

# **Public Assessment Report**

## **Decentralised Procedure**

**LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE  
50/12.5MG FILM-COATED TABLETS  
(PL 00289/0967)**

**LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE  
100/25MG FILM-COATED TABLETS  
(PL 00289/0968)**

**UK/H/0906/001-2/DC  
UK licence no: PL 00289/0967-8**

**TEVA UK Limited**

## LAY SUMMARY

On 26<sup>th</sup> March 2008, the MHRA granted Teva UK Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium and Hydrochlorothiazide 50/12.5mg and 100/25mg Film-Coated Tablets. These are prescription-only medicines that are used to reduce high blood pressure (essential hypertension).

Losartan belongs to a group of medicines called angiotensin receptor antagonists. Angiotensin is a naturally occurring chemical in the body that narrows blood vessels and makes it harder for blood to pass through, causing blood pressure to increase. Losartan blocks the effects of angiotensin, causing blood vessels to relax, which in turn lowers blood pressure.

Hydrochlorothiazide works by making your kidneys pass more water and salt, thus reducing the volume of blood passing through the body.

Together, the effects of losartan and hydrochlorothiazide reduce blood pressure.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Losartan Potassium/Hydrochlorothiazide 50/12.5mg and 100/25mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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## Module 1

|                     |  |
|---------------------|--|
| Product Name        | Losartan Potassium and Hydrochlorothiazide 50/12.5mg Film-Coated Tablets<br>Losartan Potassium and Hydrochlorothiazide 100/25mg Film-Coated Tablets  |
| Type of Application | Generic, Article 10.1  |
| Active Substance    | Losartan Potassium and Hydrochlorothiazide   |
| Form                | Film-Coated Tablets  |
| Strength            | 50mg Losartan Potassium and 12.5mg Hydrochlorothiazide<br>100mg Losartan Potassium and 25mg Hydrochlorothiazide  |
| MA Holder           | Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK  |
| RMS                 | United Kingdom   |
| CMS                 | Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Luxembourg, Latvia, The Netherlands, Norway, Portugal, Sweden, Slovakia, Slovenia and Spain |
| Procedure Number    | UK/H/0906/001-2/DC   |
| Timetable           | Day 210 – 14 <sup>th</sup> May 2007  |

## Module 2

### Summary of Product Characteristics

#### SUMMARY OF PRODUCT CHARACTERISTICS

##### 1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium and Hydrochlorothiazide 50 mg/12.5 mg Film-Coated Tablets

##### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg losartan potassium and 12.5 mg hydrochlorothiazide.

Excipients:

Each tablet contains 135 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

##### 3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval, bi-convex tablets marked with "5" and "0" on one side and a score line on both sides.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

##### 4 CLINICAL PARTICULARS

###### 4.1 Therapeutic indications

For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

###### 4.2 Posology and method of administration

*Method of administration*

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). Losartan potassium/Hydrochlorothiazide may be administered with or without food.

Where possible, titration with the individual components (i.e. losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy with losartan 50 mg or hydrochlorothiazide 12.5 mg to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual starting and maintenance dose is 1 tablet once daily for most patients. For patients who do not respond adequately, the dosage may be increased to 2 tablets once daily. The maximum dose is 2 tablets once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

*Use in the elderly:* No dose adjustment is necessary. Experience is limited in this population.

*Use in renal impairment:* No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan potassium/Hydrochlorothiazide is not recommended for patients on dialysis. It is contraindicated in patients with severe renal impairment (i.e. creatinine clearance  $\leq$ 30 ml/min).

*Use in patients with intravascular volume depletion:* Losartan potassium/Hydrochlorothiazide should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics).

*Use in hepatic impairment:* Losartan potassium/Hydrochlorothiazide is not recommended for patients with hepatic impairment. It is contraindicated in patients with severe hepatic impairment.

*Use in children and adolescents (<18 years):* Losartan potassium/Hydrochlorothiazide is not recommended for use in children and adolescents under 18 years of age due to insufficient data on safety and efficacy.

#### 4.3 **Contraindications**

Losartan potassium/Hydrochlorothiazide is contraindicated in

- hypersensitivity to losartan, hydrochlorothiazide, other sulphonamide derivatives, or to any of the excipients
- second and third trimesters of pregnancy (see section 4.6)
- lactation (see section 4.6)
- patients with anuria
- severe renal impairment (creatinine clearance < 30 ml/min)
- severe hepatic impairment

#### 4.4 **Special warnings and precautions for use**

##### **Losartan**

###### *Renovascular hypertension*

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with products that affect the renin-angiotensin-aldosterone system. In such patients, renal function should be closely monitored.

###### *Hyperkalaemia*

Hyperkalaemia may occur during treatment with products that affect the renin-angiotensin-aldosterone system. Risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes should be co-administered cautiously with losartan potassium/hydrochlorothiazide (see section 4.5).

Potassium levels and electrolyte balance should be monitored during treatment in patients at risk of hyperkalaemia.

###### *Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy*

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

###### *Primary hyperaldosteronism*

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore losartan potassium / hydrochlorothiazide is not recommended.

###### *Other conditions with stimulation of the renin-angiotensin-aldosterone system*

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria or rarely acute renal failure.

###### *Ethnic differences*

Losartan potassium is apparently less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of higher prevalence or low-renin states in the Black hypertensive population.

###### *Other*

Excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in myocardial infarction or stroke. In such patients, losartan potassium/hydrochlorothiazide should be administered under close medical supervision.

##### **Hydrochlorothiazide**

###### *Renal impairment and renal transplant*

Periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide-associated azotaemia may occur in patients with impaired renal function.

There is no experience regarding the use of losartan potassium / hydrochlorothiazide in patients with a recent kidney transplant.

#### *Hepatic impairment*

Hydrochlorothiazide 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.

#### *Metabolic and endocrine effects*

Thiazide therapy may impair glucose tolerance. In diabetic patients, dosage adjustments of insulin or oral hypoglycaemia agents may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy.

Hyperuricaemia or frank gout may be precipitated in some patients receiving thiazide therapy.

#### *Electrolyte imbalance*

Periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloraemic alkalosis).

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

#### *General*

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

#### *Anti-doping test*

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

### **Losartan and hydrochlorothiazide combination tablet**

#### *Angioedema*

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

Hepatic and renal impairment: Losartan potassium/hydrochlorothiazide is not recommended for patients with mild to moderate hepatic or renal impairment (creatinine clearance 30-50 ml/min) (see section 4.2). It is contraindicated in patients with severe renal or hepatic impairment (see section 4.3).

#### *Lithium*

The combination of lithium and losartan potassium/hydrochlorothiazide is not recommended (see section 4.5).

#### *Hypotension*

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 administration of losartan potassium/hydrochlorothiazide.

This medicinal product contains lactose monohydrate. 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****Potential interactions related to both losartan and hydrochlorothiazide**Concomitant use not recommended*Lithium*

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin-converting enzyme inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. In addition, the renal clearance of lithium is reduced by thiazides. As a consequence, the risk of lithium toxicity may be increased with losartan potassium / hydrochlorothiazide. Co-administration of lithium and losartan potassium / hydrochlorothiazide should only be allowed under strict medical supervision and should not be recommended. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Concomitant use requiring caution*Baclofen*

Potential of the antihypertensive effect may occur.

*Non-steroidal anti-inflammatory drugs (NSAIDs)*

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

Concomitant use of angiotensin II antagonists 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.

Interactions to be taken into account*Amifostine*

Potential of the antihypertensive effect may occur.

*Other antihypertensive agents*

The antihypertensive effect of losartan potassium / hydrochlorothiazide may be increased with the concomitant use of other antihypertensive agents.

*Alcohol, barbiturates, narcotics or antidepressants*

Potential of orthostatic hypotension may occur.

*Potential interactions related to losartan*

## Concomitant use not recommended

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics such as spironolactone, triamterene or amiloride, potassium supplements, salt substitutes containing potassium, ciclosporin, trimethoprim or other medicinal products such as heparin sodium)

If these medicinal products are to be prescribed with the losartan potassium / hydrochlorothiazide combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of the above medicinal products may lead to increases in serum potassium (see section 4.4).

Interactions to be taken into account*Cytochrome P450 2C9*

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



### **Potential interactions related to hydrochlorothiazide**

#### Concomitant use not recommended

*Medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives)*

If these agents are to be prescribed with the losartan potassium / hydrochlorothiazide combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4). Such combinations are therefore not recommended.

#### Concomitant use requiring caution

##### *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 adjusted accordingly.

##### *Colestyramine and colestipol resins*

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

##### *Digitalis glycosides*

Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

##### *Medicinal products affected by serum potassium disturbances*

Periodic monitoring of serum potassium and ECG is recommended when losartan potassium / hydrochlorothiazide is administered with agents affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes-inducing substances (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes:

- class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulphiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- other agents e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastine, pentamidine, sparfloxacin, terfenadine, vincamine IV.

##### *Metformin*

Metformin should be used with caution owing to the risk of lactic acidosis induced by possible functional renal failure associated with hydrochlorothiazide.

##### *Antidiabetic medicinal products (oral agents and insulin)*

Dosage adjustment of the antidiabetic therapy may be required (see section 4.4).

##### *Beta-blockers and diazoxide*

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

##### *Pressor amines (e.g. noradrenaline)*

The effect of pressor amines may be decreased.

##### *Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine)*

The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

##### *Medicinal products used in the treatment of gout (e.g. probenecid, sulfinpyrazole, allopurinol)*

Dosage adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. An increase in the dosage of probenecid or sulfinpyrazole may be necessary. Co-administration of thiazides may increase the incidence of hypersensitivity reactions to allopurinol.

##### *Amantadine*

Thiazides may increase the risk of adverse events caused by amantadine.

##### *Cytotoxic agents (e.g. cyclophosphamide, methotrexate)*

Thiazides may reduce the renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

**4.6 Pregnancy and lactation***Pregnancy (see section 4.3)*

There are no adequate data on the use of losartan potassium/hydrochlorothiazide in pregnant women. Animal studies do not indicate a teratogenic effect, but have shown fetotoxicity. Therefore, as a precautionary measure, losartan potassium / hydrochlorothiazide should preferably not be used during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

In the second and third trimesters, substances that act directly on the renin-angiotensin system can cause injury and even death in the developing fetus, therefore losartan potassium / hydrochlorothiazide is contraindicated in the second and third trimesters of pregnancy. If pregnancy is diagnosed, losartan potassium / hydrochlorothiazide should be discontinued as soon as possible.

Thiazides cross the placental barrier and appear in cord blood. They may cause fetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, fetal or neonatal jaundice have been reported with maternal thiazide therapy.

*Lactation (see section 4.3)*

Losartan potassium / hydrochlorothiazide is contraindicated during lactation since it is not known whether losartan is excreted in human milk. Thiazides appear in human milk and may inhibit lactation.

**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 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:

*Blood and lymphatic system disorders*

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

*Immune system disorders*

Rare: Anaphylactic reactions, angioedema

*Vascular disorders*

Uncommon: Vasculitis

*Respiratory, thoracic and mediastinal disorders*

Common: Cough

*Gastrointestinal disorders*

Common: Diarrhoea

*Hepato-biliary disorders*

Rare: Hepatitis

*Skin and subcutaneous tissue disorders*

Uncommon: Urticaria

*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.

**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 cholestasis), pancreatitis

*Skin and subcutaneous tissue disorders*

Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

*Musculoskeletal and connective tissue disorders*

Uncommon: Muscle cramps

*Renal and urinary disorders*

Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

*General disorders and administration site conditions*

Uncommon: Fever, dizziness

#### 4.9 Overdose

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

#### Losartan

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

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

#### Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis.

If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics

ATC code: C09D A01

#### *Losartan and hydrochlorothiazide combination tablet*

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 hyperuricaemia.

The antihypertensive effect of losartan potassium/hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of losartan potassium/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 mm Hg.

In a study comparing the combination of losartan 50 mg and hydrochlorothiazide 12.5 mg with the combination captopril 50 mg and hydrochlorothiazide 25 mg in young (<65 years) and elderly (>65 years) hypertensive patients, the antihypertensive responses were similar between the two treatments and by age groups. Overall, there were statistically significantly fewer drug-related clinical adverse experiences and discontinuations due to clinical adverse events with the combination of losartan 50 mg and hydrochlorothiazide 12.5 mg than with captopril 50 mg and hydrochlorothiazide 25 mg.

A study of 131 patients with severe hypertension has shown the beneficial effects of losartan potassium / hydrochlorothiazide administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

Losartan potassium/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 an oral, specific angiotensin-II receptor (type AT1) antagonist. 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 proliferation. Based on binding and pharmacological bioassays, angiotensin II binds selectively to the AT1 receptor. In vitro and in vivo, both 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 synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma-renin activity. Increases in plasma-renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma-aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or 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, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of oedema (losartan 1.7%, placebo 1.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study, 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 4,131 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 non-diabetic 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 <24 micromol/l (<0.4 mg/dl)) which was persistent in chronic therapy.

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

In 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; in clinical studies of up to one year the antihypertensive effect was maintained. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

In a study comparing losartan 50 mg with the once-daily administration of enalapril 20 mg, the antihypertensive responses were shown to be similar in both treatment groups. The efficacy of once-daily administration of losartan 50-100 mg in hypertension has also been found to be comparable to once-daily administration of atenolol 50-100 mg. In older hypertensives (65 years), the effect of administration of losartan 50-100 mg once daily has been reported to be equivalent to felodipine extended-release 5-10 mg after 12 weeks of therapy.

Losartan is equally effective in males and females and in younger (<65 years) and older (65 years) hypertensives. Although losartan is antihypertensive in all races, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

When given together with thiazide-type diuretics, the blood-pressure lowering effects of losartan are approximately additive.

### **Hydrochlorothiazide**

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 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 substance was administered with a standardised 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 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

#### *Hydrochlorothiazide:*

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

### **Biotransformation**

#### *Losartan:*

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

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

### **Elimination**

#### *Losartan:*

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6.9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of <sup>14</sup>C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

*Hydrochlorothiazide:*

Hydrochlorothiazide is not metabolised 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% of the oral dose is eliminated unchanged within 24 hours.

**Characteristics in Patients**

*Losartan and hydrochlorothiazide combination tablet:*

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 haemodialysis.

**5.3 Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

In female rats, the coadministration of losartan potassium and hydrochlorothiazide (10/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices at exposures (AUC) of losartan, its active metabolite and hydrochlorothiazide that were approximately 15-, 4- and 5-fold, respectively, those achieved in man following a dose of 50mg losartan potassium/12.5 mg hydrochlorothiazide. General reproductive performance and fertility in male rats was unaffected by administration of losartan potassium/hydrochlorothiazide at doses up to 135/33.75 mg/kg/day.

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium and 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 decreased bodyweight, mortality and/or renal toxicity, also occurred when pregnant rats were treated with losartan potassium and hydrochlorothiazide combination during late gestation and/or lactation. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

*Core:*

Lactose, monohydrate  
Cellulose, microcrystalline (E460a)  
Pregelatinised starch (maize)  
Magnesium stearate (E572)

*Film-coating:*

Poly(vinyl alcohol)  
Titanium dioxide (E171)  
Macrogol 3350  
Talc (E553b)  
Yellow iron oxide (E172)



**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Do not store above 25°C.

**6.5 Nature and contents of container**

1, 14, 20, 28, 30, 56, 60, 84, 90, 98 & 100 tablets  
calendar packs of 28 tablets,  
hospital packs of 50 x 1 & 280 (10 x 28) tablets,  
in PVC/PVdC/PE/Al or PVC/Aclar/Al blisters.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

TEVA UK Limited  
Eastbourne  
BN22 9AG

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 00289/0967

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26/03/2008

**10 DATE OF REVISION OF THE TEXT**

26/03/2008

**1 NAME OF THE MEDICINAL PRODUCT**

Losartan potassium and Hydrochlorothiazide 100mg/25 mg Film-Coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

Excipients:

Each tablet contains 270 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet.

Yellow, oval, bi-convex tablets marked with "100" on one side and plain on the other

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled by losartan 50 mg / hydrochlorothiazide 12.5 mg once daily.

**4.2 Posology and method of administration**

*Method of administration*

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). Losartan potassium/Hydrochlorothiazide may be administered with or without food.

The combination of 100 mg losartan potassium / 25 mg hydrochlorothiazide is not recommended as initial therapy. One losartan potassium / hydrochlorothiazide tablet once daily is recommended for those patients who do not respond adequately to a combination of 50 mg losartan potassium / 12.5 mg hydrochlorothiazide given once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

*Use in the elderly:* No dose adjustment is necessary. Experience is limited in this population.

*Use in renal impairment:* No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan potassium/Hydrochlorothiazide is not recommended for patients on dialysis. It is contraindicated in patients with severe renal impairment (i.e. creatinine clearance  $\leq$ 30 ml/min).

*Use in patients with intravascular volume depletion:* Losartan potassium/Hydrochlorothiazide should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics).

*Use in hepatic impairment:* Losartan potassium/Hydrochlorothiazide is not recommended for patients with hepatic impairment. It is contraindicated in patients with severe hepatic impairment.

*Use in children and adolescents (<18 years):* Losartan potassium/Hydrochlorothiazide is not recommended for use in children and adolescents under 18 years of age due to insufficient data on safety and efficacy.

**4.3 Contraindications**

Losartan potassium/Hydrochlorothiazide is contraindicated in

- hypersensitivity to losartan, hydrochlorothiazide, other sulphonamide derivatives, or to any of the excipients
- second and third trimesters of pregnancy (see section 4.6)
- lactation (see section 4.6)
- patients with anuria
- severe renal impairment (creatinine clearance < 30 ml/min)
- severe hepatic impairment

#### 4.4 Special warnings and precautions for use

##### **Losartan**

###### *Renovascular hypertension*

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with products that affect the renin-angiotensin-aldosterone system. In such patients, renal function should be closely monitored.

###### *Hyperkalaemia*

Hyperkalaemia may occur during treatment with products that affect the renin-angiotensin-aldosterone system. Risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes should be co-administered cautiously with losartan potassium/hydrochlorothiazide (see section 4.5).

Potassium levels and electrolyte balance should be monitored during treatment in patients at risk of hyperkalaemia.

###### *Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy*

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

###### *Primary hyperaldosteronism*

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore losartan potassium / hydrochlorothiazide is not recommended.

###### *Other conditions with stimulation of the renin-angiotensin-aldosterone system*

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria or rarely acute renal failure.

###### *Ethnic differences*

Losartan potassium is apparently less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of higher prevalence or low-renin states in the Black hypertensive population.

###### *Other*

Excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in myocardial infarction or stroke. In such patients, losartan potassium/hydrochlorothiazide should be administered under close medical supervision.

##### **Hydrochlorothiazide**

###### *Renal impairment and renal transplant*

Periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide-associated azotaemia may occur in patients with impaired renal function.

There is no experience regarding the use of losartan potassium / hydrochlorothiazide in patients with a recent kidney transplant.

###### *Hepatic impairment*

Hydrochlorothiazide 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.

###### *Metabolic and endocrine effects*

Thiazide therapy may impair glucose tolerance. In diabetic patients, dosage adjustments of insulin or oral hypoglycaemia agents may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy.

Hyperuricaemia or frank gout may be precipitated in some patients receiving thiazide therapy.

*Electrolyte imbalance*

Periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloroemic alkalosis).

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

*General*

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

*Anti-doping test*

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

**Losartan and hydrochlorothiazide combination tablet**

*Angioedema*

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

Hepatic and renal impairment: Losartan potassium/hydrochlorothiazide is not recommended for patients with mild to moderate hepatic or renal impairment (creatinine clearance 30-50 ml/min) (see section 4.2). It is contraindicated in patients with severe renal or hepatic impairment (see section 4.3).

*Lithium*

The combination of lithium and losartan potassium/hydrochlorothiazide is not recommended (see section 4.5).

*Hypotension*

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 administration of losartan potassium/hydrochlorothiazide.

This medicinal product contains lactose monohydrate. 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**

**Potential interactions related to both losartan and hydrochlorothiazide**

Concomitant use not recommended

*Lithium*

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin-converting enzyme inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. In addition, the renal clearance of lithium is reduced by thiazides. As a consequence, the risk of lithium toxicity may be increased with losartan potassium / hydrochlorothiazide. Co-administration of lithium and losartan potassium / hydrochlorothiazide should only be allowed under strict medical supervision and should not be recommended. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Concomitant use requiring caution

*Baclofen*

Potiation of the antihypertensive effect may occur.

*Non-steroidal anti-inflammatory drugs (NSAIDs)*

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

Concomitant use of angiotensin II antagonists 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.

Interactions to be taken into account

*Amifostine*

Potiation of the antihypertensive effect may occur.

*Other antihypertensive agents*

The antihypertensive effect of losartan potassium / hydrochlorothiazide may be increased with the concomitant use of other antihypertensive agents.

*Alcohol, barbiturates, narcotics or antidepressants*

Potiation of orthostatic hypotension may occur.

*Potential interactions related to losartan*

Concomitant use not recommended

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics such as spironolactone, triamterene or amiloride, potassium supplements, salt substitutes containing potassium, ciclosporin, trimethoprim or other medicinal products such as heparin sodium)

If these medicinal products are to be prescribed with the losartan potassium / hydrochlorothiazide combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of the above medicinal products may lead to increases in serum potassium (see section 4.4).

Interactions to be taken into account

*Cytochrome P450 2C9*

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

**Potential interactions related to hydrochlorothiazide**

Concomitant use not recommended

*Medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives)*

If these agents are to be prescribed with the losartan potassium / hydrochlorothiazide combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4). Such combinations are therefore not recommended.

Concomitant use requiring caution

*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 adjusted accordingly.

*Colestyramine and colestipol resins*

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

*Digitalis glycosides*

Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

*Medicinal products affected by serum potassium disturbances*

Periodic monitoring of serum potassium and ECG is recommended when losartan potassium / hydrochlorothiazide is administered with agents affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes-inducing substances (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes:

- class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulphiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- other agents e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastine, pentamidine, sparfloxacin, terfenadine, vincamine IV.

*Metformin*

Metformin should be used with caution owing to the risk of lactic acidosis induced by possible functional renal failure associated with hydrochlorothiazide.

*Antidiabetic medicinal products (oral agents and insulin)*

Dosage adjustment of the antidiabetic therapy may be required (see section 4.4).

*Beta-blockers and diazoxide*

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

*Pressor amines (e.g. noradrenaline)*

The effect of pressor amines may be decreased.

*Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine)*

The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

*Medicinal products used in the treatment of gout (e.g. probenecid, sulfinpyrazole, allopurinol)*

Dosage adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. An increase in the dosage of probenecid or sulfinpyrazole may be necessary. Co-administration of thiazides may increase the incidence of hypersensitivity reactions to allopurinol.

*Amantadine*

Thiazides may increase the risk of adverse events caused by amantadine.

*Cytotoxic agents (e.g. cyclophosphamide, methotrexate)*

Thiazides may reduce the renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

## 4.6 Pregnancy and lactation

*Pregnancy (see section 4.3)*

There are no adequate data on the use of losartan potassium/hydrochlorothiazide in pregnant women. Animal studies do not indicate a teratogenic effect, but have shown fetotoxicity. Therefore, as a precautionary measure, losartan potassium / hydrochlorothiazide should preferably not be used during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

In the second and third trimesters, substances that act directly on the renin-angiotensin system can cause injury and even death in the developing fetus, therefore losartan potassium / hydrochlorothiazide

is contraindicated in the second and third trimesters of pregnancy. If pregnancy is diagnosed, losartan potassium / hydrochlorothiazide should be discontinued as soon as possible.

Thiazides cross the placental barrier and appear in cord blood. They may cause fetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, fetal or neonatal jaundice have been reported with maternal thiazide therapy.

*Lactation (see section 4.3)*

Losartan potassium / hydrochlorothiazide is contraindicated during lactation since it is not known whether losartan is excreted in human milk. Thiazides appear in human milk and may inhibit lactation.

**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 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:  $\geq 1/10$   
 Common:  $\geq 1/100, < 1/10$   
 Uncommon:  $\geq 1/1,000, \leq 1/100$   
 Rare:  $\geq 1/10,000, \leq 1/1,000$   
 Very rare:  $\leq 1/10,000$   
 Not known:  $\leq 1/10,000$

(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:

*Blood and lymphatic system disorders*

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

*Immune system disorders*

Rare: Anaphylactic reactions, angioedema

*Vascular disorders*

Uncommon: Vasculitis

*Respiratory, thoracic and mediastinal disorders*

Common: Cough

*Gastrointestinal disorders*

Common: Diarrhoea

*Hepato-biliary disorders*

Rare: Hepatitis

*Skin and subcutaneous tissue disorders*

Uncommon: Urticaria

*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.

**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 cholestasis), pancreatitis

*Skin and subcutaneous tissue disorders*

Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

*Musculoskeletal and connective tissue disorders*

Uncommon: Muscle cramps

*Renal and urinary disorders*

Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

*General disorders and administration site conditions*

Uncommon: Fever, dizziness

**4.9 Overdose**

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

**Losartan**

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

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

### **Hydrochlorothiazide**

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hyponatraemia, hyponatraemia) and dehydration resulting from excessive diuresis.

If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics

ATC code: C09D A01

#### *Losartan and hydrochlorothiazide combination tablet*

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 hyperuricaemia.

The antihypertensive effect of losartan potassium/hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of losartan potassium/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 mm Hg.

In a study comparing the combination of losartan 50 mg and hydrochlorothiazide 12.5 mg with the combination captopril 50 mg and hydrochlorothiazide 25 mg in young (<65 years) and elderly (>65 years) hypertensive patients, the antihypertensive responses were similar between the two treatments and by age groups. Overall, there were statistically significantly fewer drug-related clinical adverse experiences and discontinuations due to clinical adverse events with the combination of losartan 50 mg and hydrochlorothiazide 12.5 mg than with captopril 50 mg and hydrochlorothiazide 25 mg.

A study of 131 patients with severe hypertension has shown the beneficial effects of losartan potassium / hydrochlorothiazide administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

Losartan potassium/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 an oral, specific angiotensin-II receptor (type AT1) antagonist. 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 proliferation. Based on binding and pharmacological bioassays, angiotensin II binds selectively to the AT1 receptor. In vitro and in vivo, both 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 synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma-renin activity. Increases in plasma-renin activity lead to increases in angiotensin II in

plasma. Even with these increases, antihypertensive activity and suppression of plasma-aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or 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, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of oedema (losartan 1.7%, placebo 1.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study, 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 4,131 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 non-diabetic 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 <24 micromol/l (<0.4 mg/dl)) which was persistent in chronic therapy.

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

In 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; in clinical studies of up to one year the antihypertensive effect was maintained. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

In a study comparing losartan 50 mg with the once-daily administration of enalapril 20 mg, the antihypertensive responses were shown to be similar in both treatment groups. The efficacy of once-daily administration of losartan 50-100 mg in hypertension has also been found to be comparable to once-daily administration of atenolol 50-100 mg. In older hypertensives (65 years), the effect of administration of losartan 50-100 mg once daily has been reported to be equivalent to felodipine extended-release 5-10 mg after 12 weeks of therapy.

Losartan is equally effective in males and females and in younger (<65 years) and older (65 years) hypertensives. Although losartan is antihypertensive in all races, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

When given together with thiazide-type diuretics, the blood-pressure lowering effects of losartan are approximately additive.

### **Hydrochlorothiazide**

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 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 substance was administered with a standardised 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 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

#### *Hydrochlorothiazide:*

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

### Biotransformation

#### *Losartan:*

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

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

### Elimination

#### *Losartan:*

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6.9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of <sup>14</sup>C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

#### *Hydrochlorothiazide:*

Hydrochlorothiazide is not metabolised 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% of the oral dose is eliminated unchanged within 24 hours.

### Characteristics in Patients

#### *Losartan and hydrochlorothiazide combination tablet:*

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 haemodialysis.

### 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

In female rats, the coadministration of losartan potassium and hydrochlorothiazide (10/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices at exposures (AUC) of losartan, its active metabolite and hydrochlorothiazide that were approximately 15-, 4- and 5-fold, respectively, those achieved in man following a dose of 50mg losartan potassium/12.5 mg hydrochlorothiazide. General reproductive performance and fertility in male rats was unaffected by administration of losartan potassium/hydrochlorothiazide at doses up to 135/33.75 mg/kg/day.

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium and 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 decreased bodyweight, mortality and/or renal toxicity, also occurred when pregnant rats were treated with losartan potassium and hydrochlorothiazide combination during late gestation and/or lactation. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Core:*

Lactose, monohydrate  
Cellulose, microcrystalline (E460a)  
Pregelatinised starch (maize)  
Magnesium stearate (E572)

*Film-coating:*

Poly(vinyl alcohol)  
Titanium dioxide (E171)  
Macrogol 3350  
Talc (E553b)  
Yellow iron oxide (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Do not store above 25°C.

### 6.5 Nature and contents of container

1, 7, 14, 20, 28, 30, 56, 60, 84, 90, 98 & 100 tablets, calendar packs of 7 & 28 tablets and hospital packs of 50 x 1 and 280 (10 x 28) tablets in PVC/PVdC/PE/Al or PVC/Aclar/Al blisters

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

TEVA UK Limited  
Eastbourne  
BN22 9AG

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 00289/0968

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26/03/2008

**10 DATE OF REVISION OF THE TEXT**

26/03/2008

## Module 3

### LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE 50 mg/12.5 mg and 100 mg/25 mg FILM-COATED TABLETS

#### PACKAGE LEAFLET: INFORMATION FOR THE USER

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

#### IN THIS LEAFLET:

1. What Losartan potassium and Hydrochlorothiazide tablets are and what they are used for
2. Before you take Losartan potassium and Hydrochlorothiazide tablets
3. How to take Losartan potassium and Hydrochlorothiazide tablets
4. Possible side effects
5. How to store Losartan potassium and Hydrochlorothiazide tablets
6. Further information

#### 1 WHAT LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE TABLETS ARE AND WHAT THEY ARE USED FOR

- Losartan potassium belongs to a group of medicines called angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Losartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure
- Hydrochlorothiazide belongs to a group of drugs called diuretics (water tablets)
- 50/12.5 mg: Losartan potassium and Hydrochlorothiazide tablets are used to treat high blood pressure. Losartan potassium and Hydrochlorothiazide tablets are a suitable alternative for those people who would otherwise have to be treated with losartan potassium and hydrochlorothiazide given as separate tablets
- 100/25 mg: Losartan potassium and Hydrochlorothiazide tablets are used to treat high blood pressure in patients who have not responded sufficiently to treatment with losartan potassium and hydrochlorothiazide 50 mg/12.5 mg.

#### 2 BEFORE YOU TAKE LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE TABLETS

Do NOT take Losartan potassium and Hydrochlorothiazide tablets:

- If you are allergic (hypersensitive) to losartan, hydrochlorothiazide or any of the other ingredients of this medicine
- If you 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)
- If you are, think you may be or are planning to become pregnant (see also 'Pregnancy and breast-feeding' below)
- If you are breast-feeding
- If you have severely impaired liver function
- If you have severely impaired kidney function or your kidneys are not producing any urine.

Take special care with Losartan potassium and Hydrochlorothiazide tablets:

Losartan potassium and Hydrochlorothiazide tablets are not generally recommended in the following cases:

- If you have primary hyperaldosteronism (Conn's syndrome), a tumour of the adrenal gland associated with muscle weakness, excessive thirst and frequent urination
- If you have liver or kidney problems or you are undergoing haemodialysis (see also 'Do NOT take Losartan potassium and Hydrochlorothiazide tablets' above)
- If you are also taking lithium for mental health problems (see also 'Taking other medicines' below).

Talk to your doctor or pharmacist:

- If you have previously suffered from swelling of the face, lips, throat or tongue
- If you take diuretics (water pills)
- If you are on a salt-restricted diet
- If you have or have had severe vomiting and/or diarrhoea
- If you have heart failure
- If you have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant
- If you have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function)
- If you have 'aortic or mitral valve stenosis' (narrowing of the valves of the heart) or 'hypertrophic cardiomyopathy' (a disease causing thickening of heart muscle)
- If you are diabetic
- If you have or have had gout
- If you have or have had an allergic condition, asthma or a condition that causes joint pain, skin rashes and fever (systemic lupus erythematosus)
- If you have high calcium or potassium levels or you are on a low potassium diet
- If you need to have an anaesthetic (even at the dentist) or before surgery, or if you are going to have tests to check your parathyroid function, you must tell the doctor or medical staff that you are taking Losartan potassium and Hydrochlorothiazide tablets.

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

Diuretic agents such as the hydrochlorothiazide contained in Losartan potassium and Hydrochlorothiazide may interact with other medicines. Preparations containing lithium should not be taken with Losartan potassium and Hydrochlorothiazide without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate if you take potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines, other diuretics ("water tablets"), some laxatives, medicines for the treatment of gout, therapeutic vitamin D supplements, medicines to control heart rhythm or for diabetes (oral agents or insulins). It is also important for your doctor to know if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers or arthritis medicines.

**Taking Losartan potassium and Hydrochlorothiazide tablets with food and drink**

You are advised not to drink alcohol whilst taking these tablets: alcohol and Losartan potassium and Hydrochlorothiazide tablets may increase each other's effects.

Dietary salt in excessive quantities may counteract the effect of Losartan potassium and Hydrochlorothiazide tablets.

Losartan potassium and Hydrochlorothiazide tablets 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 and Hydrochlorothiazide tablets 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 and Hydrochlorothiazide, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

**Breast-feeding:**

If you are breast-feeding or intend to do so, you must either stop breast-feeding or stop taking Losartan potassium and Hydrochlorothiazide tablets. Hydrochlorothiazide may suppress milk production.

**Driving and using machines**

Dizziness has been reported by people taking Losartan potassium and Hydrochlorothiazide tablets, if you experience this do not drive a car and do not operate machinery.



**Important information about some of the ingredients of Losartan potassium and Hydrochlorothiazide Tablets**

- Losartan potassium and Hydrochlorothiazide tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

**3 HOW TO TAKE LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE TABLETS**

Always take Losartan potassium Hydrochlorothiazide tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Use in adults**

**High blood pressure**

The usual dose is one tablet once daily. 50/12.5 mg tablets: If necessary your doctor may increase your dose to a maximum of two tablets once daily.

**Use in children and teenagers under 18 years of age**

Losartan potassium and Hydrochlorothiazide tablets should not be given to children and teenagers.

**If you take more Losartan potassium and Hydrochlorothiazide tablets 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 and Hydrochlorothiazide tablets**

Do not take a double dose to make up for a forgotten tablet. Take your next dose at the usual time.

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 and Hydrochlorothiazide tablets can cause side effects, although not everybody gets them. If you experience the following, stop taking Losartan potassium and Hydrochlorothiazide tablets 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 (affecting fewer than one person in 10 but more than one person 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 (affecting fewer than one person in 100 but more than one person 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
- 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, diarrhoea, wind, stomach upsets, 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 (more than 1 out of 10000 patients and less than 1 out of 1000 patients)**

- 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 AND HYDROCHLOROTHIAZIDE TABLETS**

**Keep out of the reach and sight of children.**

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

Do not store above 25°C.

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

**6 FURTHER INFORMATION**

**What Losartan potassium and Hydrochlorothiazide tablets contain**

- The active ingredients are losartan potassium and hydrochlorothiazide. Each tablet contains either 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide or 100 mg of losartan potassium and 25 mg of hydrochlorothiazide
- The other ingredients are:  
Tablet core: lactose monohydrate, cellulose microcrystalline (E460a), pregelatinised starch (maize), magnesium stearate (E572)  
Film-coat: poly (vinyl alcohol), titanium dioxide (E171), macrogol 3350, talc (E553b), yellow iron oxide (E172).

**What Losartan potassium and Hydrochlorothiazide tablets look like and contents of the pack:**

- Losartan potassium and Hydrochlorothiazide 50/12.5 mg Film-Coated Tablets are yellow, oval, bi-convex tablets, marked with "5" and "0" on one side and a score line on both sides. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- Losartan potassium and Hydrochlorothiazide 100/25 mg Film-Coated Tablets are yellow, oval, bi-convex tablets marked with "100" on one side and smooth on the other side
- The 50/12.5 mg tablets are available in pack sizes of 1, 14, 20, 28, 30, 56, 60, 84, 90, 98 and 100 tablets, calendar packs of 28 tablets and hospital packs of 50x1 and 280 (10x28) tablets
- The 100/25 mg tablets are available in pack sizes of 1, 7, 14, 20, 28, 30, 56, 60, 84, 90, 98 and 100 tablets, calendar packs of 7 and 28 tablets and hospital packs of 50x1 and 280 (10x28) tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**  
TEVA UK Limited, Eastbourne, BN22 9AG

This leaflet was last approved in: May 2007



PL 00289/0967-8

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## Module 4 Labelling

### LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE 50/12.5MG FILM-COATED TABLETS (PL 00289/0967)





# LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE 100/25MG FILM-COATED TABLETS (PL 00289/0968)





## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Losartan Potassium/Hydrochlorothiazide 50/12.5mg and 100/25mg Film-Coated Tablets to Teva UK Limited on 26<sup>th</sup> March 2008.

The products are prescription-only medicines for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

The applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be generic medicinal products to the original products Cozaar Comp 50/12.5mg and 100/25mg Tablets (Merck, Sharp and Dohme), which have been authorised in the EEA for over 10 years.

The products contain the active ingredients losartan potassium and hydrochlorothiazide. Losartan potassium is an angiotensin II receptor antagonist. Hydrochlorothiazide belongs to the thiazide group of diuretics.

**II. ABOUT THE PRODUCT**

|   |  |
|---|--|
| Name of the product in the Reference Member State | Losartan Potassium and Hydrochlorothiazide 50/12.5mg Film-Coated Tablets<br>Losartan Potassium and Hydrochlorothiazide 100/25mg Film-Coated Tablets  |
| Name(s) of the active substance(s) (INN)          | Losartan Potassium and Hydrochlorothiazide   |
| Pharmacotherapeutic classification (ATC code)     | Angiotensin II antagonist and diuretics (C09 DA01)   |
| Pharmaceutical form and strength(s)               | 50mg Losartan Potassium and 12.5mg Hydrochlorothiazide Film-Coated Tablets<br>100mg Losartan Potassium and 25mg Hydrochlorothiazide Film-Coated Tablets  |
| Reference numbers for the Decentralised Procedure | UK/H/0906/01-02/DC   |
| Reference Member State                            | United Kingdom   |
| Member States concerned                           | Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Luxembourg, Latvia, The Netherlands, Norway, Portugal, Sweden, Slovakia, Slovenia and Spain |
| Marketing Authorisation Number(s)                 | PL 00289/0967-8  |
| Name and address of the authorisation holder      | Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK  |

### III SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 QUALITY ASPECTS

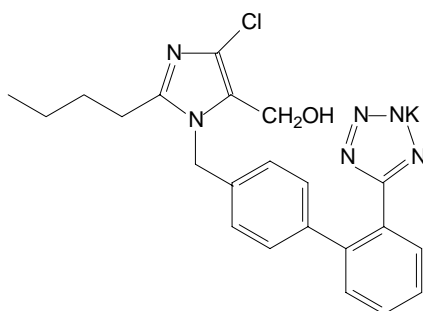
##### DRUG SUBSTANCE – LOSARTAN POTASSIUM

INN: Losartan Potassium

Chemical Names: 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<sub>22</sub>H<sub>22</sub>ClKN<sub>6</sub>O

Structure:



CAS Number: 124750-99-8

Molecular Weight: 461.01

Appearance: A white to yellowish crystalline powder, freely soluble in water and methanol, and insoluble in chloroform.

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

Appropriate specifications are provided for the active substance losartan potassium. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and all comply with the proposed specifications.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability data provided, a suitable retest period has been set. Suitable post approval commitments have been given to provide additional stability data as and when it becomes available.

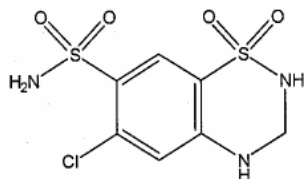
## DRUG SUBSTANCE – HYDROCHLOROTHIAZIDE

INN: Hydrochlorothiazide

Chemical Names: 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:



CAS Number: 58-93-5

Molecular Weight: 297.7

Appearance: A white to almost white crystalline powder, which is 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 active hydrochlorothiazide are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Based on stability data provided, a suitable retest period has been set. Suitable post approval commitments have been given to provide additional stability data as and when it becomes available.

## DRUG PRODUCT

### Other Ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, pregelatinised starch, magnesium stearate (E572), polyvinyl alcohol, titanium dioxide (E171), talc, macrogol 3350 and yellow iron oxide (E172).

With the exception of the yellow iron oxide, all excipients comply with their respective European Pharmacopoeia monograph. A suitable in-house specification has been provided for yellow iron oxide.

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

With the exception of lactose monohydrate, none of the excipients is of animal or human origin. The supplier of lactose monohydrate has stated that this is sourced from healthy animals under the same conditions as milk for human consumption.



### **Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce products that were tolerable and could be considered as generic medicinal products to the originator products Cozaar Comp 50/12.5mg and 100/25mg Tablets (Merck, Sharp and Dohme, UK) and its European counterparts.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Similar *in vitro* dissolution profiles and impurity profiles have been generated for the proposed products compared to the UK comparator products (Cozaar Comp) and several other European products.

### **Manufacturing Process**

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

### **Finished Product Specification**

The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been 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**

Product is packaged in polyethylene/polyvinylidene chloride (PVdC)/polyvinylchloride (PVC)/aluminium and aluminium/polyvinylchloride (PVC)/acler blisters in pack sizes of 1, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98 and 100 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

### **Stability of the product**

Stability studies were performed in accordance with current guidelines, using product manufactured by the proposed finished product manufacturer and in the packaging proposed for marketing. The results support a shelf-life of 2 years, with the storage conditions “Do not store above 25 degrees”.

### **Bioequivalence/bioavailability**

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

### **SPC, PIL, Labels**

The SPC, PIL and Labels are pharmaceutically acceptable.

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 it contains.

### CONCLUSION

It is recommended that Marketing Authorisations are granted for these applications.

The proposed products are considered to be generic medicinal products to the reference products with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

### III.2 PRE-CLINICAL ASPECTS

In these applications, the products are claiming to be generic medicinal products of Cozaar Comp 50/12.5mg and 100/25mg Tablets (Merck, Sharp and Dohme UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

### III.3 CLINICAL ASPECTS CLINICAL PHARMACOLOGY

With the exception of the bioequivalence study, no new clinical pharmacology data were submitted for these applications and none were required.

#### Bioequivalence

##### Study design

A randomised, blind, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioequivalence study to compare Losartan Potassium/Hydrochlorothiazide 50/12.5mg Film-Coated Tablets (test) versus Cozaar Comp 50/12.5mg Film-Coated Tablets (reference) in healthy fasted volunteers.

Blood samples were taken pre- and up to 36 hours post dose and each treatment arm was separated by a 7-day washout period.

##### Results

The results for losartan, its active metabolite and hydrochlorothiazide are presented below:

| Losartan  | AUC <sub>0-t</sub><br>ng/ml/h | AUC <sub>0-∞</sub><br>ng/ml/h | C <sub>max</sub><br>ng/ml     | t <sub>max</sub><br>h | T <sub>1/2el</sub><br>h |
|---|-------------------------------|-------------------------------|-------------------------------|-----------------------|-------------------------|
| Test  | 375.44 ± <sub>151.74</sub>    | 386.86 ± <sub>159.42</sub>    | 200.88 ± <sub>128.54</sub>    | 1.30 ±1.02            | 2.28 ±1.43              |
| Reference   | 378.13 ± <sub>163.65</sub>    | 389.36 ± <sub>171.64</sub>    | 200.88± <sub>107.80</sub>     | 1.25 ±0.79            | 2.28 ±1.43              |
| <b>*Ratio (90% CI)</b>  | <b>99.93</b><br>97.53-102.40% | <b>100.3</b><br>97.68-102.43% | <b>95.97</b><br>87.17-105.65% |                       |                         |
| <b>Intra-subj CV</b>  | 9.03%                         | 8.80%                         | 36.69%                        |                       |                         |
| AUC <sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity<br>AUC <sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours<br>C <sub>max</sub> maximum plasma concentration<br>T <sub>max</sub> time for maximum concentration<br>T <sub>1/2</sub> half-life |                               |                               |                               |                       |                         |

| Losartan-carboxy acid   | AUC <sub>0-t</sub><br>ng/ml/h  | AUC <sub>0-∞</sub><br>ng/ml/h  | C <sub>max</sub><br>ng/ml      | t <sub>max</sub><br>h | T <sub>1/2</sub><br>h |
|---|--------------------------------|--------------------------------|--------------------------------|-----------------------|-----------------------|
| <b>Test</b>   | 2060.92 ± 623.77               | 2125.91 ± 582.9                | 277.14 ± 106.47                | 4.01 ± 1.69           | 5.64 ± 2.10           |
| <b>Reference</b>  | 2028.74 ± 662.91               | 2094.54 ± 627.6                | 267.26 ± 105.26                | 4.13 ± 1.40           | 5.47 ± 1.09           |
| <b>*Ratio (90% CI)</b>  | <b>101.89</b><br>99.76-104.07% | <b>102.51</b><br>100.65-104.41 | <b>103.43</b><br>99.83-107.15% |                       |                       |
| <b>Intra-subj CV</b>  | 7.83%                          | 6.72%                          | 13.14%                         |                       |                       |
| AUC <sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity<br>AUC <sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours<br>C <sub>max</sub> maximum plasma concentration<br>T <sub>max</sub> time for maximum concentration<br>T <sub>1/2</sub> half-life |                                |                                |                                |                       |                       |

| Hydrochlorothiazide   | AUC <sub>0-t</sub><br>ng/ml/h   | AUC <sub>0-∞</sub><br>ng/ml/h   | C <sub>max</sub><br>ng/ml        | t <sub>max</sub><br>h | T <sub>1/2el</sub><br>h |
|---|---------------------------------|---------------------------------|----------------------------------|-----------------------|-------------------------|
| <b>Test</b>   | 512.92 ± 113.87                 | 537.06 ± 115.94                 | 85.72±26.50                      | 2.24 ± 0.93           | 9.27 ± 1.23             |
| <b>Reference</b>  | 485.77 ± 108.78                 | 511.32 ± 112.17                 | 78.66 ± 24.26                    | 2.35 ± 1.94           | 9.38 ± 1.18             |
| <b>*Ratio (90% CI)</b>  | <b>105.70</b><br>103.17-108.29% | <b>105.17</b><br>102.75-107.64% | <b>108.94</b><br>104.06 -114.06% |                       |                         |
| <b>Intra-subj CV</b>  | 8.97%                           | 8.60%                           | 17.08                            |                       |                         |
| AUC <sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity<br>AUC <sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours<br>C <sub>max</sub> maximum plasma concentration<br>T <sub>max</sub> time for maximum concentration<br>T <sub>1/2</sub> half-life |                                 |                                 |                                  |                       |                         |

### Conclusions

The 90% confidence intervals for the three analytes (losartan, losartan carboxy acid and hydrochlorothiazide) lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Note for Guidance. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria and can be approved.

As these products meet all the criteria as 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 50/12.5mg strength can be extrapolated to the 100/25mg strength tablets.

### PHARMACODYNAMICS

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

### EFFICACY

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

### SAFETY

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

### **EXPERT REPORTS**

A clinical expert report is provided, written by an appropriately qualified physician. It is satisfactory.

### **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPCs are consistent with those approved for the reference products and are satisfactory.

### **PATIENT INFORMATION LEAFLET (PIL)**

The PIL has been provided and is consistent with the SPC and that for the reference products.

### **LABELLING**

Labelling has been provided and these are satisfactory.

### **APPLICATION FORM (MAA)**

The MAA forms are satisfactory.

### **DISCUSSION**

Bioequivalence has been satisfactorily demonstrated for the 50/12.5mg product in accordance with CPMP criteria. As these products meet all the criteria as 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 50/12.5mg strength can be extrapolated to the 100/25mg strength.

The SPC, PIL and labelling are consistent with those approved in the UK for the originator product and are satisfactory.

### **MEDICAL CONCLUSION**

Marketing authorisations may be granted for these products.

## **IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY**

The important quality characteristics of Losartan Potassium and Hydrochlorothiazide 50/12.5mg and 100/25mg 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 and Hydrochlorothiazide 50/12.5mg Tablets and Cozaar Comp 50/12.5mg Tablets. As these products meet all the criteria as 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 50/12.5mg strength can be extrapolated to the 100/25mg strength.

No new or unexpected safety concerns arise from these applications.

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

**RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with losartan potassium and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|----------------|------------------|-------|---------|
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |