

**LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE
50MG/12.5MG TABLETS**

**PL 24701/0001
PL 24701/0002**

UKPAR

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**LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE
50MG/12.5MG TABLETS**

PL 24701/0001

PL 24701/0002

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Nucleus ehf Marketing Authorisations (licences) for the medicinal product Losartan Potassium/ Hydrochlorothiazide 50mg/12.5mg Tablets and its duplicate (PL 24701/0001 & PL 24701/0002) on 5th February 2008. This is a prescription-only medicine used for the treatment of high blood pressure and stroke in patients with heart disease.

The tablets contain two active ingredients, losartan potassium and hydrochlorothiazide. Losartan belongs to a group of medicines known as angiotensin-receptor antagonists. Angiotensin is a chemical occurring in the body, which tightens your blood vessels making it harder for the blood to pass through them and causing your blood pressure to increase. Losartan blocks this effect of angiotensin, causing the blood vessels to relax. Hydrochlorothiazide works by making your kidneys pass more water and salt. The combined effect of losartan and hydrochlorothiazide lowers high blood pressure.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Losartan/ Hydrochlorothiazide 50mg/12.5mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

**LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE
50MG/12.5MG TABLETS**

**PL 24701/0001
PL 24701/0002**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Nucleus ehf Marketing Authorisations for the medicinal product Losartan Potassium/ Hydrochlorothiazide 50mg/12.5mg Tablets (PL 24701/0001 & PL 24701/0002) on 5th 2008. This is a prescription-only medicine used for the treatment of high blood pressure and stroke.

Losartan Potassium/ Hydrochlorothiazide 50mg/12.5mg Tablets contain two active ingredients, losartan potassium and hydrochlorothiazide. Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists and is approved as a single agent and in combination with hydrochlorothiazide for treatment of hypertension. Hydrochlorothiazide is a thiazide diuretic used for many years in treatment of hypertension.

These are national, abridged applications, submitted according to Article 10.1 of Directive 2001/83/EC, and have been shown to be a generic medicinal product of the originator Hyzaar 50mg/12.5mg tablets (Merck Sharp & Dohme, France). The reference product has been authorised in the EU since February 1995 and so the 10-year period of data exclusivity has expired.

The application was referred to the Commission on Human Medicines (CHM) on 18th October 2006 for consideration whether the safety, quality and efficacy of the product was demonstrated. After review of responses to the Commission concerns, marketing authorisations were approved.

These applications were submitted at the same time and both depend on the bioequivalence study comparing the applicant's 50mg/12.5mg product with the reference product Cozaar-Comp Tablets (Merck Sharp & Dohme). Consequently, all sections of this Scientific Discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE (1)

Losartan potassium

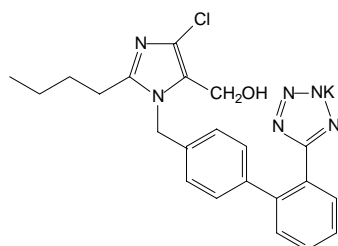
Nomenclature:

INN: Losartan potassium

Chemical name: 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol, monopotassium salt

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

Structure:



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

Molecular weight: 461.01

Physical form: White to off-white crystalline powder.

Solubility: Freely soluble in water and methanol and insoluble in chloroform

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

An appropriate specification is provided for the active substance losartan potassium.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active losartan potassium is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

ACTIVE SUBSTANCE (2)

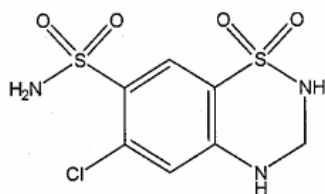
Hydrochlorothiazide

Nomenclature:

INN: Hydrochlorothiazide

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide
6-chloro-3,4-dihydro-1,2-dioxide-2H-1,2,4-benzothiazine-7-sulphonamide

Structure:



Molecular formula: C₇H₈ClN₃O₄S₂

Molecular weight: 297.7

Physical form: White to off-white odourless crystalline powder

Solubility: Very slightly soluble in water, soluble in acetone and dilute solutions of alkali hydroxides.

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

An appropriate active substance specification has been provided based on European Pharmacopeia requirements.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active hydrochlorothiazide is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely hypromellose 3 CPS, hypromellose 50 CPS, povidone, croscarmellose sodium, microcrystalline cellulose, mannitol, magnesium stearate, macrogol, purified water, titanium dioxide E171 and hydroxypropyl cellulose. Appropriate justification for the inclusion of each excipient has been provided.

The excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. There were no novel excipients used.

Pharmaceutical development

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

Dissolution and impurity profiles

Dissolution and impurity profiles of the drug product were found to be similar to those for the reference product.

Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any standards used.

Container Closure System

The tablets are packed in white, opaque PVC (polyvinylchloride) / PVDC (polyvinylidene chloride) aluminium blisters or high density polyethylene (HDPE) containers with a snap-on neck and LDPE push-fit, tamper-evident caps. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC, regarding contact with food. The product is packaged in sizes of 14, 28, 30, 50, 56, 98, 100 and 280 tablets for both types of packaging.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the

results, a shelf-life of 4 years has been set, which is satisfactory. Storage conditions are “Store below 30°C”.

Patient Information Leaflet

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion

The grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

1 INDICATIONS

The proposed indications for this product are identical to those of the reference product Cozaar-Comp tablets (Merck Sharp & Dohme; PL 00025/0338)

Treatment of hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy alone.

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

2 SCIENTIFIC EVIDENCE

Both losartan, an angiotension II inhibitor, and HCT, a thiazide diuretic, are well established anti-hypertensive products, outside patent life. The combination is also well established.

According to CPMP/EWP/QWP/1401/98, the decision as to whether Losartan HCT tablets can be considered essentially similar to the innovator product marketed as Cozaar in the UK depends upon them having the same qualitative and quantitative composition in terms of active substances, the same pharmaceutical form and being shown to be bioequivalent. The first two of these criteria are the subject of the Quality Assessment and seem likely to be fulfilled. The third criterion depends upon the bioequivalence study submitted, which is the main subject of this assessment.

No clinical pharmacodynamic, efficacy or safety studies are required. An adequate literature review has been submitted to cover those aspects.

2.1 CLINICAL PHARMACOLOGY

No new pharmacodynamic data are presented and none are required.

2.1.1 Bioavailability / bioequivalence (summarised by the Assessor)

Study AA0XXXX, "Comparative, randomised, single dose, crossover bioavailability study of Omega Farma HF Losartan potassium/12.5 mg hydrochlorothiazide tablets and MSD Chibrofarm GmbH Lorzaar Plus tablets in healthy adult volunteers under fasting conditions."

Study design

Healthy, adult volunteers were recruited to this bioequivalence study. A single oral dose of each drug was administered with a one-week washout between dosing periods. Subjects were randomised to order of dosing. Single dosing is justifiable based on the known pharmacokinetic characteristics of losartan and HCT. The one-week interval is justifiable on the basis of the known plasma half-life of the drugs,

confirmed by absence of analytes in blood prior to dosing in the second period of this study.

Batch analysis results were submitted on the drug materials used; Losartan HCT 50 mg/12.5 mg tablets and Lorzaar Plus 50 mg/12.5 mg (MSD) sourced from Germany. The drug materials used were considered suitable, in terms of content and sampling, by the Quality Assessor.

In each period, subjects were institutionalised from at least 12 hours before to 36 hours after dosing and were to return at 48 hours post-dosing for blood sampling. Subjects were fasted from 10 hours prior to dosing to 4 hours post-dosing. Appropriate restrictions on diet, fluid intake and concomitant medications were maintained. Smoking was allowed from 4 hours post-dosing although only subjects said to smoke less than 10 cigarettes per day were admitted.

Blood samples were taken at intervals appropriate to the known pharmacokinetic profiles of the drugs up to 48 hours after dosing and analysed for losartan, losartan carboxylic acid (the major active metabolite of losartan) and HCT concentrations. Analysis methods (LC/MS/MS) were assessed by the Quality Assessor and some additional information was requested regarding the reference standard used for losartan. The following pharmacokinetic parameters were reported: $AUC_{(0-inf)}$, C_{max} , $AUC_{(0-t)}$, T_{max} , $T_{1/2}$ and K_{el} . Analysis of variance was conducted using formulation, group, sequence and period as fixed effects. 90% confidence intervals (CI) for the ratio of the least squares means of the log-transformed values were presented and compared to the accepted ranges set down in CPMP/EWP/QWP/1401/98.

Overall, study design was compatible with the CPMP NfG on the Investigation of Bioavailability and Bioequivalence. Study conduct was stated to have been GCP compliant.

Results

Some minor protocol deviations were described and eleven drug concentration or pharmacokinetic parameter values were listed as missing for valid reasons. These factors are not expected to affect study results, given the substantial subject numbers.

A summary of the results is represented below

Table 1 Losartan Potassium Pharmacokinetic data

Variable	Omega 50 /12. 5 mg tablets (test)	Lorzaar Plus tablets (reference)	Point Estimate (Test/reference) (%)	90 % C.I.
<i>Losartan potassium</i>				
C_{max} (ng/ml)	220.9 ± 140.4	263.8 ± 147.9	82.3	73.3 – 92.3
$AUC_{(0-t)}$ (ngh/ml)	417.4 ± 155.7	445.5 ± 159.5	93.7	90.8 – 96.6
$AUC_{(0-inf)}$ (ngh/ml)	432.0 ± 157.8	458.8 ± 161.8	94.3	81.4 – 97.2
T_{max} (h)	1.21 ± 0.96	1.24 ± 0.85	-	-
$T_{1/2}$ (h)	2.82 ± 1.44	2.74 ± 0.75	-	-
<i>Losartan carboxylic acid</i>				
C_{max} (ng/ml)	279.7 ± 102.4	312.1 ± 123.1	93.1	90.9 – 95.4
$AUC_{(0-t)}$ (ngh/ml)	2135.4 ± 663.9	2301.9 ± 735.3	93.3	91.1 – 95.6
$AUC_{(0-inf)}$ (ngh/ml)	2173.9 ± 667.9	2338.1 ± 736.6	90.7	87.2 – 94.3

T_{max} (h)	4.04 ± 1.19	4.09 ± 1.15	-	-
T_{1/2} (h)	7.39 ± 1.97	7.70 ± 1.83	-	-

Mean ± SD represented.

Table 8 Hydrochlorothiazide Pharmacokinetic data

Variable	Actavis 50 /12.5 mg tablets (test)	Lorzaar Plus tablets (reference)	Point Estimate (Test/reference) (%)	90 % C.I.
C_{max} (ng/ml)	71.3 ± 20.7	72.0 ± 21.5	99.9	94.7 – 105.4
AUC_(0-t) (ngh/ml)	473.4 ± 126.4	472.5 ± 122.5	100.8	96.4 – 105.3
AUC_(0-inf) (ngh/ml)	478.9 ± 117.2	490.6 ± 121.9	100.0	94.7 – 105.4
T_{max} (h)	2.47 ± 1.10	2.45 ± 0.88	-	-
T_{1/2} (h)	10.88 ± 2.40	10.28 ± 1.66	-	-

Mean ± SD represented.

Discussion

On balance, the applicant's argument that the test formulation can be considered bioequivalent to reference product on the basis that the active metabolite contributes significantly to clinical efficacy and that the C_{max} for parent losartan is less important to clinical efficacy than the other pharmacokinetic parameters evaluated for parent and active metabolite, all of which showed lesser variability and fell within the specified acceptance range, can be accepted. No safety issue is anticipated on the basis of the C_{max} for parent losartan falling outside the acceptance range. Since little effect of the C_{max} for parent losartan on clinical efficacy is anticipated, it is considered that this product would be interchangeable with other losartan/HCT 50/12.5 mg products in terms of clinical efficacy although this has not been proven with a direct efficacy comparison.

2.2 EFFICACY

No new efficacy data are presented in this application and none are required.

2.3 SAFETY

No formal safety data are presented and none are required.

3 SUMMARY OF PRODUCT CHARACTERISTICS

This closely resembles the current version of the reference product and is satisfactory.

4 PATIENT INFORMATION LEAFLET

The PILs for both applications are again similar to the reference product and have been updated in their format to comply with the EC Guideline on Readability. The content is basically the same as for Cozaar-Comp tablets.

5 LABELLING

No clinical comments.

6 CONCLUSION

Sufficient clinical information and relevant literature has been submitted to support these applications. Marketing Authorisations may, therefore, be granted on medical grounds. The applicant's arguments for the relative importance of the computed C_{max} for parent versus active metabolite in demonstration of bioequivalence, were deemed acceptable for this particular application at the time of assessment.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Losartan Potassium/Hydrochlorothiazide 50mg/125mg 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 an application of this type.

EFFICACY

Products containing losartan and hydrochlorothiazide as monotherapies and combination therapy have been available in the UK for many years. Their use is well established with recognised efficacy and acceptable safety.

The applicant has submitted adequate clinical information, as well as provided a detailed argument supported by data from published literature for this application. The information submitted confirms the therapeutic effectiveness of a losartan potassium 50mg / hydrochlorothiazide 12.5mg combination therapy, and no new safety issues have arisen.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory.

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

RISK: BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with losartan and hydrochlorothiazide as monotherapies and combination therapy are considered to have demonstrated the therapeutic value of the medicinal product as a combination therapy. The data provided in support of this application are acceptable. The risk: benefit is, therefore, considered to be positive.

**LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE
50MG/12.5MG TABLETS**

PL 24701/0001

PL 24701/0002

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation application on 30th June 2005.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 29th September 2005.
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 4th July 2006.
- 4 Following assessment of the application the MHRA requested further information relating to the quality dossier on 11th July 2006.
- 5 The applicant responded to the MHRA's request, providing further information for the clinical sections of the dossier on 2nd October 2006.
- 6 Advice was sought from the Commission on Human Medicines with regards to issues raised during assessment of the application. The Commission met on 18th October 2006 and issued their advice.
- 7 The applicant responded to the CHM advice, providing further information for the clinical and quality sections on 12th June 2007.
- 8 The MHRA requested further information relating to the quality dossier on 3rd July 2007 and 21st November 2007.
- 9 The applicant responded to the MHRA's request, providing further information for the quality sections of the dossier on 15th November 2007 and 13th January 2008.
- 10 The application was determined on 5th February 2008.

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Losartan Potassium / Hydrochlorothiazide 50 mg/12.5 mg tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium / Hydrochlorothiazide 50 mg/12.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mg/12.5 mg Tablet contains 50 mg of losartan, as losartan potassium, and 12.5 mg hydrochlorothiazide.

Each tablet contains 4.24mg (0.108 mmol) of potassium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated Tablet

White round, biconvex film coated tablet, 8mm diameter, with 'LH1' marked on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy alone.

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 also section 4.4 and section 5.1)

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Where possible titration with the individual components (i.e. 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 a combination of 50mg losartan potassium/12.5mg hydrochlorothiazide once daily for most patients. For patients who do not respond adequately, the dosage may be increased to 100mg/25mg once daily. The maximum dose is 100mg/25mg 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) i.e. one 50mg/12.5mg tablet and, if needed the dose should then be increased to 100mg/12.5mg once daily. If necessary, the dose should be increased to 100mg/25mg daily.

Losartan Potassium / Hydrochlorothiazide Tablets may be administered with or without food.

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 25 mg 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 Potassium / Hydrochlorothiazide Tablets are 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 Potassium / Hydrochlorothiazide Tablets should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics).

Use in hepatic impairment: Losartan Potassium / Hydrochlorothiazide Tablets are not recommended for patients with hepatic impairment.

Concomitant therapy: Losartan Potassium / Hydrochlorothiazide Tablets may be administered with other antihypertensive agents.

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

4.3 **CONTRAINDICATIONS**

Losartan Potassium / Hydrochlorothiazide Tablets are contraindicated in:

- patients who are hypersensitive to the active substances or to any of the excipients
- patients who are hypersensitive to other sulphonamide-derived drugs
- 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
- patients with anuria.

4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Losartan Potassium and hydrochlorothiazide combination tablet

Hypersensitivity:

Angioedema. See 4.8 'Undesirable effects'.

Hepatic and renal impairment:

Losartan Potassium / Hydrochlorothiazide Tablets are 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

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.

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).

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with Losartan Potassium / Hydrochlorothiazide Tablets.

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 medicinal products 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 Potassium / Hydrochlorothiazide Tablets 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 hypertensive patients with LVH (see section 5.1 Pharmacodynamic Properties, LIFE Study Race

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, ciclosporin, 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 precautions for use').

4.6 PREGNANCY AND LACTATION

Use during pregnancy

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 ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Losartan 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 Potassium / Hydrochlorothiazide tablets may have a minor or moderate influence on the ability to drive and use machines. Losartan Potassium / Hydrochlorothiazide tablets 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.

In a controlled trial in hypertensive patients with left ventricular hypertrophy, losartan used usually with hydrochlorothiazide was generally well tolerated. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

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 Potassium / Hydrochlorothiazide Tablets 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 Potassium / Hydrochlorothiazide Tablets. Treatment is symptomatic and supportive. Therapy with Losartan Potassium / Hydrochlorothiazide Tablets should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and

correction of dehydration, electrolyte imbalance, hepatic coma, and hypotension by established procedures.

Losartan

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

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

Hydrochlorothiazide

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: C09 DA01, ATC code: Losartan and Diuretics

Losartan Potassium and hydrochlorothiazide combination tablet

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

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

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

Losartan Potassium / Hydrochlorothiazide Tablets are effective in reducing blood pressure in males and females, blacks and non-blacks, and in younger (<65 years) and older (\geq 65 years) patients and are 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 micro 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 losartan 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 losartan 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 co-administered 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 losartan resulted in a 13.0% risk reduction ($p=0.021$, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol ($p=0.001$ 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

Race: There were 533 black patients in the study. In this group, treatment with losartan 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 $\geq 99\%$ 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 ^{14}C -labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.

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

Elimination

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

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6–9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 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 Potassium and hydrochlorothiazide combination tablet:

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

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

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

5.3 PRECLINICAL SAFETY DATA

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 potassium 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 co-administration 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:

Mannitol
Microcrystalline Cellulose
Croscarmellose sodium
Povidone
Magnesium Stearate

Film coating:

Hypromellose 3cP
Hydroxypropyl cellulose
Titanium Dioxide (E171)
Macrogol
Hypromellose 50cP

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

4 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Al/PVDC Blister. Pack sizes: 14, 28, 30, 50, 56, 98,100 and 280

HDPE Container with LDPE snap on cap. Pack sizes: 14, 28, 30, 50, 56, 98,100 and 280

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

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

7 MARKETING AUTHORISATION HOLDER

Nucleus ehf
PO Box 55
Naustanes
116 Reykjavik
Iceland

8 MARKETING AUTHORISATION NUMBER(S)

PL 24701/0001
PL 24701/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/02/2008

10 DATE OF REVISION OF THE TEXT

05/02/2008

PATIENT INFORMATION LEAFLET



Nucleus ehf

Losartan Potassium / Hydrochlorothiazide 50 mg/12.5 mg Tablets

Patient Information Leaflet

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

In this leaflet:

1. What Losartan Potassium / Hydrochlorothiazide tablets are and what they are used for
2. Before you take Losartan Potassium / Hydrochlorothiazide tablets
3. How to take Losartan Potassium / Hydrochlorothiazide tablets
4. Possible side effects
5. Storing Losartan Potassium / Hydrochlorothiazide tablets
6. Further Information

1. WHAT LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE TABLETS ARE AND WHAT THEY ARE USED FOR

These tablets are used to

- treat high blood pressure (hypertension) with or without thickening of the heart muscle
- help reduce the risk of stroke in patients with high blood pressure, who have developed thickening of the heart muscle. There is no evidence to support this effect in Black patients.

The two active ingredients (which make the tablets work) are

- Losartan potassium, which causes the blood vessels to relax, making it easier for the blood to pass through them. It belongs to a group of medicines called the angiotensin II receptor antagonists.
- Hydrochlorothiazide, which works by making your kidneys pass more water and salt, thereby reducing the volume of blood passing through the body.

Together these substances lower high blood pressure.

2. BEFORE YOU TAKE LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE TABLETS

Do not take these tablets if you are

- allergic (hypersensitive) to losartan or hydrochlorothiazide or any of the other ingredients in the tablet (see section 6).
- allergic to the following sulphonamide derived medicines - co-trimoxazole or sulfadiazine or similar in the second or third trimester of your pregnancy
- not passing urine.

Check with your doctor or pharmacist before taking these tablets if you have

- liver or kidney problems
- narrowing of the blood vessels to the kidneys
- received a kidney transplant
- dialysis treatment
- recently suffered with sickness and/or diarrhoea
- diabetes
- raised calcium levels as a result of too much parathyroid hormone in your blood (hyperparathyroidism)
- high cholesterol or triglyceride levels in your blood
- high levels of uric acid in the blood or suffer from gout
- had asthma or allergies
- an inflammatory condition called systemic lupus erythematosus (SLE)
- to take other diuretics (water tablets)
- narrowing of the heart valves (aortic stenosis or outflow obstruction) or your heart muscle is weak (cardiomyopathy)
- been told that you have high levels of potassium in your blood.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines may affect how well other medicines work.

- Tell your doctor if you are taking
- potassium supplements or potassium-containing salt substitutes
 - drugs that may increase potassium levels such as potassium sparing diuretics (water tablets) including amiloride and triamterene, or the immunosuppressant ciclosporin
 - rifampicin, a drug used in the treatment of Tuberculosis (TB)
 - fluconazole, an anti fungal drug used to treat infections such as thrush
 - non steroidal anti inflammatory drugs (NSAIDs) such as indometacin, used to treat arthritis and certain types of pain
 - barbiturates, which are drugs used to treat sleep problems or epilepsy
 - non-depolarising muscle relaxants such as tubocurarine (these are usually used with an anaesthetic, so always tell your doctor or anaesthetist if you are taking Losartan/Hydrochlorothiazide tablets and have to have an operation)
 - narcotics such as morphine used to treat severe pain
 - drugs used to treat diabetes including oral drugs and insulin
 - other drugs used to treat high blood pressure
 - other diuretics (water tablets)
 - resins used to treat high cholesterol
 - ACTH, which is a test used to see whether your adrenal glands are working properly
 - corticosteroids, which are drugs used to treat inflammatory disorders such as arthritis, allergic conditions, certain skin disorders, asthma or certain blood disorders
 - lithium, a drug used in the treatment of certain mental disorders
 - pressor amines such as adrenaline (epinephrine) used to treat shock, cardiac failure, asthma and allergic reactions

Alcohol

Sometimes when people take medicines to lower their blood pressure, they become dizzy or faint, particularly when standing up. This effect can be exaggerated shortly after drinking alcohol. If you are affected, you should avoid drinking alcohol.

Surgery or blood tests

- Tell your doctor or dentist that you are taking this medicine if you are going to have
- surgery and an anaesthetic, as the blood pressure lowering effect may be enhanced
 - a blood test, as it may affect the results of some tests.

Pregnancy and breastfeeding

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

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

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

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

Driving and using machines

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

3. HOW TO TAKE LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE TABLETS

Always take Losartan Potassium / Hydrochlorothiazide tablets exactly as your doctor has told you. If you are unsure, check with your doctor or pharmacist. It is important to take them every day in order to keep your blood pressure controlled.

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

The usual dose is one 50 mg/12.5 mg tablet once a day. However, some patients may require a higher dose of two 50 mg/12.5 mg tablets once a day.

If you are over 75 years, check with your doctor before taking your tablets as your dose may need to be adjusted.

Losartan Potassium / Hydrochlorothiazide tablets should not be given to children.

If you take more tablets than you should
Your calcium, potassium or sodium levels may be affected and you may become dehydrated. If you think that you or somebody else may have taken too many Losartan Potassium / Hydrochlorothiazide tablets, please tell your doctor immediately or go to the nearest hospital casualty department. If possible, please bring the remaining tablets or this leaflet with you to the hospital.

If you forget to take your tablets:
If you forget to take a dose, just carry on with the next dose. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

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

The most common side effects are dizziness, weakness, feeling that your head is spinning, itchy skin, cough, or diarrhoea.

If any of these side effects cause you concern, please contact your doctor.

Tell your doctor if you notice any of the following side effects

- a rapid decrease in your blood pressure, which may make you feel light headed or dizzy particularly when standing up
- skin rashes and itching
- muscle pain, muscle spasm or weakness
- headache or migraine
- liver problems including jaundice (the signs of which are yellowing skin and whites of the eyes and flu like symptoms)
- anaemia symptoms including paleness, increased tiredness and shortness of breath
- loss of appetite, stomach upsets, feeling or being sick, diarrhoea, fever, stomach cramps, constipation
- inflammation of the pancreas causing pain in the abdomen and back
- swelling of the salivary glands
- spinning sensation (vertigo)
- pins and needles
- restlessness
- visual changes including blurred vision or your vision appearing yellow
- sensitivity of the skin to sunlight
- purplish brown rash on the skin, hives or a nettle like rash, blistering or peeling of the skin, mouth, eyes, or genitals
- inflammation of the blood vessels
- changes in the levels of certain chemicals in your blood or urine, or blood disorders which may result in an increase in minor infections or prolonged bleeding after injury, (which may be detected when you have a blood test)
- breathing problems due to swollen lungs
- difficulty swallowing
- kidney problems

Stop taking your tablets and contact your doctor immediately, if you develop any of the following rare symptoms

- swelling of the face, lips, tongue and/or throat, which may cause difficulty breathing or swallowing.
- inflammation of the liver and/or inflammation of blood vessels causing hard purple blotches on the skin.

Your doctor will take blood tests at intervals while you are on this medicine to check for side effects.

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

M1029

5. STORING LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE TABLETS

Keep out of the reach and sight of children
Store below 30°C.

Do not use after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of the month.

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

6. FURTHER INFORMATION

What Losartan Potassium / Hydrochlorothiazide tablets contain:

The active ingredients (which make the medicine work) are 50mg of losartan potassium and 12.5mg of hydrochlorothiazide.

The other ingredients are mannitol, microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, hypromellose, hydroxypropyl cellulose, titanium dioxide (E171), macrogol.

Each tablet contains 4.24mg (0.108 mmol) of potassium.

What Losartan Potassium / Hydrochlorothiazide tablets look like and contents of the pack:

Losartan Potassium / Hydrochlorothiazide tablets are white, round, biconvex, film-coated tablets. The tablets are provided in blister packs and bottles of 14, 28, 30, 50, 56, 98, 100 and 280 tablets.*

Marketing Authorisation Holder:

The marketing authorisation holder is Nucleus ehf, PO Box 55, Naustanes, 116 Reykjavik, Iceland

Manufacturers:

• Actavis hf, Reykjavikurvegur 78, PO Box 420, IS-222 Hafnarfjordur, Iceland

This leaflet was last approved on <date>

Revision date: January 2008

* only marketed pack sizes will be stated on actual leaflet

LABELLING

Blisters



Mock up carton artwork, with braille

