UKPAR Losartan potassium/Hydrochlorothiazide Tablets
PL 20092/0048

LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
50MG/12.5MG Tablets

PL 20092/0048

LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
100MG/25MG Tablets

PL 20092/0049

UKPAR

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LAY SUMMARY

On the 15\textsuperscript{th} December 2009 the MHRA granted Lupin (UK) Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium /Hydrochlorothiazide 50mg/12.5mg and 100mg/25mg Tablets (PL 20092/0048-9). These are prescription-only medicines (POM).

Losartan potassium/Hydrochlorothiazide tablets contain two active ingredients. These are Losartan potassium and Hydrochlorothiazide. Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II 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 potassium/Hydrochlorothiazide tablets block this effect of angiotensin II, causing the blood vessels to relax. Hydrochlorothiazide works by making your kidneys pass more water and salt. Together, losartan and hydrochlorothiazide lower high 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 50mg/12.5mg and 100mg/25mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
50MG/12.5MG Tablets

PL 20092/0048

LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
100MG/25MG Tablets

PL 20092/0049

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 50mg/12.5mg and 100mg/25mg Tablets (PL 20092/0048-9) on 15th December 2009. These products are prescription-only medicine (POM).

These are two abridged national applications (one complex and one standard) for losartan potassium/hydrochlorothiazide film-coated tablets submitted under Article 10.1 of Directive 2001/83/EC as amended. The original and UK reference products for the 50 mg/12.5 mg and 100 mg/25 mg strengths respectively are Cozaar-Comp 50 mg/12.5 mg (PL 00025/0338) and Fortzaar 100 mg/25 mg (PL 00025/0374) film coated tablets (Merck Sharp & Dohme). The 50 mg/12.5 mg strength was first licensed on 12/04/1996.

These tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.
**PHARMACEUTICAL ASSESSMENT**

**DRUG SUBSTANCE (1)**

**Nomenclature**

rINN: Losartan potassium

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

**Structure**

![Chemical Structure](image)

Molecular formula: C\textsubscript{22}H\textsubscript{22}ClKN\textsubscript{6}O

Molecular Mass: 461.01 g/mol

Losartan potassium is a white to off-white powder, which is freely soluble in water and soluble in methanol.

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

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 based on the European Pharmacopoeia has been provided.

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

Losartan potassium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided which support the re-test period.

**DRUG SUBSTANCE (2)**

Nomenclature

rINN: Hydrochlorothiazide

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

Structure

![Structure of Hydrochlorothiazide]

Molecular formula: C_{7}H_{8}ClN_{3}O_{4}S_{2}

Molecular Mass: 297.7 g/mol

Hydrochlorothiazide is a white to almost white crystalline powder.

A valid Ph. Eur. Certificate of Suitability has been provided to support the quality of the drug substance.

An appropriate specification based on the European Pharmacopoeia has been provided.

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

Hydrochlorothiazide is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

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

Appropriate stability data has been provided which support the re-test period.
**DRUG PRODUCT**

**Other ingredients**
Other ingredients consist of pharmaceutical excipients, namely colloidal anhydrous silica, lactose anhydrous, pregelatinised starch, cellulose microcrystalline, water purified, magnesium stearate and Opadry 20A52135 Yellow.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Opadry 20A 52135 Yellow which complies with in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin. The lactose used is from Meggle and appropriate TSE documentation regarding sourcing has been supplied.

**Pharmaceutical development**
The aim of development work was to produce products that were essentially similar to the originator products marketed by Merck Sharp & Dohme in Europe (Cozaar Comp and Fortzaar tablets).

**Dissolution and impurity profiles**
Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on pilot-scale batches. A commitment was provided to perform process validation studies on the first three consecutive production 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 working standards used.

**Container Closure System**
Product is packaged in Blister packs of triplex opaque white PVC /PE /PVDC and Aluminium lidding foil or blister packs of cold forming ALU/ALU as the base and hard tampered Aluminium foil as the lidding, which is further packed in cartons. 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
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage conditions “Do not store above 25 degree C” and “Store in the original package in order to protect from moisture” have been included. These are acceptable.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

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 product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.
PRECLINICAL ASSESSMENT

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

1. INTRODUCTION
These are national applications for marketing authorisations for Losartan Potassium and Hydrochlorothiazide 50mg/12.5mg and 100mg/25mg Tablets; Submitted under article 10.1 of EC Directive 2001/83.

The original and UK reference products for the 50 mg/12.5 mg and 100 mg/25 mg strengths respectively are Cozaar-Comp 50 mg/12.5 mg (PL 0025/0338) and Fortzaar 100 mg/25 mg (PL 00025/0374) film coated tablets (Merck Sharp & Dohme). The 50 mg/12.5 mg strength was first licensed on 12/04/1996.

2. BACKGROUND
Losartan is an oral medication that belongs to a class of drugs called angiotensin receptor blockers (ARBs). Losartan is the first orally available angiotensin II receptor antagonist without agonist properties. Following oral administration, losartan is rapidly absorbed, reaching maximum concentrations 1-2 hours post-administration. Losartan is currently marketed by Merck Sharp and Dohme under the trade name “Cozaar”.

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

4. DOSE & DOSE SCHEDULE
Losartan / hydrochlorothiazide tablets may be administered with other antihypertensive agents. These tablets should be swallowed with a glass of water. Losartan / hydrochlorothiazide tablets may be administered with or without food.

Hypertension
Losartan and hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of losartan potassium/hydrochlorothiazide is 50mg/12.5mg once daily. For patients who do not respond adequately to 50mg/12.5mg, the dosage may be increased to one tablet of 100mg/25mg once daily. The maximum dose is 100mg/25mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.
Use in patients with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30 -50 ml/min). Losartan and Hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

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

Use in patients with hepatic impairment:
Losartan potassium and Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see section 4.3).

Use in the elderly:
Dose adjustment is not usually necessary for the elderly (>75 years of age).

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

5. TOXICOLOGY
No new preclinical data have been submitted and none are required for these applications.

6. CLINICAL PHARMACOLOGY
The applicant submits a two-way open label single dose crossover study to evaluate the relative bioavailabilities of the two fixed dose combination formulations of losartan 100mg / hydrochlorothiazide 25mg (Lupin product versus reference product from France) in healthy adult male subjects under fasting conditions

Reference product used is Fortzaar film-coated tablets (containing losartan 100mg / hydrochlorothiazide 25mg) from Laboratories Merck Sharp & Dohme – Chibret, France. Fortzaar Film-coated Tablets is considered to be equivalent to the UK reference product, Cozaar.

Study period:  
Period I: 30 June 2006 – 3 July 2006  
Period II: 17 July 2006 – 20 July 2006

Sampling to 48 hours Washout period of 17 days

As per the protocol, 60 subjects (1-7, 9-11, 13-15, 17-25, 27-60, C08, C12, C16, and C26) were dosed in study period I. 2 subjects (5 and 59) dropped out for reasons unrelated to safety. Subject 55 withdrew from the trial on medical grounds. 57 subjects completed the study. The plasma samples of subject 55 were also analysed.
Results

Mean untransformed data for losartan (n = 57)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>874.638 ± 545.066</td>
<td>955.982 ± 588.491</td>
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<tr>
<td>Tmax (h)</td>
<td>1.50</td>
<td>1.00</td>
</tr>
<tr>
<td>AUC(o-t) (ng.h/mL)</td>
<td>1394.902 ± 612.935</td>
<td>1520.726 ± 983.550</td>
</tr>
<tr>
<td>AUC(o-α) (ng.h/mL)</td>
<td>1441.462 ± 628.146</td>
<td>1561.571 ± 991.759</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>2.508 ± 1.005</td>
<td>2.216 ± 0.841</td>
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Mean untransformed data for carboxylic acid metabolite of losartan (n = 57)

<table>
<thead>
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<th>Reference</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>1123.918 ± 458.734</td>
<td>1127.275 ± 485.912</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.00</td>
<td>2.50</td>
</tr>
<tr>
<td>AUC(o-t) (ng.h/mL)</td>
<td>6595.024 ± 2465.268</td>
<td>6718.219 ± 2869.676</td>
</tr>
<tr>
<td>AUC(o-α) (ng.h/mL)</td>
<td>7105.429 ± 2196.874</td>
<td>7216.656 ± 2646.066</td>
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<tr>
<td>t1/2 (h)</td>
<td>4.236 ± 0.818</td>
<td>4.287 ± 0.863</td>
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</table>

Mean untransformed data for hydrochlorthiazide (n = 57)

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<tr>
<td>Cmax (ng/mL)</td>
<td>138.305 ± 38.438</td>
<td>153.667 ± 34.535</td>
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<tr>
<td>Tmax (h)</td>
<td>3.00</td>
<td>2.50</td>
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<tr>
<td>AUC(o-t) (ng.h/mL)</td>
<td>1010.428 ± 270.951</td>
<td>1104.495 ± 237.130</td>
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<tr>
<td>AUC(o-α) (ng.h/mL)</td>
<td>1035.863 ± 276.567</td>
<td>1131.459 ± 241.870</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>9.253 ± 1.423</td>
<td>9.258 ± 1.207</td>
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Geometric LS Mean ratio and 90% CI for losartan (n = 57)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
<th>% Ratio (T/R)</th>
<th>90% CI (%)</th>
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</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>754.557</td>
<td>791.612</td>
<td>104.9</td>
<td>92.90 – 118.47</td>
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<tr>
<td>AUC(o-t) (ng.h/mL)</td>
<td>1294.375</td>
<td>1350.207</td>
<td>104.3</td>
<td>98.34 – 110.65</td>
</tr>
<tr>
<td>AUC(o-α) (ng.h/mL)</td>
<td>1340.076</td>
<td>1391.385</td>
<td>103.8</td>
<td>98.02 – 109.98</td>
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</tbody>
</table>

Geometric LS Mean ratio and 90% CI for losartan carboxylic acid (n = 57)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
<th>% Ratio (T/R)</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>981.582</td>
<td>979.970</td>
<td>99.8</td>
<td>94.78 – 105.18</td>
</tr>
</tbody>
</table>
There were no serious adverse events during the study. The distribution of 14 adverse events that occurred during the study was fairly evenly distributed between the test and the reference products.

Conclusions:

The two products are bioequivalent.

7. **Efficacy**
   No new efficacy data have been submitted and none are required for these applications.

8. **Safety**
   No new safety data have been submitted and none are required for these applications.

9. **Expert Report**
   A clinical expert report has been written by clinical consultant to the pharmaceutical industry. The report is satisfactory.

10. **Summary of Product Characteristics**
    Clinically satisfactory

11. **Patient Information Leaflet**
    This is satisfactory

12. **Labelling**
    These are satisfactory.

13. **Marketing Authorisation Form**
    These are satisfactory.

14. **Discussion**
    The applicant has conducted a bioequivalent study comparing the applicant’s product with the cross referred medicinal product. The study has confirmed

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### Geometric LS Mean ratio and 90% CI for hydrochlorothiazide (n = 57)

<table>
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<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
<th>% Ratio (T/R)</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>132.626</td>
<td>149.628</td>
<td>112.8</td>
<td>106.30 – 119.74</td>
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<tr>
<td>AUC(o-t) (ng.h/mL)</td>
<td>971.013</td>
<td>1080.018</td>
<td>111.2</td>
<td>105.49 – 117.27</td>
</tr>
<tr>
<td>AUC(o-α) (ng.h/mL)</td>
<td>996.010</td>
<td>1106.590</td>
<td>111.1</td>
<td>105.47 – 117.03</td>
</tr>
</tbody>
</table>
that both products are bioequivalent and therefore would exhibit the same
efficacy and safety profile.

15. CONCLUSIONS
The efficacy and safety of Losartan/hydrochlorothiazide 50mg/12.5mg Tablets
and Losartan/hydrochlorothiazide 100mg/25mg tablets are satisfactory for the
grant of product licences.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Losartan/hydrochlorothiazide 50mg/12.5mg and Losartan/hydrochlorothiazide 100mg/25mg 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
Based on the submitted bioequivalence study Losartan/hydrochlorothiazide 50mg/12.5mg and Losartan/hydrochlorothiazide 100mg/25mg Tablets are considered bioequivalent with reference products.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

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 product and the innovator product are interchangeable. Extensive clinical experience with Losartan potassium/hydrochlorothiazide 50mg/12.5mg and Losartan/hydrochlorothiazide 100mg/25mg tablets is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
50MG/12.5MG Tablets

PL 20092/0048

LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
100MG/25MG Tablets

PL 20092/0049

STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 8\textsuperscript{th} December 2006</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 28\textsuperscript{th} February 2007</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 13\textsuperscript{th} June 2007, 22\textsuperscript{nd} October 2007 and 4\textsuperscript{th} August 2009</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 21\textsuperscript{st} September 2007, 15\textsuperscript{th} January 2008 and 23\textsuperscript{rd} November 2009</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 15\textsuperscript{th} December 2009</td>
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</table>
LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
50MG/12.5MG Tablets
PL 20092/0048

LOSARTAN POTASSIUM /HYDROCHLOROTHIAZIDE
100MG/25MG Tablets
PL 20092/0049

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium/Hydrochlorothiazide 50mg/12.5mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan potassium/Hydrochlorothiazide 50mg/12.5mg Tablet contains 50 mg of Losartan potassium and 12.5 mg Hydrochlorothiazide as the active ingredients.

Excipients: Each tablet contains 95.5mg lactose anhydrous.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Losartan potassium/Hydrochlorothiazide 50mg/12.5mg Tablets are Yellow, capsule shaped, biconvex, film-coated tablets, debossed with ‘50’ on one side and plain on the other side

4 CLINICAL PARTICULARS

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Losartan / hydrochlorothiazide tablets may be administered with other antihypertensive agents. These tablets should be swallowed with a glass of water.

Losartan / hydrochlorothiazide tablets may be administered with or without food.

Hypertension
Losartan and hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of losartan potassium/hydrochlorothiazide is 50mg/12.5mg once daily. For patients who do not respond adequately to 50mg/12.5mg, the dosage may be increased to one tablet of 100mg/25mg once daily. The maximum dose is 100mg/25mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

Use in patients with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan and Hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

Use in patients with intravascular volume depletion:
Volume and/or sodium depletion should be corrected prior to administration of Losartan/hydrochlorothiazide tablets.
Use in patients with hepatic impairment:
Losartan potassium and Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see section 4.3).

Use in the elderly:
Dose adjustment is not usually necessary for the elderly (>75 years of age).

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Losartan

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

Hypotension and Intravascular volume depletion
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhea or vomiting. Such conditions should be corrected before the administration of losartan/hydrochlorothiazide tablets (see sections 4.2 and 4.3).

Electrolyte Imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored. The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan/hydrochlorothiazide is not recommended (see section 4.5).

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan/hydrochlorothiazide tablets should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore Losartan/hydrochlorothiazide tablets are contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).
As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy.

Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation
There is no experience in patients with recent kidney transplantation

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan/hydrochlorothiazide tablets is not recommended.

Coronary heart disease and cerebrovascular disease:
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure:
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

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

Hydrochlorothiazide

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

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

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked 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.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Losartan/hydrochlorothiazide tablets are contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).

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

Excipient
These tablets contain lactose and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 6.1).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Losartan

Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be coadministered with angiotensin II receptor antagonists.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses) and non-selective NSAIDs, attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cycloxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.
Hydrochlorothiazide

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

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive drugs:
There may be an additive effect.

Colestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either colestyramine 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.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

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

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

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

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.
**Digitalis glycosides**
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

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

- Class Ia antiarrhythmics (e.g quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (e.g amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g thioridazine, chlorpromazine, levoemepromazine, trifluoperazine, cyamemazine, sulpiride, sulotride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g bepridil, cisapride, diphenamid, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

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

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

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

**Iodine Contrast Media**
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product.
Patients should be rehydrated before the administration.

**Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives**
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

### 4.6 PREGNANCY AND LACTATION

**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 drug. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan 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 foetotoxicity (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).

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

Use during lactation

It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Thiazides appear in human milk and may inhibit lactation. Because of the potential for adverse effects on the breast-feeding infant, Losartan /hydrochlorothiazide tablets is contraindicated during breast-feeding (see section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 UNDESIRABLE EFFECTS

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

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

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

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

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

Hepato-biliary disorders
Rare: Hepatitis

Investigations
Rare: Hyperkalaemia, elevation of ALT

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

Losartan

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

*Immune system disorders*
Rare: Anaphylactic reactions, angioedema, urticaria

*Metabolism and nutrition disorders*
Uncommon: Anorexia, gout

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

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

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

*Ear and labyrinth disorders*
Uncommon: Vertigo, tinnitus

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

*Vascular disorders*
Uncommon: Vasculitis

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

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

*Hepato-biliary disorders*
Not known: Liver function abnormalities

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

*Musculoskeletal and connective tissue disorders*
Common: Muscle cramp, back pain, leg pain, myalgia
Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness

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

*Reproductive system and breast disorders*
Uncommon: Decreased libido, impotence

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

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

Hydrochlorothiazide

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

Immune system disorders
Rare: Anaphylactic reaction

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

Psychiatric disorders
Uncommon: Insomnia

Nervous system disorders
Common: Cephalalgia

Eye disorders
Uncommon: Transient blurred vision, xanthopsia

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

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

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

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

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

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

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

General disorders and administration site conditions
Uncommon: Fever, dizziness

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

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

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

**Hydrochlorothiazide**

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

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

5  
**PHARMACOLOGICAL PROPERTIES**

5.1  
**PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Combination containing an angiotensin-II-receptor (type AT1)-antagonist and a thiazide diuretic. Antihypertensive,  
ATC Code: C09DA01

**Losartan and hydrochlorothiazide combination tablet**

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

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

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

Losartan potassium / Hydrochlorothiazide is effective in reducing blood pressure in males and females, blacks and non-blacks, and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

**Losartan**

Losartan is a synthetically produced oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the rennin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Losartan selectively blocks the AT1 receptor. In vitro and in vivo
losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis. Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is thus no increase in bradykinin-mediated undesirable effects.

During losartan administration removal of the angiotensin-II negative feedback on renin secretion leads to increased plasma-renin activity. Increase in the plasma-renin activity leads to an increase in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of the plasma-aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade. After the discontinuation of losartan, plasma-renin activity and angiotensin II values fell within 3 days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT1 receptor than for the AT2 receptor. The active metabolite is 10- to 40-times more active than losartan on a weight for weight basis.

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 << 0.4mg/dL), which was persistent in chronic therapy.

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

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohumoral effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively.

The occurrence of hypotension was dose related in these heart failure patients.

**Hypertension Studies:**

In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement of blood pressure 24 hours post-dose relative to 5-6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood-pressure reduction at the end of the dosing interval was 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise of blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effect on heart rate.

Losartan is equally effective in males and females and in younger (below the age of 65 years) and older hypertensive patients.

**LIFE Study**

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily Losartan potassium 50 mg or once daily atenolol 50 mg. If goal blood pressure (<140/90
mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan potassium or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with Losartan potassium 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 potassium reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

**Hydrochlorothiazide**

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.

### 5.2 PHARMACOKINETIC PROPERTIES

**Absorption**

**Losartan:**

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma-concentration profile of losartan when the drug was administered with a 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, 5-fold and 1.7-fold greater than those seen in young male volunteers.

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

### 5.3 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component.

The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages).

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

### 6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Core:
- Lactose anhydrous
- Cellulose Microcrystalline
- Starch Pregelatinised
- Silica, Colloidal anhydrous
- Magnesium Stearate
Coating:
- Hypromellose
- Hydroxypropylcellulose (E463)
- Titanium dioxide (E171)
- Iron oxide yellow (E172)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister pack of triplex opaque white PVC /PE /PVDC and Aluminium lidding foil, which is further packed in cartons.

Blister pack of cold forming ALU/ALU as the base and hard tampered Aluminium foil as the lidding, which is further packed in cartons.

Packs of 1, 4, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 280 tablets.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused product or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Lupin (UK) Ltd
Victoria Court, Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20092/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/12/2009

10 DATE OF REVISION OF THE TEXT
15/12/2009
1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium/Hydrochlorothiazide 100mg/25mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan potassium/Hydrochlorothiazide 100mg/25mg Tablet contains 100 mg of Losartan potassium and 25 mg Hydrochlorothiazide as the active ingredients.

Excipients: Each tablet contains 191mg lactose anhydrous.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Losartan potassium/Hydrochlorothiazide 100mg/25mg Tablets are yellow, tear drop shaped, biconvex, film-coated tablets, debossed with ‘100’ on one side and plain on the other side

4 CLINICAL PARTICULARS

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Losartan / hydrochlorothiazide tablets may be administered with other antihypertensive agents. These tablets should be swallowed with a glass of water.

Losartan / hydrochlorothiazide tablets may be administered with or without food.

Hypertension
Losartan and hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of losartan potassium/hydrochlorothiazide is 50mg/12.5mg once daily. For patients who do not respond adequately to 50mg/12.5mg, the dosage may be increased to one tablet of 100mg/25mg once daily. The maximum dose is 100mg/25mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

Use in patients with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30 -50 ml/min). Losartan and Hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

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

Use in patients with hepatic impairment:
Losartan potassium and Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see section 4.3).
Use in the elderly:
Dose adjustment is not usually necessary for the elderly (>75 years of age).

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Losartan

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

Hypotension and Intravascular volume depletio
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhea or vomiting. Such conditions should be corrected before the administration of losartan/hydrochlorothiazide tablets (see sections 4.2 and 4.3).

Electrolyte Imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored. The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan/ hydrochlorothiazide is not recommended (see section 4.5).

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan/hydrochlorothiazide tablets should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore Losartan/hydrochlorothiazide tablets is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).
As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or
stenosis of the artery to a solitary kidney.

Renal transplantation
There is no experience in patients with recent kidney transplantation

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan/hydrochlorothiazide tablets is not recommended.

Coronary heart disease and cerebrovascular disease:
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure:
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

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

Hydrochlorothiazide

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

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

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked 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.

**Hepatic impairment**
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Losartan/hydrochlorothiazide tablets are contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).

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

**Excipient**
These tablets contain lactose and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 6.1).

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

**Losartan**
Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be coadministered with angiotensin II receptor antagonists.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses) and non-selective NSAIDs, attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

**Hydrochlorothiazide**
When given concurrently, the following drugs may interact with thiazide diuretics:
Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive drugs:
There may be an additive effect.

Colestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either colestyramine 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.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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

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

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

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.
Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Losartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):
- Class Ia antiarrythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulfopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

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

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

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

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

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

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 drug. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan 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 foetotoxicity (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).

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

Use during lactation

It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Thiazides appear in human milk and may inhibit lactation. Because of the potential for adverse effects on the breast-feeding infant, Losartan /hydrochlorothiazide tablets is contraindicated during breast-feeding (see section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 UNDESIRABLE EFFECTS

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

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

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

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

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

Hepato-biliary disorders
Rare: Hepatitis

Investigations
Rare: Hyperkalaemia, elevation of ALT

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

Losartan

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

Immune system disorders
Rare: Anaphylactic reactions, angioedema, urticaria
Metabolism and nutrition disorders
Uncommon: Anorexia, gout

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

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

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

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus

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

Vascular disorders
Uncommon: Vasculitis

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

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

Hepato-biliary disorders
Not known: Liver function abnormalities

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

Musculoskeletal and connective tissue disorders
Common: Muscle cramp, back pain, leg pain, myalgia
Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness

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

Reproductive system and breast disorders
Uncommon: Decreased libido, impotence

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

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

**Hydrochlorothiazide**

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

*Immune system disorders*
Rare: Anaphylactic reaction

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

*Psychiatric disorders*
Uncommon: Insomnia

*Nervous system disorders*
Common: Cephalalgia

*Eye disorders*
Uncommon: Transient blurred vision, xanthopsia

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

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

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

*Hepatobiliary disorders*
Uncommon: Icterus (intrahepatic cholestatis), pancreatitis

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

*Musculoskeletal and connective tissue disorders*
Uncommon: Muscle cramps

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

*General disorders and administration site conditions*
Uncommon: Fever, dizziness

### 4.9 OVERDOSE

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

**Losartan**

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Combination containing an angiotensin-II-receptor (type AT1)-
antagonist and a thiazide diuretic. Antihypertensive,
ATC Code: C09DA01

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

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

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

Losartan potassium / Hydrochlorothiazide is effective in reducing blood pressure in males and
females, blacks and non-blacks, and in younger (<65 years) and older (>65 years) patients
and is effective in all degrees of hypertension.

Losartan
Losartan is a synthetically produced oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the rennin-
angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates
smooth-muscle proliferation. Losartan selectively blocks the AT1 receptor. In vitro and in vivo
losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all
physiologically relevant actions of angiotensin II, regardless of the source or route of its
synthesis. Losartan does not have an agonist effect nor does it block other hormone receptors
or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit
ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is thus no increase in bradykinin-mediated undesirable effects.

During losartan administration removal of the angiotensin-II negative feedback on renin secretion leads to increased plasma-renin activity. Increase in the plasma-renin activity leads to an increase in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of the plasma-aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade. After the discontinuation of losartan, plasma-renin activity and angiotensin II values fell within 3 days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT1 receptor than for the AT2 receptor. The active metabolite is 10- to 40-times more active than losartan on a weight for weight basis.

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 < < 0.4mg/dL), which was persistent in chronic therapy.

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

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.

Hypertension Studies:

In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement of blood pressure 24 hours post-dose relative to 5-6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood-pressure reduction at the end of the dosing interval was 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise of blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effect on heart rate. Losartan is equally effective in males and females and in younger (below the age of 65 years) and older hypertensive patients.

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily Losartan potassium 50 mg or once daily atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan potassium or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.
The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with Losartan potassium 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 potassium reduced the risk of stroke by 25% relative to atenolol (p=0.001, 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

**Hydrochlorothiazide**

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.

### 5.2 PHARMACOKINETIC PROPERTIES

#### Absorption

**Losartan:**

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

**Hydrochlorothiazide:**

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

#### 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, 5-fold and 1.7-fold greater than those seen in young male volunteers.

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

### 5.3 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component.

The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages).

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 LIST OF EXCIPIENTS

**Core:**

- Lactose anhydrous
- Cellulose Microcrystalline
- Starch Pregelatinised
- Silica, Colloidal anhydrous
- Magnesium Stearate
Coating:
Hyromellose
Hydroxypropylcellulose (E463)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister pack of triplex opaque white PVC/PE/PVDC and Aluminium lidding foil, which is further packed in cartons.

Blister pack of cold forming ALU/ALU as the base and hard tampered Aluminium foil as the lidding, which is further packed in cartons.

Packs of 1, 4, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 280 tablets.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused product or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Lupin (UK) Ltd
Victoria Court, Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20092/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/12/2009

10 DATE OF REVISION OF THE TEXT
15/12/2009
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE
50mg/12.5mg, 100mg/25mg 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 on 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. How to store Losartan potassium / Hydrochlorothiazide Tablets.
6. Further information.

1. WHAT LOSARTAN POTASSIUM/ HYDROCHLOROTHIAZIDE TABLETS ARE AND WHAT THEY ARE USED FOR
Losartan potassium / Hydrochlorothiazide tablet contains two active ingredients. These are Losartan potassium and Hydrochlorothiazide. Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II 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 potassium / Hydrochlorothiazide tablets block this effect of angiotensin II, causing the blood vessels to relax. Hydrochlorothiazide works by making your kidneys pass more water and salt. Together, losartan and hydrochlorothiazide lower high blood pressure.

2. BEFORE YOU TAKE LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE TABLETS
Do not take losartan / hydrochlorothiazide tablets:
- if you are allergic (hypersensitive) to losartan, hydrochlorothiazide or to any of the other ingredients in this medicine.
- if you are allergic (hypersensitive) to other sulphonamide-derived medicines (e.g. other thiazides, some antibacterial drugs such as co-trimoxazole, ask your doctor if you are not sure)
- if you are, think you may be or are planning to become pregnant (see also “Pregnancy and breast-feeding”)
- if you are breast-feeding
- if you have severely impaired liver function
- if you have severely impaired kidney function or your kidneys are not producing any urine
- if you have low potassium, low sodium or high calcium levels which cannot be corrected by treatment
- if you are suffering from gout

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow the advice given.
Take special care with Losartan / Hydrochlorothiazide tablets

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

Taking Losartan Potassium and Hydrochlorothiazide with 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.

You should also tell your doctor if you are taking any of the following:

- Potassium supplements, potassium sparing agents, or potassium-containing salt substitutes
- Rifampicin, a drug used in the treatment of tuberculosis (TB)
- Fluconazole, a drug used for treating fungal infections such as thrush
- NSAIDs (non-steroidal anti-inflammatory drugs) such as indomethacin, used to treat patients with arthritis and for treating certain types of pain
- Tricyclic antidepressants, drugs used to treat depression and anxiety
- Antipsychotics, medicines used to treat conditions such as schizophrenia
- Antispasmodics such as baclofen or medicines which relax your muscles (tubocurarine)
- Anticholinergic agents such as atropine used to treat muscular spasm and asthma
- Medicines used to treat cancer such as amifostine or methotrexate
- Alcohol (this may affect your blood pressure)
- Barbiturates, sedative drugs which may be used in the treatment of sleeplessness or epilepsy
- Narcotics, morphine like drugs used for severe pain
- Antidiabetic drugs (medicines for the treatment of diabetes), including oral agents to lower blood sugar and insulin (metformin)
- Other drugs used to reduce blood pressure such as methyldopa
- Other diuretics (water tablets)
- Resins which are used to reduce high cholesterol levels (cholestyramine / colestipol)
- ACTH (corticotrophin), used to test whether your adrenal glands are working properly
- Corticosteroids, used to treat various conditions including rheumatism, arthritis, allergic conditions, certain skin diseases, asthma or certain blood disorders
- Pressor amines, such as adrenaline used for the treatment of hypotension, shock, cardiac failure, asthma or allergies
- Lithium, a drug used to treat certain mental disorders.
- Medicines used to treat gout (probenecid)
- Medicines used to treat epilepsy (such as carbamazepine)
- Digitalis glycosides such as digoxin which is used to treat certain heart conditions
- Medicines used to treat abnormal heart rhythm such as quinidine and amiodarone
- Medicines used to suppress the immune function such as ciclosporin
- Antifungal agents such as amphotericin, corticosteroids or laxatives such as semia (may increase the amount of potassium excreted)

**Taking Losartan Potassium / Hydrochlorothiazide Tablets with food and drink**
Losartan potassium / Hydrochlorothiazide Tablets does not usually interact with food therefore it can be administered with or without food. You are advised not to drink alcohol whilst taking these tablets; alcohol and losartan / hydrochlorothiazide tablets may increase each other's effects.

**Pregnancy and breast-feeding**
Your doctor will normally advise you to stop taking losartan / hydrochlorothiazide tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of losartan / hydrochlorothiazide tablets. These tablets are not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. You must not take losartan / hydrochlorothiazide tablets if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

**Use in children and adolescents:**
There is no experience with the use of losartan/hydrochlorothiazide tablets in children. Therefore, these tablets should not be given to children.

**Driving and use machines:**
When you begin treatment with this medication, you should not perform tasks which may require special attention (for example, driving an automobile or operating dangerous machinery) until you know how you tolerate your medicine.

**Important information about some of the ingredients:**
Losartan/hydrochlorothiazide tablets contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
3. HOW TO TAKE LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE TABLETS

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

The usual dose is 50 mg losartan potassium and 12.5 mg hydrochlorothiazide daily. If your blood pressure is not controlled with this, your doctor will normally prescribe one tablet of Losartan potassium and hydrochlorothiazide daily (100 mg losartan potassium and 25 mg hydrochlorothiazide).

Losartan potassium / hydrochlorothiazide tablets should be swallowed with a glass of water. You must keep taking Losartan potassium / hydrochlorothiazide tablets every day and exactly as your doctor has told you. It is important that you take Losartan potassium / hydrochlorothiazide tablets for as long as your doctor prescribes, in order to keep your blood pressure controlled.

If you are aged over 75 years you should check with your doctor before taking your tablets.

You can take Losartan potassium / hydrochlorothiazide tablets with or without food. It is recommended that you take your tablet at the same time each day.

If you take more Losartan potassium / Hydrochlorothiazide tablets than you should

If you take an overdose by mistake, contact your doctor immediately or attend the nearest hospital casualty department. Overdosage can cause a drop in blood pressure, palpitations, slow pulse, changes in blood composition and dehydration.

If you forget to take a dose or take too many

Try to take Losartan potassium and Hydrochlorothiazide daily as prescribed. However, if you miss a dose, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten tablet.

4. POSSIBLE SIDE EFFECTS

Like all medicines, losartan / hydrochlorothiazide tablets can cause side effects, although not everybody gets them.

If you experience the following, stop taking your tablets and tell your doctor immediately or go to the casualty department of your nearest hospital.

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

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

The side effects of medicines are classified as follows:

Very common: happening in more than 1 in 10 patients
common: happening in 1 in 100 to 1 in 10 patients
uncommon: happening in 1 in 1,000 to 1 in 100 patients
rare: happening in 1 in 10,000 to 1 in 1,000 patients
very rare: happening in less than 1 in 10,000 patients
not known: (cannot be estimated from the available data)
The following side effects have been reported with losartan / hydrochlorothiazide tablets:

Common:
- cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder
- dizziness, headache, insomnia
- diarrhoea, abdominal pain, nausea, indigestion
- muscle pain or cramps, leg pain, back pain
- weakness, tiredness, chest pain
- increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels.

Uncommon:
- Anaemia, red or brownish spots on the skin (sometimes especially on the feet, legs, arms and buttocks, with joint pain, swelling of the hands and feet and stomach pain), bruising, reduction in white blood cells, clotting problems and bruising.
- Loss of appetite, increased uric acid levels or frank gout, increased blood sugar levels, abnormal blood electrolyte levels.
- Anxiety, nervousness, panic disorder (recurring panic attacks), confusion, depression, abnormal dreams, sleep disorders, sleepiness, memory impairment.
- Pins and needles or similar sensations, pain in the extremities, trembling, migraine, fainting.
- Blurred vision, burning or stinging in the eyes, conjunctivitis, worsening eyesight, seeing things in yellow.
- Ringing, buzzing, roaring or clicking in the ears.
- Low blood pressure, which may be associated with changes in posture (feeling light-headed or weak when you stand up), angina (chest pain), abnormal heartbeat, cerebrovascular accident (TIA, “mini-stroke”), heart attack, palpitations.
- Inflammation of blood vessels, which is often associated with a skin rash or bruising.
- Sore throat, breathlessness, bronchitis, pneumonia, water on the lungs (which causes difficulty breathing), nosebleed, runny nose, congestion
- Constipation, wind, stomach upsets, stomach spasms, vomiting, dry mouth, inflammation of a salivary gland, toothache.
- Jaundice (yellowing of the eyes and skin), inflammation of the pancreas.
- Hives, itching, inflammation of the skin, rash, redness of the skin, sensitivity to light, dry skin, flushing, sweating, hair loss.
- Pain in the arms, shoulders, hips, knees or other joints, joint swelling, stiffness, muscle weakness.
- Frequent urination including at night, abnormal kidney function including inflammation of the kidneys, urinary infection, sugar in the urine.
- Decreased sexual appetite, impotence.
- Swelling of the face, fever.

Rare:
- Hepatitis (inflammation of the liver), abnormal liver function tests.

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 POTASSIUM / HYDROCHLOROTHIAZIDE TABLETS
Keep out of the reach and sight of children.
Do not store above 25°C. Store in original package, in order to protect from moisture.
Do not use the tablets after the expiry date, which is stated on the carton after ‘EXP’.
The expiry date refers to the last day of that month.

Disposal
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
Active ingredients:
The active substances are losartan potassium 50 mg equivalent to 45.8 mg of Losartan and 12.5 mg hydrochlorothiazide for losartan potassium/hydrochlorothiazide 50mg/12.5mg tablets.
The active substances are losartan potassium 100 mg equivalent to 91.6 mg of Losartan and 25 mg hydrochlorothiazide for losartan potassium/hydrochlorothiazide 100 mg/25mg tablets.
Other ingredients: Lactose anhydrous, Cellulose microcrystalline, Starch Pregelatinised, Silica Colloidal anhydrous, Magnesium Stearate.
The coating of Losartan potassium / hydrochlorothiazide tablets contains hypromellose, hydroxypropylcellulose, titanium dioxide, iron oxide yellow.

What Losartan Potassium / Hydrochlorothiazide Tablets look like and the contents of the pack
Losartan potassium / Hydrochlorothiazide 50mg / 12.5 mg Tablet is available as Yellow, capsule shaped, biconvex, film-coated tablets, debossed with ‘50’ on one side and plain on the other side.
Losartan potassium / Hydrochlorothiazide 100mg / 25 mg Tablet is available as yellow, tear drop shaped, biconvex, film-coated tablets, debossed with ‘100’ on one side and plain on the other side.
Losartan potassium / Hydrochlorothiazide Tablets 50mg / 12.5mg as well as 100mg / 25mg are supplied in blister packs of 28 tablets

Marketing Authorisation Holder and Manufacturer
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