigue, chest pain
Uncommon: Facial oedema, fever

Investigations
Common: Hyperkalaemia, mild reduction of haematocrit and haemoglobin
Uncommon: Mild increase in urea and creatinine serum levels
Very rare: Increase in hepatic enzymes and bilirubin.

Hydrochlorothiazide

Blood and lymphatic system disorders
Uncommon: Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia

Immune system disorders
Rare: Anaphylactic reaction
Metabolism and nutrition disorders
Uncommon: Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Psychiatric disorders
Uncommon: Insomnia

Nervous system disorders
Common: Cephalalgia

Eye disorders
Uncommon: Transient blurred vision, xanthopsia

Vascular disorders
Uncommon: Necrotizing angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
Uncommon: Respiratory distress including pneumonitis and pulmonary oedema

Gastrointestinal disorders
Uncommon: Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

Hepato-biliary disorders
Uncommon: Icterus (intrahepatic cholestatis), pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

Renal and urinary disorders
Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administration site conditions
Uncommon: Fever, dizziness

4.9 Overdose
No specific information is available on the treatment of overdose with Losartan potassium/Hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Losartan potassium/Hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan
Limited data are available in regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA01
Losartan-Hydrochlorothiazide

The components of Losartan/Hydrochlorothiazide have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

The antihypertensive effect of Losartan/Hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Losartan/Hydrochlorothiazide had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/ hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

Losartan/Hydrochlorothiazide is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Losartan

Losartan 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 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 thus no increase in bradykinin-mediated undesirable effects.

During the administration of losartan the removal of the angiotensin II negative feedback on rennin 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 the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II values fell within 3 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.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains
Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.

Hypertension Studies
In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80% of the effect seen 5-6 hours postdose.

Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effects on heart rate.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

LIFE Study
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95% confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.
5.2 Pharmacokinetic properties

**Absorption**

**Losartan**
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 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

**Distribution**

**Losartan**
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

**Hydrochlorothiazide**
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

**Biotransformation**

**Losartan**
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labeled 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 one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

**Elimination**

**Losartan**
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 excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

**Hydrochlorothiazide**
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

**Characteristics in Patients**

**Losartan-Hydrochlorothiazide**
The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

**Losartan**
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Neither losartan nor the active metabolite can be removed by hemodialysis.
5.3 **Preclinical safety data**
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse fetal and neonatal effects, including renal toxicity and fetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
*Tablet core:*
Cellulose Microcrystalline
Lactose Monohydrate
Starch, Pregelatinised (maize)
Silica Colloidal Anhydrous
Magnesium stearate

*Tablet coat:*
Hydroxypropyl Cellulose (E463)
Hypermellose 6cP (E464)
Titanium Dioxide (E171)
Quinoline Yellow Aluminium lake (E104)

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Store below 25°C.

6.5 **Nature and contents of container**
Losartan potassium/Hydrochlorothiazide is available in packs of PVC/Aclar – Aluminium foil blisters and HDPE bottle packs.

*Pack sizes:*
Blister pack: 14, 28, 30, 50, 56, 60, 90, 98, 100, 280 and 500 film-coated tablets
Bottle pack: 14 and 500 film-coated tablets

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta
PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

8 MARKETING AUTHORISATION NUMBER(S)
PL 32256/0096

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/09/2011

10 DATE OF REVISION OF THE TEXT
16/09/2011
Module 3

Product Information Leaflets

PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg,
100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

UK/H/1685/001-3/DC

1. WHAT LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE TABLETS IS AND WHAT IT IS USED FOR

Losartan potassium/Hydrochlorothiazide is a combination of an angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide).

Losartan potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension (high blood pressure).

2. BEFORE YOU TAKE LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE TABLETS

Do not take Losartan potassium/Hydrochlorothiazide Tablets if:
- you are allergic (hypersensitive) to losartan, hydrochlorothiazide, or any other ingredients in this medicine.
- you are pregnant, breastfeeding, or planning to become pregnant, or breastfeeding.
- you are breastfeeding.
- you are allergic (hypersensitive) to other sulfonamide-derived substances (e.g. other thiazides, some antibacterial drugs such as trimethoprim), ask your doctor if you are not sure.
- you have severe liver disease or have had severe anemia due to poor heart function.
- you have alcoholism.
- you have had an allergic condition, asthma, or a condition that causes joint pain, skin rash and fever (systemic lupus erythematosus).
- you have high calcium or low potassium levels or you are on a low potassium diet.
- you need to have an anesthetic (even at the dentist) or before surgery, or if you are going to have less to check your parathyroid function, you must tell the doctor or medical staff that you are taking Losartan potassium and Hydrochlorothiazide tablets.
- you suffer from hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland).

3. HOW TO TAKE LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE TABLETS

Always take Losartan potassium/Hydrochlorothiazide exactly as your doctor has instructed you. Your doctor will decide on the appropriate dose of Losartan potassium/Hydrochlorothiazide depending on your condition and whether you are taking other medicines. It is important to continue taking Losartan potassium/Hydrochlorothiazide for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

This medicinal product is available in three strengths: 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg.

High Blood Pressure

The usual dose of Losartan potassium/Hydrochlorothiazide for most patients with high blood pressure is 1 tablet of Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg per day to control blood pressure over the 24-hour period. This can be increased to 2 tablets once daily of Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-Coated Tablets or changed to 1 tablet daily of Losartan potassium/Hydrochlorothiazide 100 mg/25 mg Film-Coated Tablets (a stronger strength) per day. The maximum daily dose is 2 tablets per day of Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-Coated Tablets or 1
PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

UK/H/1685/001-3/DC

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE TABLETS

Keep out of the reach and sight of children.

Do not use Losartan potassium/Hydrochlorothiazide after the expiry date which is stated on the carton and blister pack. The expiry date refers to the last day of that month.

Store below 28°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losartan potassium/Hydrochlorothiazide Tablets contains

The active substances are losartan potassium and hydrochlorothiazide. Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg tablet contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Losartan potassium/Hydrochlorothiazide 100 mg/25 mg tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

The other ingredients are cellulose microcrystalline, lactose monohydrate, starch pregelatinised, silica colloidal anhydrous, magnesium stearate. Tablet coat: Hydroxypropyl cellulose (E463), hypromellose 6cp (E464), titanium dioxide (E171), quinoline yellow aluminium lake (E104) [only in 50 mg/12.5 mg & 100 mg/25 mg].

What Losartan potassium/Hydrochlorothiazide Tablets looks like and contents of the pack

Film coated tablets

Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg

Yellow coloured, oval shaped, bevelled edge, biconvex film-coated tablets deboosed with “E” on one side and “49” on the other side.

Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg

White, oval shaped, bevelled edge, biconvex film-coated tablets deboosed with “F” on one side and “74” on the other side.

Losartan potassium/Hydrochlorothiazide 100 mg/25 mg

Yellow coloured, oval shaped, bevelled edge, biconvex film-coated tablets deboosed with “E” on one side and “49” on the other side.

Losartan potassium/Hydrochlorothiazide is available in packs of PVC/Alar – Aluminium foil blisters and HDPE bottle packs.

Pack sizes:

Blister pack: 14, 28, 30, 50, 60, 90, 98, 100, 280 and 500 film-coated tablets

Bottle pack: 14 and 500 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Aurobindo Pharma (Malta) Limited

Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1513
Malta

Manufacturer

API Pharmacies (Services) (Malta) Limited

HF26, Hal Far Industrial Estate, Hal Far
Birzebbuga, B&G 3000
Malta

This medicinal product is authorized in the Member States of the EEA under the following names:

France: SENSIBREK 50 mg/12.5 mg, 100 mg/12.5 mg & 100 mg/25 mg, comprimé pelliculé

Germany: Losartan Kaliyum/Hydrochlorothiazide Aurobindo 50 mg/12.5 mg, 100 mg/12.5 mg & 100 mg/25 mg filmtabletten

Italy: Losartan e idrozolico Aurobindo 50/12.5 mg, 100/12.5 mg & 100/25 mg compresse rivestite con film

Netherlands: KaliyumLosartan/Hydrochlorothiazide Aurobindo 50/12.5 mg, 100/12.5 mg & 100/25 mg, filmomhulde tabletten

Portugal: Losartan + Hidroclorotiazida Aurobindo

United Kingdom: Losartan potassium/Hydrochlorothiazide 50/12.5 mg, 100/12.5 mg & 100/25 mg film-coated tablets

This leaflet was last approved in 08/2011.
Module 4
Labelling

Cartons:

Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg,
100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

Each tablet contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta
Each tablet contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.
Each tablet contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.
Losartan potassium/Hydrochlorothiazide
50 mg/12.5 mg
film-coated tablets

Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta
Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.

PL 32255/0095

POM

Aurobindo Pharma (Malta) Limited
Vault 18, Level 2, Valletta
Waterfront Piazza
FRN 1913 Malta
PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.

Losartan potassium/Hydrochlorothiazide

50 mg/12.5 mg film-coated tablets

500 film-coated tablets

Losartan potassium/Hydrochlorothiazide

50 mg/12.5 mg film-coated tablets

500 film-coated tablets

Losartan potassium/Hydrochlorothiazide

50 mg/12.5 mg film-coated tablets

500 film-coated tablets

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta
Waterfront Floriana
FRN 1913 Malta

M.L. No.: 19/HD/AP/95/P/R

EXP

Lot

PL 32256/0095

POM

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta
Waterfront Floriana
FRN 1913 Malta

PL 32256/0095

POM
Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.
Losartan potassium/Hydrochlorothiazide
100 mg/25 mg
film-coated tablets

Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta
PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.
Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.

PL 32256/0096

POM

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront Floriana
FRN 1913 Malta
Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide (HCTZ).

Contains lactose, see leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store below 25°C.
PAR Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets

UK/H/1685/001-3/DC

Blisters:
Module 5  
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Germany, France, Italy, the Netherlands, Portugal and the UK considered that the applications for Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets could be approved. Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets are prescription only medicines (POM) and are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

These applications for Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets were submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Hyzaar 50 mg/12.5 mg, Cozaar® Plus 100 mg/12.5 mg and Fortzaar 100 mg/25 mg film-coated tablets first authorised in the Netherlands in 1996 to Merck Sharp & Dohme B.V.

The UK reference products are Cozaar® Comp 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets (PL 00025/0338, 0473 and 0374 respectively), first authorised to Merck Sharpe & Dohme Limited on 12th April 1996, 17th October 2007 and 22nd December 1999 respectively.

Losartan potassium is an angiotensin-II (AT₁) receptor blocker that is used for control of hypertension as monotherapy or in combination with other agents, primarily thiazide diuretics. Hydrochlorothiazide is a thiazide diuretic that has been in clinical use since the 1970s, for hypertension and heart failure. However, only the use in hypertension has remained while its use in heart failure has been superseded by more potent diuretics including potassium sparing diuretics.

No new non-clinical studies were conducted, which is acceptable given that the products contain widely-used, well-known active substances. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of losartan potassium and hydrochlorothiazide is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for the absence of a Risk Management Plan.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets  
Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg film-coated tablets  
Losartan potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets |
|--------------------------|--------------------------------------------------------------------------------------------------|
| Name(s) of the active substance(s) (INN) | Losartan potassium  
Hydrochlorothiazide |
| Pharmacotherapeutic classification (ATC code) | Angiotensin II antagonists and diuretics  
ATC code: C09DA01 |
| Pharmaceutical form and strength(s) | 50 mg/12.5 mg  
100 mg/12.5 mg  
100 mg/25 mg |
| Reference numbers for the Decentralised Procedure | UK/H/1658/001/DC  
UK/H/1658/002/DC  
UK/H/1658/003/DC |
| Reference Member State | United Kingdom (UK) |
| Member States concerned | Germany (DE), France (FR), Italy (IT), the Netherlands (NL), Portugal (PT) |
| Marketing Authorisation Number(s) | PL 32256/0069,  
PL 32256/0095  
PL 32256/0096 |
| Name and address of the authorisation holder | Aurobindo Pharma (Malta) Limited  
Vault 14, Level 2, Valletta Waterfront  
Floriana FRN 1913  
Malta |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Losartan Potassium

Chemical name: 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl]-imidazole-5-methanol monopotassium salt

2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2’-1H-tetrazol-5-yl)biphenyl-4-yl)methyl] imidazole potassium salt

Structure:

Physical form: A white or almost white crystalline powder.

Solubility Freely soluble in water and very soluble in acetonitrile.

Molecular formula: C_{22}H_{22}ClK_{6}N_{6}O

Molecular weight: 461.01 g/mol

Losartan potassium complies with its European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
INN/Ph.Eur name: Hydrochlorothiazide
Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide

Structure:

Physical form: A white or almost white almost odourless crystalline powder.
Solubility Very slightly soluble in water, sparingly soluble in ethanol and methanol, soluble in acetone.

Molecular formula: C₇H₇ClN₃O₄S₂
Molecular weight: 297.7 g/mol

Hydrochlorothiazide complies with its European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance from its starting materials are controlled by a Certificate of Suitability. Characterisation of the active substance is covered by the Certificate of Suitability.

An appropriate specification with suitable test methods and limits is provided for the active substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

The reference standards, container closure system and stability of the active substance are all on covered by the Certificate of Suitability. This is satisfactory.

P. Medicinal Product
Other Ingredients
Other ingredients in the tablet core consist of pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, pregelatinised starch (maize), anhydrous colloidal silica, and magnesium stearate.

The tablet coating consists of hydroxypropyl cellulose (E463), hypromellose 6cP (E464) and titanium dioxide (E171).
Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets also have the additional excipient Quinoline Yellow Aluminium Lake (E104).

With the exception of Quinoline Yellow Aluminium Lake (E104), all excipients comply with their respective European Pharmacopoeia monographs. Quinoline Yellow Aluminium Lake (E104) complies with in-house specifications.
None of the excipients used contain material of human origin. The supplier has confirmed that the magnesium stearate contained in this product is sourced from vegetable origin. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to produce safe, efficacious products containing losartan potassium and hydrochlorothiazide that could be considered generic medicinal products of Cozaar® Comp 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative *in vitro* dissolution, assay and impurity profiles have been provided for the proposed and reference products.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches of each strength have been provided and are satisfactory.

The applicant has committed to perform process validation on future production-scale batches.

**Finished Product Specification**
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
These products are packaged in:

i) blisters composed of polyvinyl chloride (PVC), aclar and aluminium

ii) high-density polyethylene (HDPE) bottles.

The products come in the following pack sizes:

Blister pack: 14, 28, 30, 50, 56, 60, 90, 98, 100, 280 and 500 film-coated tablets

HDPE bottle: 14 and 500 film-coated tablets

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage instructions ‘Store below 25°C’. This is satisfactory.
Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs), Labels
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved PIL and label mock-ups are included in modules 3 and 4 of this report.

User testing results of the PIL for Losartan potassium 25 mg, 50 mg, 100 mg film-coated tablets (PL 20532/0124-6; UK/H/1167/001-3/DC) have been submitted. A satisfactory bridging statement has been provided. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of losartan potassium and hydrochlorothiazide are well-known. As losartan potassium and hydrochlorothiazide are widely used, well-known active substances, the applicant has not provided any new non-clinical data and none are required. An overview based on literature is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory Environmental Risk Assessment (ERA) was submitted. The ERA contains a calculation of predicted environmental concentration in surface water (PEC_{surface water}) using the default values in the formula in the guidance on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). On this basis, the PEC_{surface water} of both losartan potassium and hydrochlorothiazide exceed the trigger value for a Phase II assessment. However use of the products should not result in an increase in environmental exposure to losartan potassium or to hydrochlorothiazide, and the absence of a Phase II, Tier A risk assessment is acceptable.

From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3  CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

**Pharmacokinetics**

An open-label, randomised, two-treatment, two-sequence, two-period, crossover, single-dose study to compare the pharmacokinetics of the test product Losartan potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets versus the reference product Cozaar® Comp (losartan potassium and hydrochlorothiazide) 100 mg/25 mg film-coated tablets (Merck Sharp & Dohme Limited, UK) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 48 hours post dose. There was a washout period of 9 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for losartan, losartan carboxy acid and hydrochlorothiazide are presented below as non-transformed values:

### Losartan

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng/ml/h)</th>
<th>$\text{AUC}_{0-\infty}$ (ng/ml/h)</th>
<th>$\text{C}_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>1889.36 ± 1374.284</td>
<td>1920.53 ± 1383.113</td>
<td>1276.97 ± 1125.88</td>
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<tr>
<td>Reference (R)</td>
<td>2012.14 ± 1415.277</td>
<td>2045.92 ± 1421.469</td>
<td>1300.84 ± 115.96</td>
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* $\text{T/R Ratio}$

* (90% CI)

### Losartan carboxy acid

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng/ml/h)</th>
<th>$\text{AUC}_{0-\infty}$ (ng/ml/h)</th>
<th>$\text{C}_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>5436.37 ± 2709.14</td>
<td>5691.11 ± 2667.61</td>
<td>987.44 ± 548.94</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>5399.07 ± 2694.27</td>
<td>5640.43 ± 2636.38</td>
<td>945.62 ± 589.11</td>
</tr>
</tbody>
</table>

* $\text{T/R Ratio}$

* (90% CI)

*log transformed values

The $[1-\text{AUCt/\text{AUCin}}]$ ratio (extrapolated AUC) was 1.956 ±1.57 % vs 2.94 ± 3.03 % for test and reference products respectively.

### Losartan half-life

The half-life of losartan carboxy acid was 84.75 – 113.13 hours.

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to $t$ hours

$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

$\text{C}_{\text{max}}$ maximum plasma concentration

$\text{T}_{\text{max}}$ time for maximum concentration

$\text{T}_{1/2}$ half-life

* log transformed values
Losartan carboxy acid is the pharmacologically active metabolite of losartan and therefore was also measured.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC₀₋ₜ, AUC₀₋∞, and Cₓₐₘₚ for losartan, losartan carboxy acid (metabolite) and hydroxychlorothiazide lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) for a biowaiver for the lower strengths, the results and conclusions of the bioequivalence study on the 100 mg/25 mg strength can be extrapolated to Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg and 100 mg/12.5 mg film-coated tablets.

**EFFICACY**

No new efficacy data were submitted with these generic applications and none were required.

**SAFETY**

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

**SUMMARY OF PRODUCT CHARACTERISTICS (SmPCS), PATIENT INFORMATION LEAFLETS (PILS) AND LABELLING**

The SmPCS, PILs and labelling are medically satisfactory and consistent with those for the reference products, where appropriate.

**CLINICAL EXPERT REPORT**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**MAA FORM**

The MAA Forms are medically satisfactory.

**CONCLUSIONS**

From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Losartan potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets and the reference product Cozaar® Comp 100 mg/25 mg film-coated tablets. These bioequivalence results and conclusions can be extrapolated to Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg and 100 mg/12.5 mg film-coated tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with losartan potassium and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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