Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Losartan Potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets

UK PLs 04416/0850, 0852 and 0854

&

Losartan Potassium / Hydrochlorothiazide 100mg / 25mg film-coated tablets

UK PLs 04416/0851, 0853 and 0855

(Losartan potassium, hydrochlorothiazide)

UK/H/1176/01-02/DC

UK/H/1177/01-02/DC

UK/H/1178/01-02/DC

Sandoz Limited

LAY SUMMARY

On 16th January 2009, the MHRA granted Sandoz Limited Marketing Authorisations (licences) for the medicinal products Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets and Losartan potassium / Hydrochlorothiazide 100mg / 25mg film-coated tablets. These are prescription-only medicines.

Losartan potassium / Hydrochlorothiazide film-coated tablets contain two active ingredients, losartan potassium and hydrochlorothiazide. This medicine is used for treatment of high blood pressure. The active ingredients work in different ways within the body to lower blood pressure. Losartan works by promoting relaxation of blood vessels while hydrochlorothiazide works by making your kidneys pass more water and salt.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking these medicines, for the conditions described in the attached Summary of Product Characteristics, outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	Losartan potassium / hydrochlorothiazide 50mg / 12.5mg film-coated tablets Losartan potassium / hydrochlorothiazide 100mg / 25mg film-coated tablets
Type of Application	Generic, Article 10.1
Active Substances	Losartan potassium and hydrochlorothiazide
Form	Film-coated tablets
Strength	50mg / 12.5mg ; 100mg / 25mg
MA Holder	Sandoz Limited 37 Woolmer Way Bordon Hampshire GU35 9QE
Reference Member State (RMS)	UK
Concerned Member State / s (CMS)	**UK/H/1176/01-02/DC:** AT, BE, CZ, DE, DK, ES, FI, FR, HU, IT, LT, NL, NO, PL, PT, RO, SE, SI, SK **UK/H/1177/01-02/DC:** AT, DE, ES, IE, IT, LU **UK/H/1178/01-02/DC:** AT, CZ, DE, DK, ES, HU, PL
Procedure Number	UK/H/1176/01-02/DC UK/H/1177/01-02/DC UK/H/1178/01-02/DC
Timetable	Day 210 –8th December 2008

Module 2

Summary of Product Characteristics

Losartan Potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets

PL 04416/0850, 0852 and 0854 (differences indicated in blue text)

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium / Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 50 mg losartan potassium and 12.5 mg hydrochlorothiazide.

One film-coated tablet contains 26.9 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Light yellow, round, biconvex film-coated tablet.

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 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 is one tablet of Losartan Potassium / Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets (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 Film-coated Tablets, the dosage may be increased to maximum 2 tablets daily of Losartan Potassium / Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets or one tablet of Losartan Potassium / Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets (losartan 100 mg/ HCTZ 25 mg) once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

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 and hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/HCTZ 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/HCTZ tablets.

Use in patients with hepatic impairment
Losartan/HCTZ 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/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
- Symtomatic hyperuricaemia/gout
- 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
- Lactation (see section 4.6)
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)
- Anuria

4.4 Special warnings and precautions for use

Losartan

Angiooedema
Patients with a history of angiooedema (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/ 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 pre-existing 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 cardiomyophathy
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 nonblacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy
Losartan Potassium / 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 Potassium / Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

<u>Hydrochlorothiazide</u>

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 diureticinduced 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.

Anti-doping test
Hydrochlorothiazide could produce a positive analytical result in an anti-doping test.

Special warnings regarding excipients
Losartan Potassium / Hydrochlorothiazide contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 antiinflammatory 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.

Ciclosporin:
Concomitant treatment with ciclosporin 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 antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. 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 Pregnancy and lactation

Pregnancy
The use of Losartan Potassium / Hydrochlorothiazide is not recommended during the first trimester of pregnancy (see section 4.4). The use of Losartan Potassium / Hydrochlorothiazide 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 Losartan Potassium / Hydrochlorothiazide should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan/hydrochlorothiazide therapy exposure 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 Losartan Potassium / Hydrochlorothiazide have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan/hydrochlorothiazide should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide may reduce both plasma volume and uteroplacental blood flow. Thiazides pass the placental barrier and are found in cord blood. They may cause fetal electrolyte disturbances and possibly other reactions that have been observed in adults. Cases of thrombocytopenia in neonates and fetal or neonatal jaundice were reported after treating the mothers with thiazides.

Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because no information is available regarding the use of losartan during breast-feeding, losartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant. Thiazides pass into human milk and may inhibit lactation. Because of the potential for adverse effects on the nursing infant, Losartan Potassium / Hydrochlorothiazide is contraindicated during breast-feeding (see section 4.3).

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

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

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse events peculiar to this combination of substances were observed. The adverse events 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 events that have been seen with one of the individual components and may be potential adverse events 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

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.

<u>Hydrochlorothiazide</u>

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 overdosage with losartan/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 overdosage in humans. The most likely manifestation of overdosage 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: Combination containing an angiotensin II-receptor(type AT1)-antagonist and a thiazide diuretic, Antihypertensive, ATC code: C09DA01

Losartan-Hydrochlorothiazide

The components of Losartan Potassium / 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/hydrochlorothiazde 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 hormon 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 renin secretion leads to increased plasma-renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of 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 bloodbrain 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 oncedaily 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. Foetal 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 foetal and neonatal effects, including renal toxicity and foetal death, occurred when pregnant rate were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Cellulose, microcrystalline
Lactose monohydrate
Maize starch, pregelatinized
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:
Hypromellose
Hydroxypropylcellulose
Iron oxide yellow (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blister: Store below 30°C.
Bottle: Store below 30°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Aluminium//Aluminium blisters.
ACLAR//Aluminium blisters.

HDPE bottle with PP screw cap.

Blister: 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98 and 100 film-coated tablets
Blister (unit dose): 50 film-coated tablets
Bottle: 100, 250 film-coated tablets

Pack sizes for 04416/0852:

Blister: 7, 10, 14, 28, 30, 56, 98 and 100 film-coated tablets
Blister (unit dose): 50 film-coated tablets
Bottle: 100 film-coated tablets

Pack sizes for 04416/0854:

Blister: 10, 14, 28, 30, 56, 60, 90, 98 and 100 film-coated tablets
Blister (unit dose): 50 film-coated tablets
Bottle: 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
37 Woolmer Way
Bordon
Hampshire
GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0850
PL 04416/0852
PL 04416/0854

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/01/2009

10 DATE OF REVISION OF THE TEXT

16/01/2009

Losartan Potassium / Hydrochlorothiazide 100mg / 25mg film-coated tablets
PL 04416/0851, 0853 and 0855 (differences indicated in blue text)

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium / Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

One film-coated tablet contains 53.8 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Light yellow, round, biconvex film-coated tablet.

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 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 maximum dose is one tablet of Losartan Potassium / Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

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 and hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/HCTZ 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/HCTZ tablets.

Use in patients with hepatic impairment
Losartan/HCTZ 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/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
- Symtomatic hyperuricaemia/gout
- 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
- Lactation (see section 4.6)
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)
- Anuria

4.4 Special warnings and precautions for use

Losartan

Angiooedema
Patients with a history of angiooedema (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/ 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 pre-existing 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 cardiomyophathy
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 nonblacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy
Losartan Potassium / 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 Potassium / Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

<u>Hydrochlorothiazide</u>

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 diureticinduced 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.

Anti-doping test
Hydrochlorothiazide could produce a positive analytical result in an anti-doping test.

Special warnings regarding excipients
Losartan Potassium / Hydrochlorothiazide contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 antiinflammatory 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.

Ciclosporin:
Concomitant treatment with ciclosporin 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 antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. 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 Pregnancy and lactation

Pregnancy
The use of Losartan Potassium / Hydrochlorothiazide is not recommended during the first trimester of pregnancy (see section 4.4). The use of Losartan Potassium / Hydrochlorothiazide 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 Losartan Potassium / Hydrochlorothiazide should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan/hydrochlorothiazide therapy exposure 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 Losartan Potassium / Hydrochlorothiazide have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan/hydrochlorothiazide should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide may reduce both plasma volume and uteroplacental blood flow. Thiazides pass the placental barrier and are found in cord blood. They may cause fetal electrolyte disturbances and possibly other reactions that have been observed in adults. Cases of thrombocytopenia in neonates and fetal or neonatal jaundice were reported after treating the mothers with thiazides.

Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because no information is available regarding the use of losartan during breast-feeding, losartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant. Thiazides pass into human milk and may inhibit lactation. Because of the potential for adverse effects on the nursing infant, Losartan Potassium / Hydrochlorothiazide is contraindicated during breast-feeding (see section 4.3).

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

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

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse events peculiar to this combination of substances were observed. The adverse events 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 events that have been seen with one of the individual components and may be potential adverse events with losartan potassium/hydrochlorothiazide are the following:

<u>Losartan</u>

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

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 overdosage with losartan/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 overdosage in humans. The most likely manifestation of overdosage 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: Combination containing an angiotensin II-receptor(type AT1)-antagonist and a thiazide diuretic, Antihypertensive, ATC code: C09DA01

Losartan-Hydrochlorothiazide

The components of Losartan Potassium / 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/hydrochlorothiazde 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 hormon 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 renin secretion leads to increased plasma-renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of 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 bloodbrain 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 oncedaily 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. Foetal 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 foetal and neonatal effects, including renal toxicity and foetal death, occurred when pregnant rate were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Cellulose, microcrystalline
Lactose monohydrate
Maize starch, pregelatinized
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:
Hypromellose
Hydroxypropylcellulose
Iron oxide yellow (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blister: This medicinal product does not require special storage conditions.
Bottle: Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

ACLAR//Aluminium blisters
HDPE bottles with PP screw cap.

Blister: 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98 and 100 film-coated tablets
Blister (unit dose): 50 film-coated tablets
Bottle: 100, 250 film-coated tablets

Pack sizes for 04416/0853:

Blister: 7, 10, 14, 28, 30, 56, 98 and 100 film-coated tablets
Blister (unit dose): 50 film-coated tablets
Bottle: 100 film-coated tablets

Pack sizes for 04416/0855:

Blister: 10, 14, 28, 30, 56, 60, 90, 98 and 100 film-coated tablets
Blister (unit dose): 50 film-coated tablets
Bottle: 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
37 Woolmer Way
Bordon
Hampshire
GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0851
PL 04416/0853
PL 04416/0855

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/01/2009

10 DATE OF REVISION OF THE TEXT

16/01/2009

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER SZ00000LT000

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets

Losartan Potassium/Hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

SANDOZ

1 What Losartan Potassium/ Hydrochlorothiazide is and what it is used for

Losartan potassium belongs to a group of medicines called angiotensin-II receptor antagonists. These cause the blood vessels to relax which in turn lowers the blood pressure. *Hydrochlorothiazide* belongs to a group of drugs called diuretics (water tablets).

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets:
These tablets are used to treat high blood pressure. The combination of losartan and hydrochlorothiazide is a suitable alternative for those people who would otherwise have to be treated with losartan potassium and hydrochlorothiazide given as separate tablets.

Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets:
These tablets are used to treat high blood pressure in patients who have not responded sufficiently to treatment with Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets.

2 Before you take Losartan Potassium/ Hydrochlorothiazide

Do not take Losartan Potassium/Hydrochlorothiazide if you:
- are allergic (hypersensitive) to *losartan*, *hydrochlorothiazide* or any of the other ingredients of this medicine (see Section 6 and end of Section 2).
- are allergic (hypersensitive) to *sulphonamide derived substances* (e.g. other thiazides, some antibacterial

Talk to your doctor if you are an athlete taking a doping test, as Losartan Potassium/Hydrochlorothiazide contain an active ingredient that can cause positive results in a doping test.

Losartan Potassium/Hydrochlorothiazide may be less effective in black people.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is essential that you tell the doctor if you use the following medicines:

- lithium (a medicine for treatment of mania or depression)
- potassium supplements
- potassium-containing salt substitutes
- potassium-sparing medicines
- other diuretics (water tablets)
- some laxatives
- medicines for the treatment of gout
- therapeutic vitamin D supplements
- medicines to control heart rhythm
- medicines for diabetes (oral agents or insulins)
- medicines to reduce your blood pressure
- steroids
- medicines to treat cancer
- pain killers or arthritis medicines
- medicines to treat fungal infections
- resins used for high cholesterol (e.g. colestyramine)
- medicines which relax muscles
- sleeping tablets
- opioid medicines (e.g. morphine)
- medicines called pressor amines (e.g. adrenaline)

drugs such as co-trimoxazole, ask your doctor if you are not sure).
- are, think you may be or are planning to become pregnant (see also 'Pregnancy and breast-feeding' below).
- are breast-feeding.
- have severely impaired liver function.
- have severely impaired kidney function or your kidneys are not producing any urine.
- have low potassium, low sodium or high calcium levels which cannot be corrected by treatment.
- are suffering from gout.

Losartan Potassium/Hydrochlorothiazide should not be given to children and teenagers under 18 years.

If you think any of the above conditions applies to you, consult your doctor or pharmacists.

Take special care with Losartan Potassium/ Hydrochlorothiazide
These tablets are not generally recommended in the following cases if you:
- have previously suffered from swelling of the face, lips, throat or tongue
- take diuretics (water pills)
- are on a salt-restricted diet
- have or have had severe vomiting and/or diarrhoea
- have heart failure
- have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant
- have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function)
- have 'aortic or mitral valve stenosis' (narrowing of the valves of the heart) or 'hypertrophic cardiomyopathy' (a disease causing thickening of heart muscle)
- are diabetic
- have or have had gout
- have or have had an allergic condition, asthma or a condition that causes joint pain, skin rashes and fever (systemic lupus erythematosus)
- have high calcium or potassium levels or you are on a low potassium diet
- need an anaesthetic (even at the dentist) or before surgery, you must tell the doctor or medical staff that you are taking Losartan potassium and Hydrochlorothiazide tablets
- have primary hyperaldosteronism (Conn's syndrome), a tumour of the adrenal gland associated with muscle weakness, excessive thirst and frequent urination
- are going to have tests to check your parathyroid function

Ask your doctor if you are not sure what these medicines are.

Taking Losartan Potassium/Hydrochlorothiazide with food and drink
You are advised not to drink alcohol whilst taking these tablets: alcohol and Losartan Potassium/ Hydrochlorothiazide may increase each other's effects.

Dietary salt in excessive quantities may counteract the effect of Losartan Potassium/Hydrochlorothiazide.

Losartan Potassium/Hydrochlorothiazide may be taken with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
You **should not** take Losartan Potassium/ Hydrochlorothiazide in the **first 12 weeks** of pregnancy, and you **must not take** them at all **after the 13th week** as their use during pregnancy may possibly be harmful to the baby.

If you **become pregnant** while on Losartan Potassium/ Hydrochlorothiazide, **tell your doctor immediately.** A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. You **must not take** Losartan Potassium/Hydrochlorothiazide if you are breast-feeding. Your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely. Hydrochlorothiazide may suppress milk production.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. Dizziness has been reported by people taking Losartan Potassium/ Hydrochlorothiazide, if you experience this do not drive a car and do not operate machinery.

Important information about some of the ingredients of Losartan Potassium/Hydrochlorothiazide
Lactose is an ingredient in Losartan Potassium/ Hydrochlorothiazide. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Continued on the next page >>

3 How to take Losartan Potassium/ Hydrochlorothiazide

Always take Losartan Potassium/Hydrochlorothiazide exactly as your doctor has told you. Please ask your doctor or pharmacist if you are not sure.

Take the tablet with a glass of water. It may be taken with or without food.

Use in adults
Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets:
The usual dose is one tablet once daily. If necessary your doctor may increase your dose to a maximum of 2 tablets once daily or one tablet of Losartan Potassium/ Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets once daily.

Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets:
The usual dose is one tablet once daily.

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

Use in kidney impairment and haemodialysis
Do not take Losartan Potassium/Hydrochlorothiazide if your kidney function is severely impaired (i.e. creatinine clearance ≤30 ml/min). Losartan Potassium/ Hydrochlorothiazide is not recommended for patients on haemodialysis.

Use in patients with intravascular volume depletion
Volume and /or sodium depletion should be corrected prior you are given Losartan Potassium/Hydrochlorothiazide.

Use in liver impairment
Losartan Potassium/Hydrochlorothiazide is not recommended for patients with liver impairment. Do not take Losartan Potassium/Hydrochlorothiazide if your liver function is severely impaired (see section 2. "Do not take Losartan Potassium/Hydrochlorothiazide").

Use in children and teenagers under 18 years of age
Losartan Potassium/Hydrochlorothiazide should not be given to children and teenagers.

If you take more Losartan Potassium/ Hydrochlorothiazide than you should
If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department / your doctor immediately / a poison centre. An overdose is

- blurred vision, burning or stinging in the eyes, conjunctivitis, worsening eyesight, seeing things in yellow
- ringing, buzzing, roaring or clicking in the ears
- low blood pressure, which may be associated with changes in posture (feeling light-headed or weak when you stand up, angina (chest pain), abnormal heartbeat, cerebrovascular accident (TIA, "mini-stroke"), heart attack, palpitations
- inflammation of blood vessels, which is often associated with a skin rash or bruising
- sore throat, breathlessness, bronchitis, pneumonia, water on the lungs (which causes difficulty breathing), nosebleed, runny nose, congestion
- constipation, wind, stomach upsets, stomach spasms, nausea, vomiting, dry mouth, inflammation of a salivary gland, toothache
- jaundice (yellowing of the eyes and skin), inflammation of the pancreas
- hives, itching, inflammation of the skin, rash, redness of the skin, sensitivity to light, Lyell syndrome (skin looking as if it were burnt and peeling off), dry skin, flushing, sweating, hair loss
- pain in the arms, shoulders, hips, knees or other joints, joint swelling, stiffness, muscle pain, weakness or cramps
- frequent urination including at night, abnormal kidney function including inflammation of the kidneys, urinary infection, sugar in the urine
- decreased sexual appetite, impotence
- swelling of the face, fever

Rare (affects 1 to 10 users in 10,000)
- hepatitis (inflammation of the liver), abnormal liver function tests

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

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/ bottle/ blister after EXP. The expiry date refers to the last day of that month.

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets:
Blister: Store below 30°C.
Bottle: Store below 30°C. Keep the bottle tightly closed in order to protect from moisture.

likely to cause heart and dehydration problems. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know what tablets were consumed.

If you forget to take Losartan Potassium/ Hydrochlorothiazide
Do not take a double dose to make up for a forgotten tablet. Take your next dose at the usual time.

If you stop taking Losartan Potassium/ Hydrochlorothiazide
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, Losartan Potassium/ Hydrochlorothiazide can cause side effects, although not everybody gets them.

If you experience the following, stop taking Losartan Potassium/Hydrochlorothiazide and tell your doctor immediately or go to the casualty department of your nearest hospital:

A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients. You may need urgent medical attention or hospitalisation.

The following side effects have been reported:
Common (affects 1 to 10 users in 100):
- cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder
- diarrhoea, abdominal pain, nausea, indigestion
- muscle pain or cramps, leg pain, back pain
- insomnia, headache, dizziness
- weakness, tiredness, chest pain
- increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels

Uncommon (affects 1 to 10 users in 1,000):
- anaemia, red or brownish spots on the skin (sometimes especially on the feet, legs, arms and buttocks, with joint pain, swelling of the hands and feet and stomach pain), bruising, reduction in white blood cells, clotting problems and bruising
- loss of appetite, increased uric acid levels or frank gout, increased blood sugar levels, abnormal blood electrolyte levels
- anxiety, nervousness, panic disorder (recurring panic attacks), confusion, depression, abnormal dreams, sleep disorders, sleepiness, memory impairment
- pins and needles or similar sensations, pain in the extremities, trembling, dizziness, migraine, fainting

Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets:
Blister: This medicinal product does not require special storage conditions.
Bottle: Keep the bottle tightly closed in order to protect from moisture.

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 contains
- **The active substance(s)** are losartan potassium and hydrochlorothiazide.

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets contain 50 mg losartan potassium and 12.5 mg hydrochlorothiazide.
Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets contain 100 mg losartan potassium and 25 mg hydrochlorothiazide.

- **The other ingredients are:**

Tablet core: lactose monohydrate, cellulose, microcrystalline, maize starch, pregelatinized, magnesium stearate, silica, colloidal anhydrous.
Tablet film-coating: hypromellose, hydroxypropylcellulose, iron oxide yellow (E172), titanium oxide (E171).

What Losartan Potassium/Hydrochlorothiazide looks like and contents of the pack
Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets are light yellow, round and biconvex film- coated tablets with a diameter of 8 mm.

Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets are light yellow, round and biconvex film- coated tablets with a diameter of 10 mm.

Tablets are packed in aluminium foil blisters or plastic bottles with a screw cap.

Blister: 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98 and 100 film-coated tablets
Blister (unit dose): 50 film-coated tablets
Bottle: 100, 250 film-coated tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sandoz Ltd, Woolmer Way, Bordon, Hampshire, GU35 9QE.

Manufacturer
Lek Pharmaceuticals d.d., Verovskova 57, SI-1526 Ljubljana, Slovenia *or* Lek S.A., Ul. Domaniewska 50 C, 02- 672 Warsaw, Poland *or* Salutas Pharma GmbH, Otto von Guericke Allee 1, 39179 Barleben, Germany *or* Salutas Pharma GmbH, Dieselstrasse 5, 70839 Gerlingen, Germany.

This leaflet was last approved in 12/2008 *(to be amended after approval).* SZ00000LT000

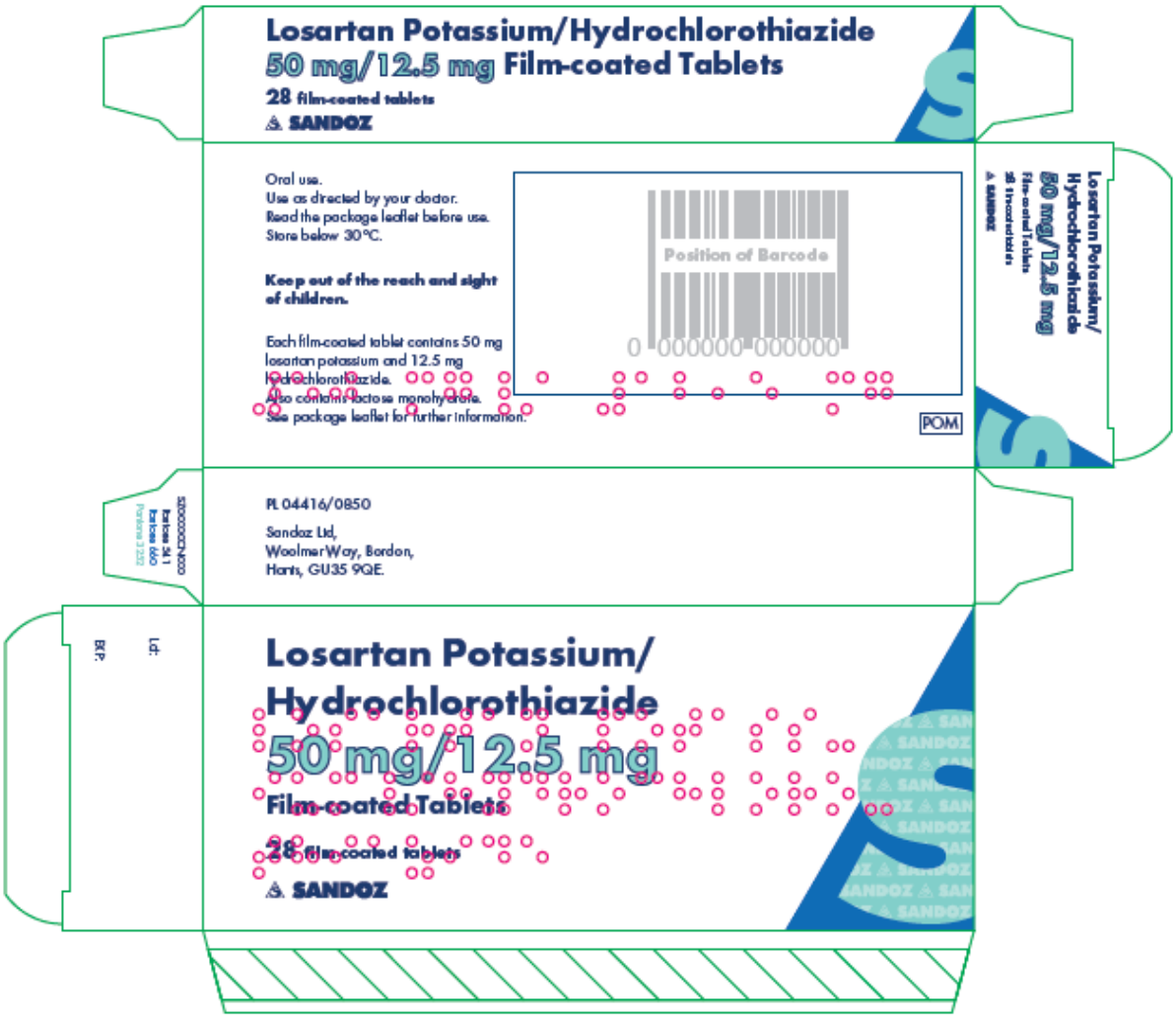
Module 4

Labelling

Losartan potassium / hydrochlorothiazide 50mg / 12.5mg film-coated tablets

PL 04416/0850: Blister carton - pack size 28 tablets.

Labelling for other pack sizes is the same apart from quantity.



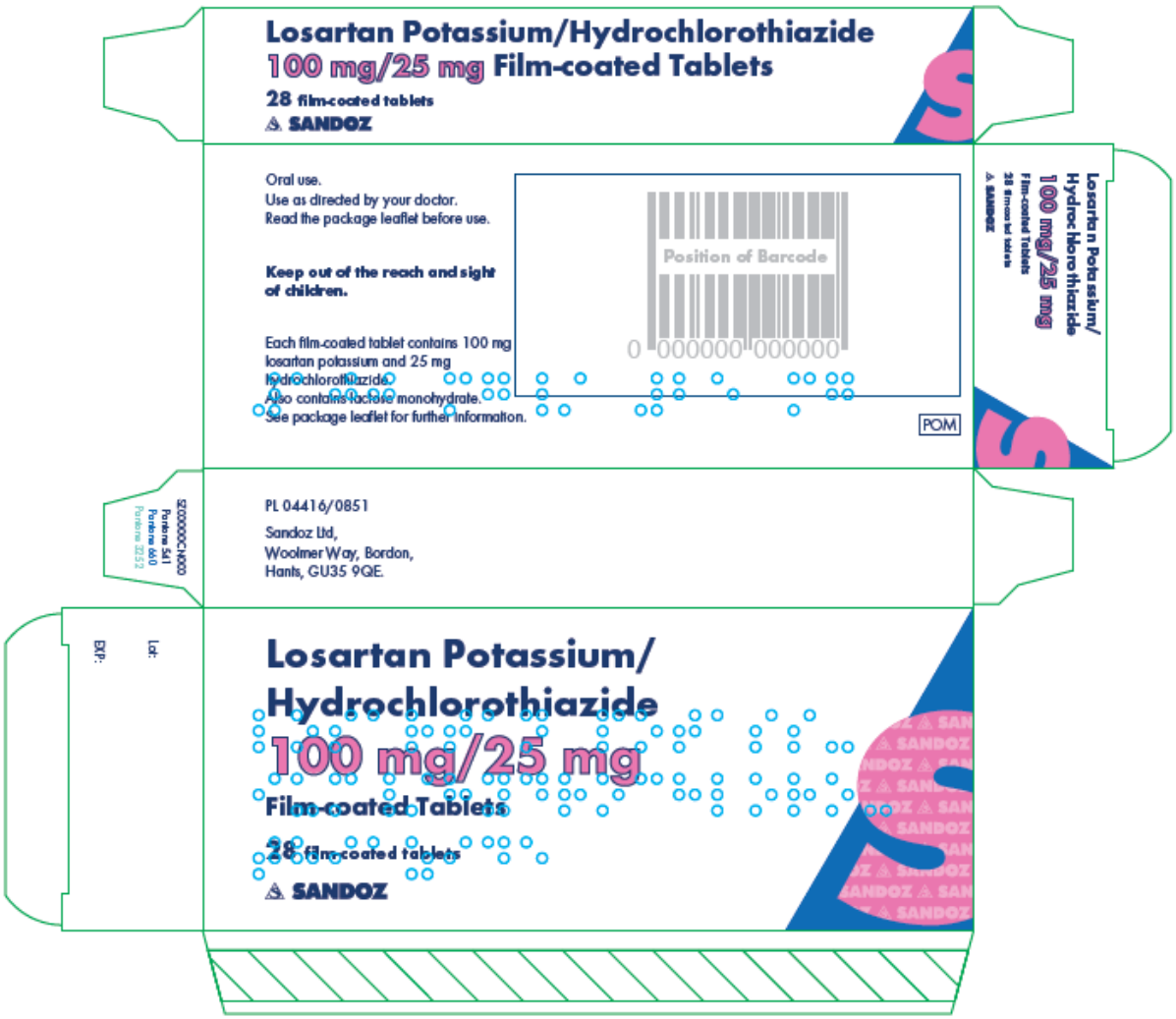
Braille is split over two sides:

Available in packs of:
7, 10, 14, 30, 50, 56, 60, 84, 90, 98 and 100 film-coated tablets.
Not all pack sizes may be marketed.
Only the quantity will change.

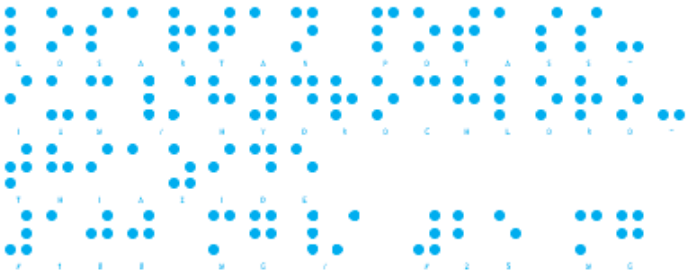
Losartan potassium / hydrochlorothiazide 100mg / 25mg film-coated tablets

PL 04416/0851: Blister carton - pack size 28 tablets.

Labelling for other pack sizes is the same apart from quantity.



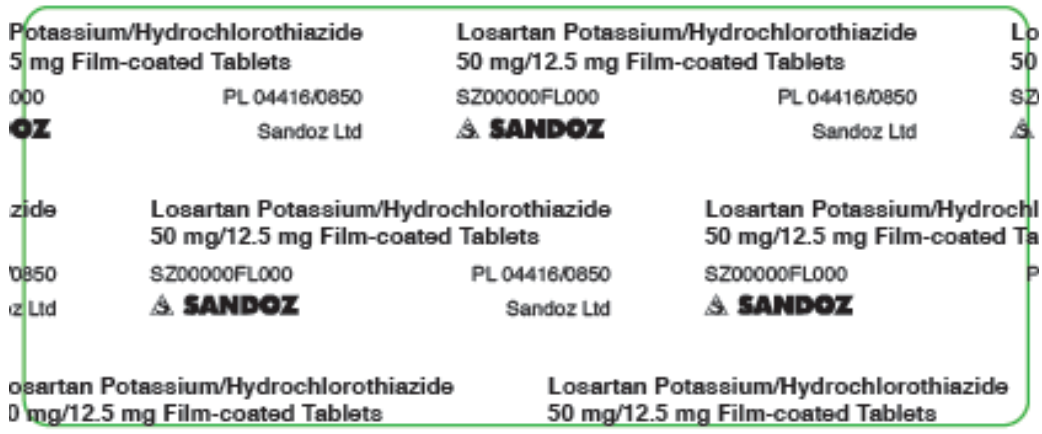
Braille is split over two sides:



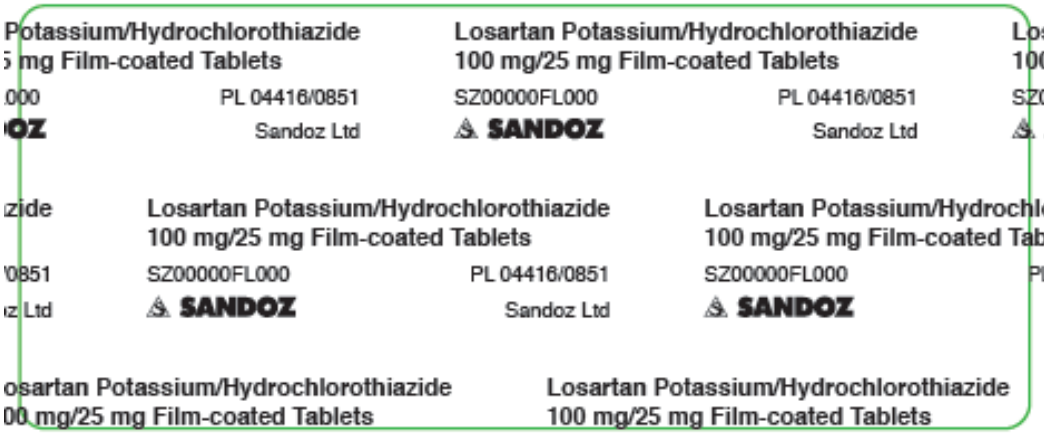
Available in packs of:
7, 10, 14, 30, 50, 56, 60, 84, 90, 98 and 100 film-coated tablets.
Not all pack sizes may be marketed.
Only the quantity will change.

Blister foils

Losartan potassium / hydrochlorothiazide 50mg / 12.5mg film-coated tablets



Losartan potassium / hydrochlorothiazide 100mg / 25mg film-coated tablets



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Sandoz Limited Marketing Authorisations for the medicinal products Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets (PLs 04416/0850, 0852 & 0854; UK/H/1176-8/01/DC) and Losartan potassium / Hydrochlorothiazide 100mg / 25mg film-coated tablets (PLs 04416/0851, 0853 & 0855, UK/H/1176-8/02/DC) on 16th January 2009. The products are prescription-only medicines.

These are abridged applications for Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets and Losartan potassium / Hydrochlorothiazide 100mg / 25mg film-coated tablets, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the reference products, Cozaar-Comp 50/12.5 film-coated tablets and Cozaar-Comp 100/25 film-coated tablets (PLs 00025/0338 & 0374 respectively), authorised to Merck Sharp & Dohme Limited. The innovator product, Cozaar-Comp 50/12.5 film-coated tablets, was granted a UK licence on 12/04/1996. The innovator product has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

These medicinal products contain two active ingredients, losartan potassium and hydrochlorothiazide. 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.

Hydrochlorothiazide is a thiazide diuretic. 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.

Losartan Potassium / Hydrochlorothiazide film-coated tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone. Losartan Potassium and Hydrochlorothiazide in combination 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. The antihypertensive effect of losartan/hydrochlorothiazde is sustained for a 24-hour period.

No new preclinical studies were conducted, which is acceptable given that the applications cross-refer to a product that has been licensed for over 10 years.

The applications are supported by the bioequivalence study presented by the applicant comparing the test product, Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets, to the reference product, Lorzaar ® Plus 50mg / 12.5mg (MSD Chibropharm, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Losartan potassium / hydrochlorothiazide 50mg / 12.5mg film-coated tablets Losartan potassium / hydrochlorothiazide 100mg / 25mg film-coated tablets
Name(s) of the active substance(s) (INN)	Losartan potassium and hydrochlorothiazide
Pharmacotherapeutic classification (ATC code)	Losartan and diuretics (C09D A01)
Pharmaceutical form and strength(s)	Film-coated tablets – 50mg / 12.5mg & 100mg / 25mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1176-78/01-02/DC
Reference Member State	United Kingdom
Member States concerned	**UK/H/1176/01-02/DC:** AT, BE, CZ, DE, DK, ES, FI, FR, HU, IT, LT, NL, NO, PL, PT, RO, SE, SI, SK **UK/H/1177/01-02/DC:** AT, DE, ES, IE, IT, LU **UK/H/1178/01-02/DC:** AT, CZ, DE, DK, ES, HU, PL
Marketing Authorisation Number(s)	PL 04416/0850-0855
Name and address of the authorisation holder	Sandoz Limited 37 Woolmer Way Bordon Hampshire GU35 9QE

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

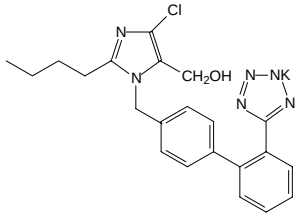
ACTIVE SUBSTANCE

Losartan potassium

Nomenclature:

INN:	Losartan potassium
Chemical names:	(i) 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl]-imidazole-5-methanol monopotassium salt
	(ii) 2-n-butyl-4-chloro-5-hydroxymethyl-1-[((2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl] imidazole potassium salt

Structure:



Molecular formula:	$C_{22}H_{22}ClKN_6O$
Molecular weight:	461.0
CAS No:	124750-99-8
Physical form:	White to off-white free flowing crystalline powder
Solubility:	Freely soluble in water and methanol and insoluble in chloroform

The active substance, losartan potassium, is not the subject of a European Pharmacopeia (EP) 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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 4 years.

ACTIVE SUBSTANCE

Hydrochlorothiazide

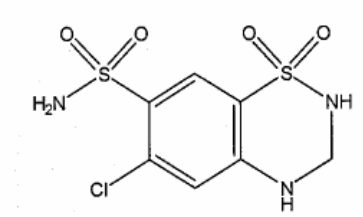
Nomenclature:

INN: Hydrochlorothiazide

Chemical names: (i) 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide

(ii) 6-chloro-3,4-dihydro-1,2-dioxide-2H-1,2,4-benzothiazine-7-sulphonamide

Structure:



Molecular formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297.7
CAS No: 58-93-5

Physical form: White or almost white crystalline powder
Solubility: Very slightly soluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides

The active substance, hydrochlorothiazide, is the subject of a European Pharmacopeia (EP) monograph.

All aspects of the manufacture and control of hydrochlorothiazide are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of hydrochlorothiazide for inclusion in this medicinal product.

DRUG PRODUCT

Description and Composition

The drug products are presented as light yellow, round, biconvex, film-coated tablets; the lower strength tablets containing 50mg of losartan potassium and 12.5mg hydrochlorothiazide; and the higher strength tablets containing 100mg of losartan potassium and 25mg hydrochlorothiazide.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, lactose monohydrate, pregelatinized maize starch, colloidal anhydrous silica, and magnesium stearate making up the tablet core; and hypromellose, hydroxypropylcellulose, titanium dioxide (E171), and iron oxide yellow (E172) making up the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of iron oxide yellow (E172), which complies with the NF. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution and impurity profiles were provided for the test products and the originator products from several EU Member States. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Three types of primary packaging are proposed for the marketed product:

(1) ACLAR - aluminium blisters
(2) Aluminium - aluminium blisters
(3) HDPE containers with polypropylene closures

The tablets are packed in the blisters / HDPE containers, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The tablets are packaged in blister pack sizes of 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98 or 100; and in HDPE container pack sizes of 100 or 250 tablets (please refer to the SmPCs for pack sizes specific to the individual licences). The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set for all Product Licences. For Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets (PLs 04416/0850, 0852 & 0854) the storage instructions are 'Store below 30°C' for the blisters and 'Store below 30°C. Keep the bottle tightly closed in order to protect from moisture.' for the HDPE containers. For Losartan potassium / Hydrochlorothiazide 100mg / 25mg film-coated tablets (PLs 04416/0851, 0853 & 0855) there are no special storage conditions for the blisters and the storage instructions are 'Keep the bottle tightly closed in order to protect from moisture.' for the HDPE containers.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets, to the reference product, Lorzaar ® Plus 50mg / 12.5mg (MSD Chibropharm, Germany).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets is a generic medicinal product of Cozaar-Comp 50/12.5 film-coated tablets (Merck Sharp & Dohme Limited) appears justified.

As the test products, Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets and Losartan potassium / Hydrochlorothiazide 100mg / 25mg film-coated tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg / 12.5mg strength were extrapolated to the 100mg / 25mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of a product that has been licensed within the EU for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of losartan potassium / hydrochlorothiazide in combination, a widely used and well-known combination.

III.3 CLINICAL ASPECTS

BACKGROUND

Losartan is an Angiotensin-II receptor blocker that is used for control of hypertension as monotherapy or in combination with other agents, primarily thiazide diuretics. The other agents in this class are Irbesartan, Valsartan, Telmisartan, Eprosartan, and Candesartan. Losartan (the originator product; Cozaar, MSD) was first authorised in 1994 for treatment of hypertension. The role of Losartan in the treatment of hypertension could be considered well established.

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. Although initially authorised in many EU member states for monotherpay in hypertension, its use is primarily limited as a combination agent with ACE inhibitors (Lisinopril, Enalapril, Captopril), angiotensin receptor blockers (Losartan, Valsartan or telmisartan), or betablockers (Bisoprolol or Nebivolol).

Combination of Losartan potassium & Hydrochlorothiazide:

The combination has been authorised since 1996 in the UK and other EU member states, for treatment of hypertension that is not adequately controlled by monotherapy (losartan potassium or hydrochlorothiazide).

INDICATIONS

Losartan Potassium / Hydrochlorothiazide film-coated tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

The indication is consistent with the reference products and is satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of the combination of losartan potassium and hydrochlorothiazide is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

The applicant has conducted a single bioequivalence study comparing the pharmacokinetic profiles of Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets (test) and Lorzaar ® Plus 50mg / 12.5mg, MSD Chibropharm, Germany (reference). The study was of an appropriate design and was conducted to principles of good clinical practice. The lower strength of Losartan potassium 50mg / Hydrochlorothiazide 12.5mg was selected because of safety concerns if healthy subjects were to be treated with the Losartan potassium 100mg / Hydrochlorothiazide 25mg strength. This was considered satisfactory.

This was a blind, randomised, two-treatment, two-sequence, two-period, two-way, single dose crossover bioavailability and bioequivalence study conducted in 34 (32 completed) healthy adult human male subjects under fasting conditions.

A single dose of the investigational products was administered orally to each subject in each period, under fasted conditions. A satisfactory washout period of 7 days was maintained between the two dosing days in each group. Blood samples were taken pre-dosing and over a 36 hour period after administration of test or reference product. The samples were extracted and analysed using a validated LC-MS/MS bio-analytical method.

The primary pharmacokinetic parameters for this study were $\mathbf{C}_{max}$, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Results:

One volunteer was withdrawn prior to dosing due to a failed drugs test and replaced by one of the stand-by volunteers. Plasma samples of the other stand-by volunteer were not analysed. There were no reports of serious adverse events during the study. The summary of the results of the bioequivalence study are tabulated below:

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Losartan (n=32)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	331.92 $\pm_{96.24}$	370.23 $\pm_{98.29}$	213.80 $\pm_{89.79}$	0.77±0.43
Reference	317.91 $\pm_{99.06}$	356.25 $\pm_{103.95}$	210.10$\pm_{107.27}$	1.00±0.53
***Ratio (90% CI)**	**104.82** 98.31 to 111.76%	**104.48** 98.61 to 110.71%	**102.58** 88.65 to 118.70%	

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

Table 2. Pharmacokinetic parameters for Losartan-carboxy acid (metabolite) (n=32)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	2133.42 ± 895,.64	231.25.26 ± 860.55	297.56 ± 115.45	3.63± 0.85
Reference	2146.68 ± 903.05	2333.56 ± 863.85	312.69 ± 139.75	3.46±0.85
***Ratio (90% CI)**	**99.20** 93.27 – 105.50%	**98.99** 94.21 – 104.01	**97.29** 92.60 – 102.21%	

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

Table 3. Pharmacokinetic parameters for Hydrochlorothiazide (n=32)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	361.27 ± 91.63	381.82 ± 94.11	66.80± 16.66	1.79 ± 0.60
Reference	355.57 ± 97.57	376.59 ± 100.27	62.47 ±15.96	1.95 ± 0.65
***Ratio (90% CI)**	**102.51** 97.02 to 108.31%	**102.07** 96.95-107.47%	**107.30** 99.81 -115.36%	

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test product and reference product are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for these applications. As Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg and 100mg / 25mg film-coated tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg / 12.5mg strength were extrapolated to the 100mg / 25mg strength product.

Clinical efficacy

Efficacy is reviewed in the clinical overview. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

No new data are submitted and none are required for these types of application.

Clinical safety

No new data have been submitted and none are required for applications of this type. Safety is reviewed in the clinical overview. The safety profile of losartan potassium / hydrochlorothiazide combination products is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets) and reference (Cozaar-Comp 50/12.5 film-coated tablets, Merck Sharp & Dohme Limited) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 50mg / 12.5mg strength were extrapolated to the 100mg / 25mg strength product.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg and 100mg / 25mg 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg film-coated tablets, and the reference product, Cozaar-Comp 50/12.5 film-coated tablets (PL 00025/0338; Merck Sharp & Dohme Limited).

As Losartan potassium / Hydrochlorothiazide 50mg / 12.5mg and 100mg / 25mg film-coated tablets were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg / 12.5mg strength were extrapolated to the 100mg / 25mg strength product, and no separate bioequivalence studies were necessary.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

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

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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 the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed. They have committed to submitting mock-ups for all packaging for assessment before those packs are commercially marketed.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and the valid extrapolation of its results and conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with losartan potassium / hydrochlorothiazide combination products is considered to have demonstrated the therapeutic value of these medicinal products. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome