COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Kaliumlosartan/Hydrochloorthiazide Sandoz 100/12.5 mg, film-coated tablets (losartan potassium/hydrochlorothiazide)

NL/H/4473/003/DC

Date: 20 February 2023

This module reflects the scientific discussion for the approval of Kaliumlosartan/Hydrochloorthiazide Sandoz 100/12.5 mg, film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/1176/003/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

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

Procedure No: UK/H/1176-8/003/DC

UK Licence No: PL 04416/1197-9

Sandoz Limited

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

On 06 September 2011, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Sandoz Limited for medicines called Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets (PL 04416/1197-9; UK/H/1176-8/003/DC). Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets are available on prescription from your doctor and are used to treat high blood pressure in patients who require additional blood pressure control and are already taking either losartan or hydrochlorothiazide monotherapy. 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/12.5 mg Film-coated Tablets contain two active substances called losartan potassium and hydrochlorothiazide. Losartan potassium belongs to a group of medicines called angiotensin II receptor antagonists. These cause the blood vessels to relax, which in turn lower the blood pressure. Hydrochlorothiazide belongs to a group of medicines called diuretics (water tablets).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations were granted.

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Module 1
Information about the initial procedure

Product Name(s)	Losartan potassium/hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets
Type of Application(s)	Generic, Article 10.1
Active Substances	Losartan potassium/hydrochlorothiazide
Form	Film-coated tablets
Strength(s)	100 mg/12.5 mg
MA Holder	Sandoz Ltd Frimley Business Park, Frimley Camberley Surrey, GU16 7SR United Kingdom
Reference Member State (RMS)	UK
Concerned Member States (CMS)	**UK/H/1176/003/DC:** Germany, Denmark, Finland, the Netherlands, Norway, Poland, Sweden and Slovenia **UK/H/1177/003/DC:** Germany and Luxembourg **UK/H/1178/003/DC:** Germany
Procedure Number	UK/H/1176-8/003/DC
Timetable	Day 210 – 03 August 2011

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 100 mg losartan potassium and 12.5 mg hydrochlorothiazide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

white, round, biconvex, film coated tablets, embossed with 100 and 12.5 on one side.

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

4.2 Posology and method of administration
For oral 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 (losartan potassium 50 mg/hydrochlorothiazide 12.5 mg) once daily. For patients who do not respond adequately to Losartan potassium/Hydrochlorothiazide, the dosage may be increased to 2 tablets daily of Losartan potassium/Hydrochlorothiazide or one tablet of Losartan potassium/Hydrochlorothiazide (losartan potassium 100 mg/ hydrochlorothiazide 25 mg) once daily. The maximum dose is one tablet of Losartan potassium/Hydrochlorothiazide once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy. Losartan potassium/Hydrochlorothiazide (losartan potassium 100 mg/ hydrochlorothiazide 12.5 mg) is available for those patients titrated to 100 mg of losartan potassium mono therapy who require additional blood pressure control.

Use in patients with renal impairment and haemodialysis patients
Losartan potassium and hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan potassium /hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

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

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Losartan

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 non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy
AIIRAs should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs Losartan Potassium/Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

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

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

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

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

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

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

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

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

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

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

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

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

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

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

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

Calcium salts
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

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

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

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

Patients should be rehydrated before the administration.

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs):

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during second and third trimesters may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women, except in rare situations where no other alternative treatment could be used.

Lactation

Angiotensin II Receptor Antagonists (AIIRAs):
Losartan:
Because no information is available regarding the use of Losartan Potassium/Hydrochlorothiazide during breastfeeding, Losartan Potassium/Hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Losartan Potassium/Hydrochlorothiazide during breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

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

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

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

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

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

Hepato-biliary disorders
Rare: Hepatitis

Investigations
Rare: Hyperkalaemia, elevation of ALT

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

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

Immune system disorders
Rare: Anaphylactic reactions, angioedema, urticaria

Metabolism and nutrition disorders
Uncommon: Anorexia, gout

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

Nervous system disorders
Common: Headache, dizziness
Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

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

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus

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

Vascular disorders
Uncommon: Vasculitis

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

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

Hepato-biliary disorders
Not known: Liver function abnormalities

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

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

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

Reproductive system and breast disorders
Uncommon: Decreased libido, impotence

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

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

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

Immune system disorders
Rare: Anaphylactic reaction

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

Psychiatric disorders
Uncommon: Insomnia

Nervous system disorders
Common: Cephalalgia

Eye disorders
Uncommon: Transient blurred vision, xanthopsia

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

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

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

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

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

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

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

General disorders and administration site conditions
Uncommon: Fever, dizziness

4.9 Overdose

No specific information is available on the treatment of 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: Angiotensin II antagonists and diuretics
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 hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle cell proliferation.

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

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

During the administration of losartan the removal of the angiotensin II negative feedback on 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. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse fetal and neonatal effects, including renal toxicity and fetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Silicified microcrystalline cellulose
Silica colloidal anhydrous
Croscarmellose sodium
Silica
Magnesium stearate

Film-coating:
Hypromellose
Hydroxypropyl Cellulose
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

After first opening the bottle: 6 months

6.4 Special precautions for storage
OPA/Al/PVC/Al blisters: Do not store above 25 ° C. Keep in the original packaging.
White Aclar/PVC/Al blisters: Do not store above 25 ° C. Keep in the original packaging.
HDPE bottle with PP screw cap: Do not store above 25° C. Keep in the original packaging. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container
- OPA/Al/PVC/Al blisters.
- White Aclar/PVC/Al blisters.
- White HDPE bottle with PP screw cap.

HPDE bottle contains a silica gel desiccant (for absorbing moisture) either in the plastic screw cap or in a capsule/sachet. Do not swallow the silica gel capsule/sachet.

Blister: 7, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98 and 100 film-coated tablets
Bottle: 100, 250 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 Ltd
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1197
PL 04416/1198
PL 04416/1199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/09/2011

10 DATE OF REVISION OF THE TEXT

06/09/2011

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER SZ00000LT000

Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 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).

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 is available for patients who require additional blood pressure control and already are taking either 100 mg of losartan or hydrochlorothiazide monotherapy.

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 drugs such as co-trimoxazole, ask your doctor if you are not sure)
- are more than 3 months pregnant. (It is also better to avoid Losartan Potassium/Hydrochlorothiazide in early pregnancy – see Pregnancy)
- 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.

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

Take special care with Losartan Potassium/Hydrochlorothiazide
You must tell your doctor if you think you are (or might become) pregnant. Losartan Potassium/Hydrochlorothiazide is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

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 impaired liver function (see sections 2 "Do not take Losartan Potassium/Hydrochlorothiazide" and "Dosage in special patient groups")
- have **narrow arteries to your kidneys** (renal artery stenosis) or only have **one functioning kidney,** or you have recently had a **kidney transplant**
- are on haemodialysis
- 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 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 low **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** associated with increased secretion of the hormone aldosteron by the adrenal gland, caused by an abnormality within the gland.
- are going to have tests to check your **parathyroid** function

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.

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**
- 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**
- **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**)
- **glycyrrhizin** (found in liquorice root)

Ask your doctor if you are not sure what these medicines are.
Please also inform your doctor you are taking Losartan Potassium/Hydrochlorothiazide if you will be undergoing a radiographic procedure and will be given iodine contrast media.

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
Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Losartan Potassium/Hydrochlorothiazide before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Losartan Potassium/Hydrochlorothiazide. Losartan Potassium/Hydrochlorothiazide is not recommended in pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Losartan Potassium/Hydrochlorothiazide is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is a newborn, or born prematurely.'

Ask your doctor or pharmacist for advice before taking any medicine.

Use in children and adolescents
There is no experience with the use of Losartan Potassium/Hydrochlorothiazide in children. Therefore, Losartan Potassium/Hydrochlorothiazide should not be given to children.

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.

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. It is important to continue taking Losartan Potassium/Hydrochlorothiazide for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

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

Use in adults
The usual dose is one tablet once daily.

Continued on the next page >>

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

Use in kidney impairment and haemodialysis:
In case of moderate kidney problems dosage adjustment is not usually necessary. However, do not take Losartan Potassium/Hydrochlorothiazide if your kidney function is severely impaired. Losartan Potassium/Hydrochlorothiazide is not recommended for patients on haemodialysis.

Use in liver impairment:
Losartan Potassium/Hydrochlorothiazide should be used with caution in patients with history of mild to moderate liver impairment. However, 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.

Use in black patients:
Dosage adjustment may be necessary as Losartan Potassium/Hydrochlorothiazide may be **less effective in black patients than in non-black patients.**

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 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 1000):
- 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, high level of uric acid in the blood or frank gout, high blood sugar level, abnormal level of electrolyte in the blood
- 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
- 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 10000)
- hepatitis (inflammation of the liver), abnormal liver function tests

Unknown (frequency cannot be estimated from the available data)
- muscle damage in adults (any unusual aches or pains in your muscles which go on for longer than expected)

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.

- OPA/Al/PVC//Al blisters: Do not store above 25° C. Keep in the original packaging.
- White Aclar/PVC//Al blisters: Do not store above 25° C. Keep in the original packaging.
- White HDPE bottle with PP screw cap: Do not store above 25° C. Keep in the original packaging. Keep the container tightly closed in order to protect from moisture.

HPDE bottle contains a silica gel desiccant (for absorbing moisture) either in the plastic screw cap or in a capsule/sachet. Do not swallow the silica gel capsule/sachet.

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 substances** are losartan potassium and hydrochlorothiazide.

Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets contain 100 mg of losartan Potassium and 12.5 mg of hydrochlorothiazide

The ***other ingredients*** are:
Tablet core: silicified microcrystalline cellulose, croscarmellose sodium, silica, silica colloidal anhydrous, magnesium stearate.
Film-coating: hypromellose, hydroxypropyl cellulose, titanium dioxide (E171).

What Losartan Potassium/Hydrochlorothiazide looks like and contents of the pack
Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets are white, round, biconvex, film-coated tablets, embossed with 100 and 12.5 on one side.

Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets are packed in OPA/Al/PVC//Al blisters or Aclar/PVC//Al blister or HPDE bottles with a PP screw cap.

Blister: 7, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98 and 100 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,
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR,
United Kingdom.

Manufacturer
Lek Pharmaceuticals d.d.,
Verovškova 57, 1526 Ljubljana, Slovenia

or

Lek S.A., ul. Podlipie 16, 95 010 Stryków, Poland

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 08/2011 *(to be amended after approval).*

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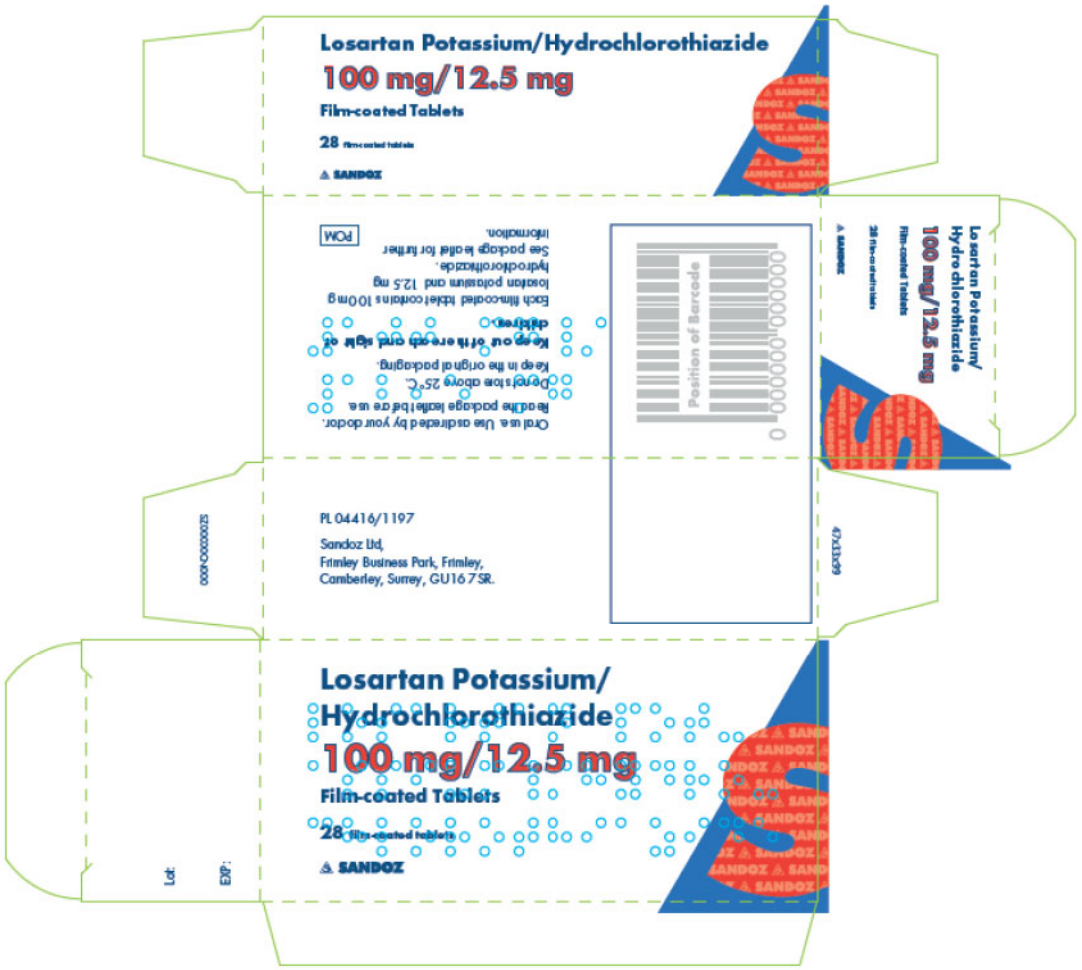
Module 4

Please note that representative labelling for Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets (PL 04416/1197; UK/H/1176/003/DC) is shown below. The labelling details for Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets (PL 04416/1198-9; UK/H/1177-8/003/DC) are consistent with this text, with the exception of the Marketing Authorisation number.



Module 5
Scientific discussion during initial procedure

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets (PL 04416/1197-9; UK/H/1176-8/003/DC) could be approved. The products are prescription-only medicines indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets contain the active ingredients losartan potassium and hydrochlorothiazide. Losartan potassium is an angiotensin-II (AT_1) receptor blocker that is used for the control of hypertension as monotherapy, or in combination with other agents, primarily thiazide diuretics. Hydrochlorothiazide is a thiazide diuretic. Thiazides increase urinary excretion of sodium, potassium and chloride via an action on renal tubules. The co-administration of an angiotensin-II (AT_1) receptor blocker counteracts potassium loss associated with thiazide diuretics.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, Denmark, Finland, Luxembourg, the Netherlands, Norway, Poland, Sweden and Slovenia as Concerned Member States (CMS). These abridged applications were submitted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the combination Losartan potassium/Hydrochlorothiazide (Cozaar-Comp) that has been established in the EU for over 10 years The applications cross-refer to the originator product Cozaar Comp 50 mg /12.5mg (Merck, Sharp & Dohme, UK), which was first authorised in the UK on 12 April 1996. Cross-reference has also been made to the UK brand leader product, Cozaar-Comp 100 mg/12.5 mg Tablets. (Merck, Sharp and Dohme, UK), which was first authorised in the UK on 17 October 2007, as a line extension.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support these applications, comparing the test product Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg (Sandoz Limited) versus the reference product Lorzaar Plus Forte 100 mg-12.5 mg Filmtabletten (MSD Chibropharm GmbH, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. 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.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 03 August 2011. After a subsequent national phase, licences were granted in the UK on 06 September 2011.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Losartan potassium/hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Losartan potassium/Hydrochlorothiazide
Pharmacotherapeutic classification (ATC code)	Angiotensin II antagonists and diuretics (C09DA01)
Pharmaceutical form and strength(s)	Film-coated tablets 100 mg/12.5 mg
Reference numbers for the Decentralised Procedure	UK/H/1176-8/003/DC
Reference Member State (RMS)	United Kingdom
Concerned Member States (CMS)	**UK/H/1176/003/DC:** Germany, Denmark, Finland, the Netherlands, Norway, Poland, Sweden and Slovenia **UK/H/1177/003/DC:** Germany and Luxembourg **UK/H/1178/003/DC:** Germany
Marketing Authorisation Number(s)	PL 04416/1197-9
Name and address of the authorisation holder	Sandoz Limited Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

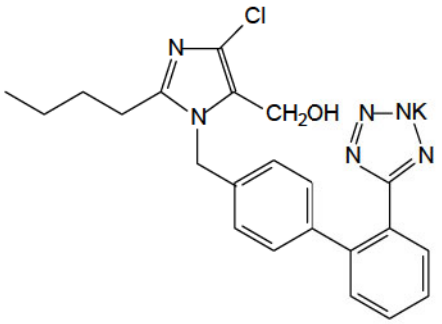
ACTIVE SUBSTANCE – LOSARTAN POTASSIUM

INN: Losartan potassium

Chemical Name: 5-(hydroxymethyl)-1H-imidazol-1-yl]methyl]biphenyl- 2-yl]tetrazol-1-ide
2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl]-imidazole-5-methanol monopotassium salt;
2-n-butyl-4-chloro-5-hydroxymethyl-1-[((2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl] imidazole potassium salt

Molecular Formula: $C_{22}H_{22}ClKN_6O$

Structure:



Molecular mass: 461.0

Appearance: A white to almost white crystalline powder, freely soluble in water and methanol and slightly soluble in acetonitrile.

Losartan potassium is not the subject of a European Pharmacopoeia monograph.

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

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

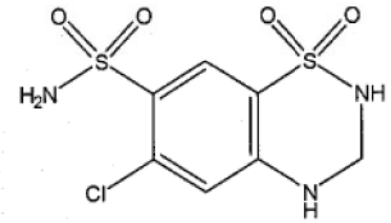
ACTIVE SUBSTANCE - HYDROCHLOROTHIAZIDE

INN: Hydrochlorothiazide

Chemical Name(s): 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide;
6-chloro-3,4-dihydro-1,2-dioxide-2H-1,2,4-benzothiazine-7-sulphonamide

Molecular Formula: $C_7H_8ClN_3O_4S_2$

Structure:



Molecular mass: 297.7

Appearance: A white to almost white, crystalline powder, very slighty soluble in water, sparingly soluble in ethanol (96%), and soluble in acetone and dilute solutions of alkali hydroxides.

Hydrochlorothiazide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance hydrochlorothiazide are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the tablet core and film coating, namely silicified microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, silica, magnesium stearate, hypromellose, hydroxypropyl cellulose and titanium dioxide (E171).Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of silica and silicified microcrystalline cellulose, all excipients comply with their respective European Pharmacopoeia monograph. Silica is controlled to its US National Formulary specification and silicified microcrystalline cellulose is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference product Lorzaar Plus Forte 100 mg-12.5 mg Filmtabletten (MSD Chibropharm GmbH Germany).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and the reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are are packaged in:

1. oriented polyamide/aluminium/polvinylchloride/aluminium or white Aclar/polyvinylchloride/aluminium blisters in pack sizes of 7, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98 and 100 film-coated tablets
2. white high-density polyethylene bottles, with polypropylene screw caps, containing silica gel dessicant (for absorbing moisture), in pack sizes of 100 and 250 film-coated tablets.

Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with foodstuff.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, the following shelf-life/storage conditions have been accepted:

- 2 years for product packaged in blister packs, with the storage conditions, "Do not store above 25°C. Keep in the original packaging."
- 2 years for product stored in the unopened HDPE bottle and 6 months for the product after the HDPE bottle is first opened, with the storage conditions "Do not store above 25°C. Keep in the original packaging. Keep the container tightly closed in order to protect from moisture."

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PIL) and Labelling

The SmPCs, PIL and labelling are pharmaceutically satisfactory.

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, as amended. 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 it contains.

MAA Forms

All aspects of the MAA forms are pharmaceutically satisfactory.

Expert Report

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

Conclusion

The grant of Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of losartan potassium and hydrochlorothiazide are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with a product (or products) that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION

The grant of Marketing Authorisations is recommended.

III.3 CLINICAL ASPECTS

The clinical pharmacology of losartan potassium and hydrochlorothiazide is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-treatment, three-way, semi-replicate, crossover study comparing the pharmacokinetics of the test product Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets (Sandoz Limited, UK) and the reference product Lorzaar Plus Forte 100 mg-12.5 mg Filmtabletten (MSD Chibropharm GmbH Germany) in healthy male adult subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240 ml of water after at least a 12-hour overnight fast. Blood samples were collected before and up to 36 hours after each administration. The washout period between the treatment arms was 7 days. Although this was a single-dose study, each subject received the product they were randomised to in the first period again in the third period. This was done to analyse and account for any intra-subject variability. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (arithmetic means±SD) of losartan (parent)

	First Administration		Second Administration	
	Losartan /HCTZ (Test)	Lorzaar Plus Forte (Reference)	Losartan /HCTZ (Test)	Lorzaar Plus Forte (Reference)
AUC_{0-t} (ng h/mL)	874.42±301.13	839.51±331.98	799.30±208.08	907.75±383.37
AUC_{0-inf} (ng.h/mL)	882.84±303.64	848.97±336.74	807.61±210.86	916.38±386.69
C_{max} (ng/mL)	583.93±255.49	488.00±218.26	496.57±177.51	598.66±306.15

AUC_{0-inf} 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
HCTZ hydrochlorothiazide

Pharmacokinetic parameters (ratios, confidence intervals [CI] and intra-subject CV) of losartan(parent)

Statistical Analysis	Test/Ref Ratio (%)	90% CI	Intra-Subject CV (%)	
			Losartan/HCTZ (Test)	Lorzaar Plus Forte (Reference)
AUC_{0-t} (ng h/mL)	103.78	100.70-106.96	10.29	10.57
AUC_{0-inf} (ng.h/mL)	103.66	100.59-106.82	10.26	10.55
C_{max} (ng/mL)	113.83	102.11-126.90	38.07	28.89

AUC_{0-inf} 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
CV coefficient variant
HCTZ hydrochlorothiazide
Ratios and 90% geometric CI calculated from ln-transformed data

Pharmacokinetic parameters (arithmetic means±SD) of losartan carboxy acid (metabolite)

	First Administration		Second Administration	
	Losartan /HCTZ (Test)	Lorzaar Plus Forte (Reference)	Losartan /HCTZ (Test)	Lorzaar Plus Forte (Reference)
AUC_{0-t} (ng h/mL)	4775.97±1066.09	4648.83±1053.07	4553.88±1122.38	4900.89±966.82
AUC_{0-inf} (ng.h/mL)	4820.00±1073.06	4694.51±1059.66	4594.87±1126.62	4947.34±971.13
C_{max} (ng/mL)	818.05±236.65	774.47±237.53	769.02±266.15	822.39±233.52

AUC_{0-inf} 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
K potassium
HCTZ hydrochlorothiazide

Pharmacokinetic parameters (ratios, confidence intervals [CI] and intra-subject CV) of losartan carboxy acid (metabolite)

Statistical Analysis	Test/Ref Ratio (%)	90% CI	Intra-Subject CV (%)	
			Losartan/HCTZ (Test)	Lorzaar Plus Forte (Reference)
AUC_{0-t} (ng h/mL)	102.71	100.70-104.76	4.13	7.51
AUC_{0-inf} (ng.h/mL)	102.66	100.67-104.70	4.08	7.46
C_{max} (ng/mL)	105.59	101.78-109.54	8.23	12.40

AUC_{0-inf} 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
CV coefficient variant
HCTZ hydrochlorothiazide
Ratios and 90% geometric CI calculated from ln-transformed data

Pharmacokinetic parameters (arithmetic means±SD) of hydrochlorothiazide

	First Administration		Second Administration	
	Losartan /HCTZ (Test)	Lorzaar Plus Forte (Reference)	Losartan /HCTZ (Test)	Lorzaar Plus Forte (Reference)
AUC_{0-t} (ng h/mL)	874.42±301.13	839.51±331.98	799.30±208.08	907.75±383.37
AUC_{0-inf} (ng.h/mL)	882.84±303.64	848.97±336.74	807.61±210.86	916.38±386.69
C_{max} (ng/mL)	583.93±255.49	488.00±218.26	496.57±177.51	598.66±306.15

AUC_{0-inf} 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
HCTZ hydrochlorothiazide

Pharmacokinetic parameters (ratios, confidence intervals [CI] and intra-subject CV) of hydrochlorothiazide

Statistical Analysis	Test/Ref Ratio (%)	90% CI	Intra-Subject CV (%)	
			Losartan/HCTZ (Test)	Lorzaar Plus Forte (Reference)
AUC_{0-t} (ng h/mL)	105.66	102.09-109.36	7.76	12.09
AUC_{0-inf} (ng.h/mL)	105.64	102.28-109.10	7.42	11.49
C_{max} (ng/mL)	109.99	103.99-116.34	13.11	19.95

AUC_{0-inf} 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
CV coefficient variant
HCTZ hydrochlorothiazide
Ratios and 90% geometric CI calculated from ln-transformed data

The *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80% to 125% for C_{max} and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC_{0-t} and AUC_{0-inf} for all parameters lie within the acceptable limits. However, the 90% CI upper value for C_{max} for losartan lies outside the acceptable limit. The protocol defined bioequivalence as 90% CI between 80-125% for AUC_t and AUC_{inf}, but chose widened criteria of 75-133% for C_{max} on the basis of C_{max} variability, and the lack of relation between C_{max} and efficacy/safety. It is accepted that the marginally higher C_{max} (90% CI upper value of 126.90) in this semi-replicate design study is neither a safety nor an efficacy issue, given that this combination will not be used either independently or for initiation therapy (i.e. without titration). Moreover, there have been other instances of other procedures for losartan ending positively that have had similar marginal results.

It is considered that the arguments are acceptable and the test product Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets (Sandoz Limited, UK) could be considered a generic medicinal product to the reference product Lorzaar Plus Forte 100 mg-12.5 mg Filmtabletten (MSD Chibropharm GmbH, Germany).

As the German product used in the bioequivalence study is considered identical to the UK reference product (Cozaar-Comp 100 mg/12.5 mg Tablets. (Merck, Sharp & Dohme, UK), bioequivalence has also been shown between the test product and the UK reference product.

EFFICACY

The efficacy of losartan potassium and hydrochlorothiazide is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose from the bioequivalence data.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
A suitable justification has been provided for not submitting a Risk Management Plan for these products.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with that for the UK brand leader. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT

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

CONCLUSION

The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

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

NON-CLINICAL

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of losartan potassium and hydrochlorothiazide are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's test product Losartan Potassium/Hydrochlorothiazide 100 mg/12.5 mg Film-coated Tablets and the reference product Lorzaar Plus Forte 100 mg-12.5 mg Filmtabletten (MSD Chibropharm GmbH, Germany). As the German product used in the bioequivalence study is considered identical to the UK reference product (Cozaar-Comp 100 mg/12.5 mg Tablets. (Merck, Sharp & Dohme, UK), bioequivalence has also been shown between the test product and the UK reference product.

SAFETY

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profiles of losartan potassium and hydrochlorothiazide are well-known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with that for the reference product. The PIL is consistent with the details in the SmPCs and in-line with current guidelines. The labelling is in-line with current guidelines.

BENEFIT/RISK ASSESSMENT

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome