

**LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE
50/12.5MG FILM-COATED TABLETS
(PL 20176/0056)**

**LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE
100/25MG FILM-COATED TABLETS
(PL 20176/0057)**

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LAY SUMMARY

On 28th February 2008, the MHRA granted Technopharm Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium/Hydrochlorothiazide 50/12.5mg and 100/25mg Film-Coated Tablets. These are prescription only medicines that are used to reduce high blood pressure.

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.

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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SCIENTIFIC DISCUSSION

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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 Technopharm Limited on 28th February 2008.

The products are prescription-only medicines for the treatment of hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan potassium monotherapy. In hypertensive patients with left ventricular hypertrophy, a reduced risk of stroke was demonstrated with losartan administered usually in combination with hydrochlorothiazide. The data do not support the use of losartan for this indication in Black patients.

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.

PHARMACEUTICAL ASSESSMENT

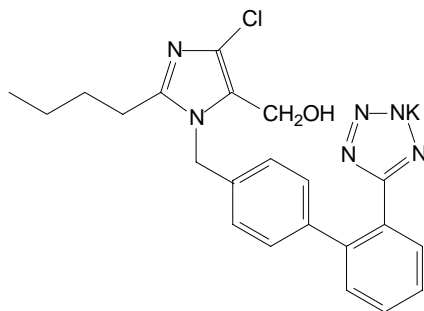
DRUG SUBSTANCE – LOSARTAN POTASSIUM

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

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.

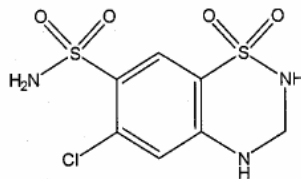
DRUG SUBSTANCE – HYDROCHLOROTHIAZIDE

INN: Hydrochlorothiazide

Chemical Names: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-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 is 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 microcrystalline cellulose, calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, croscarmellose sodium, talc, magnesium stearate and a coating (Opadry II) made up of hypromellose, lactose monohydrate, titanium dioxide (E171) and glycerol triacetate. In addition, the 50/12.5mg strength contains iron oxide red (E172).

With the exception of the Opadry II coatings, all excipients have a respective European Pharmacopoeia monograph. For each Opary II coating, suitable in-house specifications have been provided.

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).

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.

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results.

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 oriented polyamide (OPA)/polyvinylchloride (PVC) blisters with aluminium lidding, in pack sizes of 7 and 28 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 no specific storage conditions.

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.

PRECLINICAL ASSESSMENT

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), 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.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours.

Distribution

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

Hydrochlorothiazide appears to be preferentially bound to red blood cells.

Metabolism

About 14% of an orally-administered dose of losartan is converted to its active metabolite (carboxylosartan) by CYP2C9 and CYP3A4. The active metabolite is 10-40-fold more potent than the parent drug. 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.

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

Excretion

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 accumulate significantly in plasma.

Hydrochlorothiazide is excreted mainly unchanged (up to 61% of dose administered) in the urine.

Special populations

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.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups (> 1 month to < 16 years) and consistent with pharmacokinetic historic data in adults.

BIOEQUIVALENCE**Study design**

A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioequivalence study to compare Losartan Potassium/Hydrochlorothiazide 100/25mg Tablets (test) versus Fortzaar 100/25mg Tablets (reference) in healthy fasted volunteers.

Blood samples were taken pre- and up to 96 hours post dose and each treatment arm was separated by an 11-day washout period.

Results

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

Variable	Test	Reference	Point Estimate (test/reference) (%)	90 % C.I.
<i>Losartan</i>				
C _{max} (ng/ml)	482 ± 330	480 ± 364	100.3	85.3 – 117.8
AUC _(0-t) (ngh/ml)	792 ± 335	814 ± 345	97.3	93.1 – 101.7
AUC _(0-inf) (ngh/ml)	834 ± 337	853 ± 345	97.8	93.5 – 102.2
T _{max} (h)	1.0 ± 0.9	1.2 ± 1.1	-	-
T _{el} (h)	2.3 ± 1.0	2.1 ± 0.9	-	-
<i>Carboxylosartan (active metabolite)</i>				
C _{max} (ng/ml)	662 ± 306	685 ± 285	96.6	92.2 – 101.3
AUC _(0-t) (ngh/ml)	4021 ± 1758	4089 ± 1671	98.3	93.4 – 103.5
AUC _(0-inf) (ngh/ml)	4153 ± 1775	4213 ± 1686	98.6	93.8 – 103.5
T _{max} (h)	2.7 ± 1.2	2.9 ± 1.2	-	-
T _{el} (h)	5.0 ± 1.6	5.0 ± 1.5	-	-
<i>Hydrochlorothiazide</i>				
C _{max} (ng/ml)	170 ± 81	164 ± 81	103.7	94.8 – 113.5
AUC _(0-t) (ngh/ml)	1143 ± 399	1153 ± 415	99.2	94.2 – 104.4
AUC _(0-inf) (ngh/ml)	1185 ± 400	1194 ± 422	99.2	94.8 – 113.5
T _{max} (h)	1.9 ± 0.8	2.1 ± 1.4	-	-
T _{el} (h)	10.3 ± 2.5	10.8 ± 2.7	-	-

Geometric mean ± SD represented

Conclusions

The 90% confidence intervals for the test/reference 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 100/25mg strength can be extrapolated to the 50/12.5 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 product.

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 100/25mg 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 100/25mg strength can be extrapolated to the 50/12.5 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.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Losartan Potassium/Hydrochlorothiazide 50/12.5mg and 100/12.5mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Losartan Potassium/Hydrochlorothiazide 100/25mg Tablets and Fortzaar 100/25mg 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 100/25mg strength can be extrapolated to the 50/12.5 strength.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent.

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.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 11 th July 2006
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 17 th August 2006
3	Following assessment of the applications the MHRA requested further information relating to the dossier on 4 th December 2006, 7 th June 2007, 21 st November 2007 and 16 th January 2008.
4	The applicant responded to the MHRA's requests, providing further information on 6 th June 2007, 27 th July 2007, 15 th January 2008 and 6 th February 2008
5	The applications were determined on 28 th February 2008

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredients are losartan and hydrochlorothiazide. Each tablet contains 50 mg / 12.5mg of losartan potassium and hydrochlorothiazide.

Excipients: Lactose Monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pink, round, biconvex, film-coated tablets with a score line on one side and marked 'LS 62' on the other.

The scoreline 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 hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated with losartan administered usually in combination with hydrochlorothiazide. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race.)

4.2 Posology and method of administration

Where possible titration with the individual components (ie losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combinations 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 weeks after initiation of therapy.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed the dose should then be increased to losartan 100 mg/hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to Losartan potassium/ Hydrochlorothiazide 100mg/ 25mg daily.

Use in the elderly: Patients over 75 years: Presently there is limited clinical experience in this group. Any therapy involving the angiotensin II antagonist, losartan, should be initiated with 25mg losartan in these patients.

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). Losartan/ hydrochlorothiazide (HCTZ) is not recommended for patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis.

Use in patients with intravascular volume depletion: Losartan/ 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/ hydrochlorothiazide is not recommended for patients with hepatic impairment.

Concomitant therapy: Losartan/ hydrochlorothiazide may be administered with other antihypertensive agents.

Losartan/ hydrochlorothiazide may be administered with or without food.

Use in children: Safety and efficacy in children have not been established.

4.3 **Contraindications**

Losartan/ hydrochlorothiazide is contra-indicated in the 2nd and 3rd trimester of pregnancy (see sections 4.4 'Special warnings' and 4.6 'Pregnancy and lactation'), in patients who are hypersensitive to any component of this product, in patients with anuria, and in patients who are hypersensitive to other sulphonamide-derived drugs.

4.4 **Special warnings and precautions for use**

Losartan and hydrochlorothiazide combination tablet

Hypersensitivity: Angioedema (see 4.8 'Undesirable effects').

Hepatic and renal impairment: Losartan/ HCTZ is not recommended for patients with hepatic impairment or moderate to severe renal impairment (creatinine clearance <20 ml/min.) (See 4.2 'Posology and method of administration'.)

Losartan

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

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

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

Caution should be exercised in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance: As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients, but was more likely in the presence of fluid depletion or electrolyte imbalance. Periodic determination of serum electrolytes should be performed at appropriate intervals, as in any patients receiving diuretics.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see 4.5 'Interaction with other medicaments and other forms of interaction').

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

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

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

Other

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

The use of losartan in patients with haemodynamically significant obstructive valvular disease and cardiomyopathy has not been adequately studied.

Race (Black patients)

There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, Race').

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Losartan

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (phenobarbitone), (see Hydrochlorothiazide; Alcohol, barbiturates, or narcotics below) ketoconazole and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indometacin.

Hydrochlorothiazide

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

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—there may be an additive effect.

Cholestyramine and colestipol resins—absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH—there may be intensified electrolyte depletion, particularly hypokalaemia.

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

Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Therefore, concomitant use is not recommended. Refer to the prescribing information for lithium preparations before use of such preparations.

Non-steroidal anti-inflammatory drugs—in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

Drug/laboratory test interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see 4.4 'Special warnings and special precautions for use').

4.6 Pregnancy and lactation

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

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

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data')

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

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

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard, including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxæmia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxæmia.

Use during lactation

It is not known whether losartan is excreted in human milk. Significant levels of losartan and the active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the breast-feeding infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Losartan/hydrochlorothiazide may have a minor or moderate influence on the ability to drive and use machines. Losartan can cause dizziness, asthenia and vertigo. If the patient experiences these adverse reactions, they should not drive or use machines.

4.8 Undesirable effects

In clinical trials with the combination tablet of losartan and hydrochlorothiazide, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

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

The following adverse reactions have been reported in post-marketing experience:

Hypersensitivity

Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely with losartan.

Gastro-intestinal: Hepatitis has been reported rarely in patients treated with losartan; diarrhoea.

Respiratory: cough has been reported with losartan.

Skin: Urticaria.

Additional side effects that have been seen with one of the individual components and may be potential side effects with Losartan/ HCTZ are the following:

Losartan

Dose-related orthostatic effects, liver function abnormalities, myalgia, migraine, rash, anaemia, pruritus.

Hydrochlorothiazide

Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, paraesthesiae, headache, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, fever, necrotising angitis, respiratory distress (including pneumonitis and pulmonary oedema), anaphylactic reactions, toxic epidermal necrolysis, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), renal dysfunction, interstitial nephritis, renal failure, muscle spasm, weakness, restlessness, transient blurred vision.

Laboratory test findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium-hydrochlorothiazide. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 0.7% of patients, but in these trials discontinuation of losartan potassium-hydrochlorothiazide due to hyperkalaemia was not necessary. Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

4.9 Overdose

No specific information is available on the treatment of overdosage with Losartan/ HCTZ. Treatment is symptomatic and supportive. Therapy with Losartan/ HCTZ 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

Therapeutic Classification: C09D A01

Pharmacotherapeutic group: Angiotensin II Antagonists, Combinations

Losartan and hydrochlorothiazide combination tablet

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

The combination of losartan and 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 $<24 \mu\text{mol/l}$) 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, as with other drugs that affect the renin-angiotensin system, 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.

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80

years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily 'Cozaar' 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of 'Cozaar' or atenolol was then increased to 100 mg once daily. Other antihypertensives (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists or beta-blockers) were added if necessary to reach the goal blood pressure. In efforts to control blood pressure, the patients in both arms of the LIFE study were coadministered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms respectively). The mean length of follow up was 4.8 years.

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

Race: There were 533 black patients in the study. In this group, treatment with 'Cozaar' resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

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 drug 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 ¹⁴C-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 ¹⁴C-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, fivefold 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

The toxic potential of losartan potassium and hydrochlorothiazide was evaluated in repeated-dose oral toxicity studies for up to six months in rats and dogs. There were no findings that would preclude administration to man at the therapeutic dosage level.

There was no evidence of direct genotoxicity in studies conducted with the losartan and hydrochlorothiazide combination.

Losartan potassium and hydrochlorothiazide administration had no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day losartan in combination with 33.75 mg/kg/day hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite and

hydrochlorothiazide that were approximately 260-, 120-, and 50-fold greater than those achieved in man with 50 mg losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, 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. Compared to plasma concentrations in man (see above) these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium and hydrochlorothiazide combination. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Calcium hydrogen phosphate dihydrate
Colloidal anhydrous silica
Croscarmellose sodium
Talc
Magnesium stearate

Tablet coating:

Opadry 32K28708 pink
Hypromellose
Lactose monohydrate
Titanium dioxide (E171)
Glycerol triacetate
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Al/PVC blister
Available in packs of 7 and 28 tablets.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

TechnoPharm Ltd
Fanin House, South County Business Park
Leopardstown, Dublin 18, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20176/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/02/2008

10 DATE OF REVISION OF THE TEXT

28/02/2008

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredients are losartan and hydrochlorothiazide. Each tablet contains 100mg/25mg of losartan potassium and hydrochlorothiazide.

Excipients: Lactose Monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, round, biconvex, film-coated tablets with a score line on one side and marked 'LS 125' on the other.

The scoreline 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 hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated with losartan administered usually in combination with hydrochlorothiazide. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race.)

4.2 Posology and method of administration

Where possible titration with the individual components (ie losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combinations 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 weeks after initiation of therapy.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed the dose should then be increased to losartan 100 mg/hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to Losartan potassium/ Hydrochlorothiazide 100mg/ 25mg daily.

Use in the elderly: Patients over 75 years: Presently there is limited clinical experience in this group. Any therapy involving the angiotensin II antagonist, losartan, should be initiated with 25mg losartan in these patients.

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). Losartan/ hydrochlorothiazide (HCTZ) is not recommended for patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis.

Use in patients with intravascular volume depletion: Losartan/ 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/ hydrochlorothiazide is not recommended for patients with hepatic impairment.

Concomitant therapy: Losartan/ hydrochlorothiazide may be administered with other antihypertensive agents.

Losartan/ hydrochlorothiazide may be administered with or without food.

Use in children: Safety and efficacy in children have not been established.

4.3 **Contraindications**

Losartan/ hydrochlorothiazide is contra-indicated in the 2nd and 3rd trimester of pregnancy (see sections 4.4 'Special warnings' and 4.6 'Pregnancy and lactation'), in patients who are hypersensitive to any component of this product, in patients with anuria, and in patients who are hypersensitive to other sulphonamide-derived drugs.

4.4 **Special warnings and precautions for use**

Losartan and hydrochlorothiazide combination tablet

Hypersensitivity: Angioedema (see 4.8 'Undesirable effects').

Hepatic and renal impairment: Losartan/ HCTZ is not recommended for patients with hepatic impairment or moderate to severe renal impairment (creatinine clearance <20 ml/min.) (See 4.2 'Posology and method of administration').

Losartan

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

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

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

Caution should be exercised in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance: As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients, but was more likely in the presence of fluid depletion or electrolyte imbalance. Periodic determination of serum electrolytes should be performed at appropriate intervals, as in any patients receiving diuretics.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see 4.5 'Interaction with other medicaments and other forms of interaction').

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

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

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

Other

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

The use of losartan in patients with haemodynamically significant obstructive valvular disease and cardiomyopathy has not been adequately studied.

Race (Black patients)

There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, Race').

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Losartan

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (phenobarbitone), (see Hydrochlorothiazide; Alcohol, barbiturates, or narcotics below) ketoconazole and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indometacin.

Hydrochlorothiazide

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

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—there may be an additive effect.

Cholestyramine and colestipol resins—absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH—there may be intensified electrolyte depletion, particularly hypokalaemia.

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

Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Therefore, concomitant use is not recommended. Refer to the prescribing information for lithium preparations before use of such preparations.

Non-steroidal anti-inflammatory drugs—in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

Drug/laboratory test interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see 4.4 'Special warnings and special precautions for use').

4.6 Pregnancy and lactation

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

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

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data')

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

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

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard, including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Use during lactation

It is not known whether losartan is excreted in human milk. Significant levels of losartan and the active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the breast-feeding infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Losartan/hydrochlorothiazide may have a minor or moderate influence on the ability to drive and use machines. Losartan can cause dizziness, asthenia and vertigo. If the patient experiences these adverse reactions, they should not drive or use machines.

4.8 Undesirable effects

In clinical trials with the combination tablet of losartan and hydrochlorothiazide, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

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

The following adverse reactions have been reported in post-marketing experience:

Hypersensitivity

Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely with losartan.

Gastro-intestinal: Hepatitis has been reported rarely in patients treated with losartan; diarrhoea.

Respiratory: cough has been reported with losartan.

Skin: Urticaria.

Additional side effects that have been seen with one of the individual components and may be potential side effects with Losartan/ HCTZ are the following:

Losartan

Dose-related orthostatic effects, liver function abnormalities, myalgia, migraine, rash, anaemia, pruritus.

Hydrochlorothiazide

Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, paraesthesiae, headache, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, fever, necrotising angitis, respiratory distress (including pneumonitis and pulmonary oedema), anaphylactic reactions, toxic epidermal necrolysis, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), renal dysfunction, interstitial nephritis, renal failure, muscle spasm, weakness, restlessness, transient blurred vision.

Laboratory test findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium-hydrochlorothiazide. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 0.7% of patients, but in these trials discontinuation of losartan potassium-hydrochlorothiazide due to hyperkalaemia was not necessary. Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

4.9 Overdose

No specific information is available on the treatment of overdosage with Losartan/ HCTZ. Treatment is symptomatic and supportive. Therapy with Losartan/ HCTZ 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

Therapeutic Classification: C09D A01

Pharmacotherapeutic group: Angiotensin II Antagonists, Combinations

Losartan and hydrochlorothiazide combination tablet

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

The combination of losartan and 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 $<24 \mu\text{mol/l}$) 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, as with other drugs that affect the renin-angiotensin system, 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.

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily 'Cozaar' 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of 'Cozaar' or atenolol was then increased to 100 mg once daily. Other antihypertensives (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists or beta-blockers) were added if necessary to reach the goal blood pressure. In efforts to control blood pressure, the patients in both arms of the LIFE study were coadministered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms respectively). The mean length of follow up was 4.8 years.

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

Race: There were 533 black patients in the study. In this group, treatment with 'Cozaar' resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint ($p=0.033$, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke ($p=0.030$, 95% confidence interval 1.08-4.40).

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 drug 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 ¹⁴C-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 ¹⁴C-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, fivefold 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

The toxic potential of losartan potassium and hydrochlorothiazide was evaluated in repeated-dose oral toxicity studies for up to six months in rats and dogs. There were no findings that would preclude administration to man at the therapeutic dosage level.

There was no evidence of direct genotoxicity in studies conducted with the losartan and hydrochlorothiazide combination.

Losartan potassium and hydrochlorothiazide administration had no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day losartan in combination with 33.75 mg/kg/day hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite and hydrochlorothiazide that were approximately 260-, 120-, and 50-fold greater than those achieved in man with 50 mg losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, 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. Compared to plasma concentrations in man (see above) these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium and hydrochlorothiazide combination. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Calcium hydrogen phosphate dihydrate
Colloidal anhydrous silica
Croscarmellose sodium
Talc
Magnesium stearate

Tablet coating:

Opadry 32K28708 white
Hypromellose
Lactose monohydrate
Titanium dioxide (E171)
Glycerol triacetate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Al/PVC blister
Available in packs of 7 and 28 tablets.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

TechnoPharm Ltd
Fanin House, South County Business Park
Leopardstown, Dublin 18, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20176/0057

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
28/02/2008
- 10** **DATE OF REVISION OF THE TEXT**
28/02/2008

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Losartan potassium and hydrochlorothiazide
(Losartan/Hydrochlorothiazide Tablets)

Read all of this leaflet carefully before you start taking this medicine.

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

In this leaflet:

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

1 What Losartan/ Hydrochlorothiazide Tablets are and what they are used for

Losartan belongs to a group of medicines called the angiotensin II receptor antagonists.

Angiotensin II is a chemical naturally occurring in your body which narrows your blood vessels making it harder for the blood to pass through them and causing your blood pressure to increase. Losartan blocks the effect of Angiotensin II causing the blood vessels to

relax. Hydrochlorothiazide works by making your kidneys pass more water and salt and thereby reducing the volume of blood passing through the body. Together, losartan and hydrochlorothiazide lower high blood pressure.

Your doctor has prescribed Losartan/Hydrochlorothiazide Tablets because you have high blood pressure with or without thickening of the heart muscle (left ventricular hypertrophy).

Losartan/Hydrochlorothiazide Tablets may help to reduce the risk of stroke in patients with high blood pressure who have developed thickening of the heart muscle. However there is no evidence to support this effect in Black patients.

2 Before you take Losartan/ Hydrochlorothiazide Tablets

Please read the following information carefully as this may stop you from being able to have this medicine.

Do not take Losartan/Hydrochlorothiazide Tablets:

- if you are allergic (hypersensitive) to losartan potassium, hydrochlorothiazide or any of the other ingredients of Losartan/Hydrochlorothiazide Tablets
- if you are more than 13 weeks pregnant or breast-feeding
- If you have a condition where your kidneys are not working properly and you are not passing urine (anuria).

If any of these apply to you and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking your tablets.

Take special care with Losartan/ Hydrochlorothiazide Tablets

Before treatment with Losartan/Hydrochlorothiazide Tablets you should tell your doctor if any of the following apply to you. Your doctor may need to adjust your dose:

- if you are taking other diuretics (water tablets)
- if you have recently suffered from sickness and/or diarrhoea
- if you have liver problems

- if you have kidney problems or have had a kidney transplant
- if you have narrowing of the blood vessels to the kidneys
- if you are diabetic
- if you suffer from gout
- if you have an inflammatory condition called systemic lupus erythematosus (SLE)
- if you have raised potassium levels or are on a potassium-restricted diet
- if you have raised calcium levels as a result of too much parathyroid hormone in your blood (hyperparathyroidism).
- if you have high cholesterol or triglyceride levels in your blood
- if you have had asthma or allergies
- if you have a condition called 'aortic stenosis' which is the narrowing of a valve in the heart
- if you have a condition called hypertrophic cardiomyopathy

Taking other medicines

The following medicinal products may affect the ability of losartan to work properly:

- non-steroidal anti-inflammatory drugs (NSAIDs, e.g. indometacin)
- fluconazole (an anti-fungal)
- rifampicin (an antibiotic)
- potassium-sparing diuretics (e.g. triamterene, amiloride), or potassium supplements or salt alternatives which contain potassium
- alcohol, barbiturates (e.g. sedatives, anaesthetics or anticonvulsants) or narcotics (e.g. morphine or other opioids)
- antidiabetic drugs including oral agents and insulin
- other drugs to lower your blood pressure
- colestyramine and colestipol
- corticosteroids (synthetic hormones usually used following a transplant) or adrenocorticotrophic hormone (ACTH)
- adrenaline and other similar drugs
- muscle relaxants
- lithium

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

You should not take Losartan/hydrochlorothiazide tablets in the first 12 weeks of pregnancy. You must not take losartan/hydrochlorothiazide tablets at all after the 13th week as its use during pregnancy may be harmful to the baby. During treatment with Losartan/hydrochlorothiazide you should avoid becoming pregnant. If you become pregnant while taking this medicine, please tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. You must not take losartan/hydrochlorothiazide if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines

This medicine may make you feel dizzy, tired or make your head spin. Do not drive or operate machinery if this happens.

Important information about some of the ingredients of Losartan/ Hydrochlorothiazide film-coated Tablets

This product contains lactose monohydrate. 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/ Hydrochlorothiazide Tablets

Swallow your tablets whole with a glass of water. The tablets may be taken with or without food. It is best to take your tablets at the same time each day.

Adults

The usual starting dose is 50mg/12.5mg once daily. You will probably have to wait for 3 weeks to see the effect on your blood pressure. Your doctor may tell you to increase this dose to 100mg/25mg once daily.

If you are over 75 years old you may begin with a lower dose.

If you suffer from low blood volume as a result of taking water tablets or have liver or severe kidney problems you should not be given this medicine.

Children

The safety and effectiveness of Losartan/hydrochlorothiazide has not been established in children.

If you take more Losartan/Hydrochlorothiazide Tablets than you should

If you take too much losartan you may experience drop in your blood pressure (this can make you feel short of breath, dizzy or light-headed or cause a headache, diarrhoea or vomiting) and an increased or decreased heart rate. Your calcium, potassium or sodium levels may be affected and you may become dehydrated. If you think you or someone else may have taken too much Losartan/hydrochlorothiazide, please tell your doctor immediately or go the nearest hospital casualty department. If possible, please take the remaining tablets or this leaflet with you to hospital.

If you miss a dose

If you have forgotten to take your tablet, take it as soon as you remember, unless it is almost time for your next tablet.

Do not take a double dose to make up for a forgotten dose.

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/hydrochlorothiazide can cause side effects, although not everybody gets them. The following side effects have been observed in patients treated with Losartan/hydrochlorothiazide:

Allergic reactions:

- Anaphylactic reaction – this is a very severe allergic reaction and may be life threatening. You must seek urgent medical attention if you experience any of the following symptoms:
 - swelling of the face, lips, tongue or throat
 - breathlessness
 - rash
- vasculitis (inflammation of blood vessel) including Henoch-Schonlein purpura (with

symptoms of purple spots on the skin and joint pain).

Other side effects:

- stomach cramps, upset stomach, diarrhoea, constipation
- loss of appetite
- inflammation of the salivary glands
- inflammation of the liver, jaundice (yellowing of the skin or the whites of the eyes), liver problems
- pancreatitis (inflammation of the pancreas)
- presence of sugar in your urine
- kidney problems
- anaemia (drop in red blood cells)
- thrombocytopenia (drop in some other types of blood cells needed for blood clotting)
- changes to levels of potassium
- decrease in blood pressure
- increase in sugar levels
- high levels of uric acid which may precipitate gout
- agranulocytosis
- muscle and joint pain, muscle spasms
- weakness, fatigue, restlessness
- dizziness, vertigo (spinning feeling)
- migraine, headache
- pins and needles
- vision that is blurred or which makes things appear yellow
- fever
- cough
- difficulty breathing, lung infection, fluid on the lungs
- rashes, hives, itching
- sun sensitivity
- severe skin reactions including blistering, peeling and swelling

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

5 How to store Losartan/Hydrochlorothiazide Tablets

This medicinal product does not require any special storage requirements.

Do not use Losartan/hydrochlorothiazide after the expiry date which is shown on the carton after 'EXPIRY'. The expiry date refers to the last day of that month.

Keep out of the reach and sight of children.

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/Hydrochlorothiazide Tablets contain**

- The active substances are losartan potassium and hydrochlorothiazide.
- The other ingredients are microcrystalline cellulose, calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, croscarmellose sodium, talc and magnesium stearate.
- The tablet coating for the 50mg/12.5mg tablets consists of hypromellose, lactose monohydrate, titanium dioxide (E171), glycerol triacetate and iron oxide red (E172).
- The tablet coating for the 100mg/25mg tablets consists of hypromellose, lactose monohydrate, titanium dioxide (E171) and glycerol triacetate.

What Losartan/Hydrochlorothiazide Tablets look like and contents of pack

Losartan/Hydrochlorothiazide 50mg/12.5mg Tablets are pink, round, biconvex film-coated tablet with a score line on one side and debossed LS 62 on the other side. They are available in packs of 7 or 28 tablets.

Losartan/Hydrochlorothiazide 100mg/25mg Tablets are white, round, biconvex film-coated tablets with a score line on one side and debossed LS 125 on the other side. They are available in packs of 7 or 28 tablets.

The scorelines are only to facilitate breaking for ease of swallowing, and not to divide into equal doses.

Marketing Authorisation Holder and Manufacturer:**Marketing Authorisation Holder:**

TechnoPharm Limited,
Fannin House
South County Business Park
Leopardstown
Dublin 18
Ireland.

Manufacturer:

PLIVA Krakow S.A.,
80 Mogilska Str.,
31 546 Krakow,
Poland


These medicinal products are authorised in the Member States of the EEA under the following names:

United Kingdom:


Losartan potassium/Hydrochlorothiazide 50mg/12.5mg film-coated Tablets
Losartan potassium/Hydrochlorothiazide 100mg/25mg film-coated Tablets

This leaflet was last approved in 09/2007.

Losartan potassium/Hydrochlorothiazide
50mg/12.5mg film-coated Tablets




**Losartan potassium/
 Hydrochlorothiazide**
50mg/12.5mg
 film-coated Tablets



28 tablets

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

Losartan potassium/Hydrochlorothiazide
50mg/12.5mg film-coated Tablets



Losartan potassium/Hydrochlorothiazide
 50mg/12.5mg film-coated Tablets
 28 tablets

Read the package leaflet before use.
 Contains lactose monohydrate.
 See enclosed leaflet for further information.
 For oral use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

MA Holder:
 TechnoPharm Ltd,
 Chapelizod, Dublin 20, Ireland

Distributed by:
 PLIVA Pharma Ltd,
 Vision House, Bedford Road, Petersfield,
 Hampshire, GU32 3QB, United Kingdom

PLIVA

POM PL 20176/0056 xxxxx-C1

Bar code

Batch:
 Expiry:

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Losartan potassium/Hydrochlorothiazide
100mg/25mg film-coated Tablets

**Losartan potassium/
Hydrochlorothiazide**
100mg/25mg
film-coated Tablets

28 tablets

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

Losartan potassium/Hydrochlorothiazide
100mg/25mg film-coated Tablets

Bar code

PLIVA

Batch:
Expiry:

Read the package leaflet before use.
Contains lactose monohydrate.
See enclosed leaflet for further information.
For oral use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

MA Holder:
TechnoPharm Ltd,
Chapelizod, Dublin 20, Ireland

Distributed by:
PLIVA Pharma Ltd,
Vision House, Bedford Road, Petersfield,
Hampshire, GU32 3QB, United Kingdom

POM PL 20176/0057 xxxxx-C1

Losartan potassium/Hydrochlorothiazide
100mg/25mg film-coated Tablets

**Losartan potassium/
Hydrochlorothiazide**
100mg/25mg
film-coated Tablets

28 tablets

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

Losartan potassium/Hydrochlorothiazide
100mg/25mg film-coated Tablets

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PLIVA

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POM PL 20176/0057 xxxxx-C1