Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg Film-Coated Tablets

Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets

PL 20242/0004-11

UKPAR

TABLE OF CONTENTS

Lay Summary .............................................. Page 2
Scientific discussion ..................................... Page 3
Steps taken for assessment ............................. Page 13
Steps taken after authorisation – summary ........ Page 14
Summary of Product Characteristics
Product Information Leaflet
Labelling
Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg Film-Coated Tablets

Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets

PL 20242/0004-11

LAY SUMMARY

On 19th August 2009, the MHRA granted Fair-Med Healthcare GMBH Marketing Authorisations (licences) for Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets (PL 20242/0004-11).

This medicine contains losartan, which is an angiotensin II receptor antagonist and hydrochlorothiazide, which is a diuretic.

Losartan Potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension (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 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg Film-Coated Tablets

Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets

PL 20242/0004-11

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction  Page 4
Pharmaceutical assessment  Page 5
Preclinical assessment  Page 9
Clinical assessment (including statistical assessment)  Page 10
Overall conclusions and risk benefit assessment  Page 12
UKPAR Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and
Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets

INTRODUCTION

The UK granted Fair-Med Healthcare GMBH Marketing Authorisations for the medicinal products Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets (PL 20242/0004-11) on 19th August 2009. The product is prescription only medicine (POM) indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

These applications for Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products to Cozaar Comp 50mg/12.5mg and 100mg/25mg Filmovertrukne tabletter, first authorised in the EEA to Merck Sharp & Dohme B.V. in April 1996. Six applications (PL 20242/0006-11) have been submitted as duplicates.

The product contains losartan, which is an angiotensin II receptor (type AT1) antagonist and hydrochlorothiazide, which is a thiazide diuretic.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Losartan Potassium

INN: Losartan Potassium
Chemical name: (i) 2-butyl-4-chloro-1-[(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:

Physical form: A white or almost white crystalline powder.
Solubility: Freely soluble in ethanol and methanol, soluble in water, very slightly soluble in chloroform. Freely soluble in dilute alkaline solution. In acid solution, it becomes insoluble when the pH decreased from 6 to 0.

Molecular formula: C_{22}H_{22}ClKN_{6}O
Molecular weight: 461.01 g/mol

Losartan Potassium complies with in-house specifications.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance losartan potassium.

Hydrochlorothiazide

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

6-chloro-3,4-dihydro-1,2-dioxide-2H-1,2,4-benzothiazine-7-sulphonamide
Structure:

![Structure Diagram]

Physical form: A white or almost white crystalline powder.
Solubility: Soluble in acetone and dilute solutions of alkali hydroxides

Molecular formula: $\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$
Molecular weight: 297.7 g/mol

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

All aspects of the manufacture of the active substance hydrochlorothiazide from its starting materials are controlled by a Ph. Eur. Certificate of Suitability.

Synthesis of the drug substances from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredients.

Appropriate specifications are provided for both active substances, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for both active pharmaceutical ingredients. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing both active substances to be physically and chemically stable drugs, and supporting an appropriate retest period.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose (E460a), lactose monohydrate, pregelatinised maize starch, sodium starch glycolate type A, magnesium stearate (E572).
The tablet film-coating (opadry white (20A18334)) contains hydroxypropyl cellulose (E463), hypromellose 6cP (E464), titanium dioxide (E171).

All the ingredients with the exception of opadry white (20A18334) comply with their relevant European Pharmacopoeia monographs. Opadry white (20A18334) complies with in-house specifications.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

**Product development**

The objective of the development programme was to produce products that could be considered generic medicinal products of Cozaar Comp 50mg/12.5mg and 100mg/25mg Filmovertrukne tabletter (Merck Sharp & Dohme B.V., April 1996).

The reference product used in the bioequivalence study (Fortzaar 100mg/25mg Film-Coated Tablets) is qualitatively and quantitatively identical to the UK reference product.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution and impurity profiles have been provided for the finished product versus the reference product Cozaar Comp 50mg/12.5mg and 100mg/25mg Filmovertrukne tabletter (Merck Sharp & Dohme B.V., April 1996).

**Manufacture**

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on three pilot scale batches of each strength of finished product and the results appear satisfactory. The applicant has committed to perform process validation on three future production-scale batches.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**

The product is packaged in polyvinylchloride and aluminium foil blister packs in sizes of 14 or 28 capsules.

Specifications and certificates of analysis have been provided. 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 3 years has been set, with storage conditions ‘Store below 25°C’, which is satisfactory.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
These are pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
These are pharmaceutically satisfactory.

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

These applications for Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets are submitted as abridged standard applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Cozaar Comp 50mg/12.5mg and 100mg/25mg Filmovertrukne tabletter, first authorised in the EEA to Merck Sharp & Dohme B.V. in April 1996.

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

CLINICAL PHARMACOLOGY

To support the applications, the marketing authorisation holder has included a single bioequivalence study:

A single-dose randomized, 2-way, crossover, open-label, controlled bioequivalence study comparing the pharmacokinetics of Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets (Test) versus Fortzaar 100mg/25mg Film-Coated Tablets (Reference) under fasted conditions.

Blood sampling was performed pre-drug administration, during the study and up to 24 hours post dose in each treatment period. There was a washout period of 11 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval

Pharmacokinetic parameters of Losartan

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan Potassium:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>969.676</td>
<td>1010.162</td>
<td>655.729</td>
</tr>
<tr>
<td>Reference</td>
<td>969.590</td>
<td>1010.132</td>
<td>651.497</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>(94.803-105.674)</td>
<td>(94.767-105.030)</td>
<td>(90.173-114.989)</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters of Hydrochlorothiazide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>1001.253</td>
<td>1034.958</td>
<td>140.549</td>
</tr>
<tr>
<td>Reference</td>
<td>1004.302</td>
<td>1033.338</td>
<td>142.452</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>(94.892-103.416)</td>
<td>(95.646-103.964)</td>
<td>(93.320-106.230)</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters of Losartan carboxy active metabolite

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan carboxy active metabolite:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>4643.474</td>
<td>4750.939</td>
<td>768.590</td>
</tr>
<tr>
<td>Reference</td>
<td>4732.194</td>
<td>4840.199</td>
<td>802.171</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>(92.824-101.309)</td>
<td>(93.088-101.370)</td>
<td>(90.313-102.904)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for hydrochlorothiazide, losartan and its metabolite lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.
EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets can be considered as generic medicinal products to the originator products Cozaar Comp 50mg/12.5mg and 100mg/25mg Filmovertrukne tabletter (Merck Sharp & Dohme B.V.)

The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets and the reference product. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the Losartan Potassium 100mg/Hydrochlorothiazide 25mg Tablets can be extrapolated to the other strength of Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg.

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with losartan potassium and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg Film-Coated Tablets

Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets

PL 20242/0004-11

### STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 3\textsuperscript{rd} July 2006.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 15\textsuperscript{th} August 2006.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on the clinical sections of the dossier on 16\textsuperscript{th} February 2007 and 20\textsuperscript{th} June 2007. Further information was requested by the MHRA on the quality sections of the dossier on 24\textsuperscript{th} July 2007, 30\textsuperscript{th} October 2008 and 15\textsuperscript{th} January 2009.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical sections of the dossier on 25\textsuperscript{th} May 2007 and 6\textsuperscript{th} July 2007. Further information was provided by the applicant on the quality sections of the dossier on 11\textsuperscript{th} October 2007, 9\textsuperscript{th} January 2009 and 21\textsuperscript{st} February 2009.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 19\textsuperscript{th} August 2009.</td>
</tr>
</tbody>
</table>
Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg Film-Coated Tablets

Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets

PL 20242/0004-11

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium/ Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of losartan (as potassium salt) and 12.5 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Excipients
Each tablet contains 61.50 mg lactose monohydrate/film-coated tablet
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet
White, oblong, biconvex film-coated tablets with dimensions 13.7 × 6.7 mm approximately, bearing a breakline on both sides.
The scoreline is to facilitate breaking for ease of swallowing and not to divide into equal doses.

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Losartan Potassium/ Hydrochlorothiazide may be administered with other antihypertensive agents.
Losartan Potassium/ Hydrochlorothiazide tablets should be swallowed with a glass of water.
Losartan Potassium/ Hydrochlorothiazide may be administered with or without food.

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

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

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

The usual maintenance dose of Losartan Potassium/ Hydrochlorothiazide is one tablet of Losartan Potassium/ Hydrochlorothiazide 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Losartan Potassium/ Hydrochlorothiazide 50 mg/12.5 mg, the dosage may be increased to one tablet of Losartan Potassium/ Hydrochlorothiazide 100 mg/25 mg (losartan 100 mg/ HCTZ 25 mg) once daily. The maximum dose is one tablet of Losartan Potassium/ Hydrochlorothiazide 100 mg/25 mg 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/HCTZ 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/HCTZ tablets.

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

Use in the elderly
Dosage adjustment is not usually necessary for the elderly.
Use in children and adolescents (< 18 years)
There is no experience in children and adolescents. Therefore, Losartan Potassium/ Hydrochlorothiazide should not be administered to children and adolescents.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Losartan

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

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

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

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

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

Renal transplantation
There is no experience in patients with recent kidney transplantation.
Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan Potassium/Hydrochlorothiazide tablets is not recommended.

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

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

Aortic and mitral valve stenosis, obstructive hypertrophic 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 Potassium/ Hydrochlorothiazide should not be initiated during pregnancy. Unless continued Losartan/HTCZ 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 Potassium/ Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

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

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

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

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

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Losartan Potassium/ Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).
Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Excipient
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-medicinal is not advisable.

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

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

In some patients with compromised renal function who are being treated with non-steroidal 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
Additive effect

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.
Pressor amines (e.g. adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration 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 Potassium/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 (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (eg 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

Pregnancy
The use of Losartan Potassium/ Hydrochlorothiazide is not recommended during the first trimester of pregnancy (see section 4.4). The use of Losartan Potassium/ Hydrochlorothiazide is contraindicated during the 2nd and 3rd trimesters of pregnancy (see section 4.3 and 4.4). Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded.

Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Losartan Potassium/ Hydrochlorothiazide should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan Potassium/ Hydrochlorothiazide therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3 ‘Preclinical safety data’).

Should exposure to Losartan Potassium/ Hydrochlorothiazide have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken Losartan Potassium/ Hydrochlorothiazide should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide may reduce both plasma volume and uteroplacental blood flow. Thiazides pass the placental barrier and are found in cord blood. They may cause fetal 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.

Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Thiazides pass into human milk and may inhibit lactation. Because of the potential for adverse effects on the nursing infant, Losartan Potassium/ Hydrochlorothiazide 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 and hydrochlorothiazide.

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

**Hepato-biliary disorders**
Rare: Hepatitis

**Investigations**
Rare: Hyperkalaemia, elevation of ALT

Additional adverse 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 angitis (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/Hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Losartan Potassium/Hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

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

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

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

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

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

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

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

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 renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle cell proliferation.

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

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

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

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

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

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

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.
Hypertension Studies
In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80 % of the effect seen 5-6 hours post-dose.

Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effects on heart rate.
Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

LIFE Study
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg.

If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.
The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke.

Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

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

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

5.2 PHARMACOKINETIC PROPERTIES
Absorption
Losartan
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.
Distribution
Losartan
Both losartan and its active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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

Biotransformation
Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of $^{14}$C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

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

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

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During 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 $^{14}$C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

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

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

Neither losartan nor the active metabolite can be removed by hemodialysis.
5.3 PRECLINICAL SAFETY DATA
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of Losartan Potassium/ 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 Potassium/ 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 Potassium/ 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 Potassium/ Hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Tablet Core:
Microcrystalline Cellulose (E460a),
Lactose Monohydrate,
Pregelatinised Maize Starch,
Sodium Starch Glycolate Type A,
Magnesium Stearate (E572)

Film-coating:
Hydroxypropyl Cellulose (E463),
Hypermellose 6cP (E464),
Titanium Dioxide (E171)

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

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
Tablets are provided in PVC/PE/PVDC/Aluminium blisters.
Pack sizes:
7, 10, 14, 20, 28, 30, 56, 60, 90, 98, 112 film-coated tablets
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Fair-Med Healthcare GmbH
Buxtehuder Str. 112A, 21073
Hamburg, Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 20242/0004
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/08/2009

10 DATE OF REVISION OF THE TEXT
19/08/2009
1 **NAME OF THE MEDICINAL PRODUCT**
Losartan Potassium/ Hydrochlorothiazide 100 mg/25 mg film-coated tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 100 mg of losartan (as potassium salt) and 25 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

*Excipients*
Each tablet contains 123.00 mg lactose monohydrate/film-coated tablet.
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Film coated tablet
White, oblong, biconvex film-coated tablets with dimensions 15.3 × 6.7 mm approximately, bearing a breakline on both sides.
The tablet can be divided into equal halves.

4 **CLINICAL PARTICULARS**

4.1 **THERAPEUTIC INDICATIONS**
Losartan Potassium/ Hydrochlorothiazide is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

4.2 **POSOLOGY AND METHOD OF ADMINISTRATION**
Losartan Potassium/ Hydrochlorothiazide may be administered with other antihypertensive agents.
Losartan Potassium/ Hydrochlorothiazide tablets should be swallowed with a glass of water.
Losartan Potassium/ Hydrochlorothiazide may be administered with or without food.

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

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

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

The usual maintenance dose of Losartan Potassium/ Hydrochlorothiazide is one tablet of Losartan Potassium/ Hydrochlorothiazide 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Losartan Potassium/ Hydrochlorothiazide 50 mg/12.5 mg, the dosage may be increased to one tablet of Losartan Potassium/ Hydrochlorothiazide 100 mg/25 mg (losartan 100 mg/ HCTZ 25 mg) once daily. The maximum dose is one tablet of Losartan Potassium/ Hydrochlorothiazide 100 mg/25 mg 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/HCTZ 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/HCTZ tablets.

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

**Use in the elderly**
Dosage adjustment is not usually necessary for the elderly.
Use in children and adolescents (<18 years)
There is no experience in children and adolescents. Therefore, Losartan Potassium/ Hydrochlorothiazide should not be administered to children and adolescents.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Losartan

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

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

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored.

The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan/ hydrochlorothiazide is not recommended (see section 4.5).

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

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

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

Renal transplantation
There is no experience in patients with recent kidney transplantation.
Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan Potassium/Hydrochlorothiazide tablets is not recommended.

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

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

Aortic and mitral valve stenosis, obstructive hypertrophic 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 Potassium/ Hydrochlorothiazide should not be initiated during pregnancy. Unless continued Losartan/HTCZ 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 Potassium/ Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

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

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

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

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

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Losartan Potassium/ Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).
Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Excipient
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 co-administered with angiotensin II receptor antagonists.

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

In some patients with compromised renal function who are being treated with non-steroidal 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
Additive effect

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.
Pressor amines (e.g. adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfapyrazone 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 sulfapyrazone may be necessary. Co-administration 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 Potassium/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 (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulotride, 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

Pregnancy
The use of Losartan Potassium/ Hydrochlorothiazide is not recommended during the first trimester of pregnancy (see section 4.4). The use of Losartan Potassium/ Hydrochlorothiazide is contra-indicated during the 2nd and 3rd trimesters of pregnancy (see section 4.3 and 4.4). Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded.

Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Losartan Potassium/ Hydrochlorothiazide should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan Potassium/ Hydrochlorothiazide therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3 ‘Preclinical safety data’).

Should exposure to Losartan Potassium/ Hydrochlorothiazide have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken Losartan Potassium/ Hydrochlorothiazide should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide may reduce both plasma volume and uteroplacental blood flow. Thiazides pass the placental barrier and are found in cord blood. They may cause fetal 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.

Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Thiazides pass into human milk and may inhibit lactation. Because of the potential for adverse effects on the nursing infant, Losartan Potassium/ Hydrochlorothiazide 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 (cannot be estimated from the available data)

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

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

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

**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/ Hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Losartan Potassium/ Hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Neither losartan nor the active metabolite can be removed by hemodialysis.

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMAcodynamic PROPERTIES
Pharmacotherapeutic group: Combination containing an angiotensin II-receptor (type AT1)-antagonist and a thiazide diuretic, Antihypertensive, ATC code: C09DA01

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

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

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 hormon of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle cell proliferation.

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

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

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

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

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

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

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.
Hypertension Studies
In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80 % of the effect seen 5-6 hours post-dose.

Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effects on heart rate.

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

LIFE Study
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg.

If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke.

Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

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

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

5.2 PHARMACOKINETIC PROPERTIES
Absorption
Losartan
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.
Distribution
Losartan
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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

Biotransformation
Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of $^{14}$C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

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

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

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During 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 $^{14}$C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

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

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

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

5.3 PRECLINICAL SAFETY DATA
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of Losartan Potassium/ 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 Potassium/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 Potassium/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 Potassium/Hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet Core:
Microcrystalline Cellulose (E460a),
Lactose Monohydrate,
Pregelatinised Maize Starch,
Sodium Starch Glycolate Type A,
Magnesium Stearate (E572)

Film-coating:
Hydroxypropyl Cellulose (E463),
Hypromellose 6cP (E464),
Titanium Dioxide (E171)

Each tablet contains 8.48 mg (0.216 mEq) of potassium.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets are provided in PVC/PE/PVDC/Aluminium blisters.
Pack sizes:
7, 10, 14, 20, 28, 30, 56, 60, 90, 98, 112 film-coated tablets
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Fair-Med Healthcare GmbH
Buxtehuder Str. 112A, 21073
Hamburg, Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 20242/0004-11

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/08/2009

10 DATE OF REVISION OF THE TEXT

19/08/2009
UKPAR Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets  
PL 20242/0004-11

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets

losartan potassium and hydrochlorothiazide

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

In this leaflet:
1. What Losartan Potassium/Hydrochlorothiazide is and what it is used for
2. Before you take Losartan Potassium/Hydrochlorothiazide
3. How to take Losartan Potassium/Hydrochlorothiazide
4. Possible side effects
5. How to store Losartan Potassium/Hydrochlorothiazide
6. Further information

1. WHAT LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE IS AND WHAT IT IS USED FOR

Losartan Potassium/Hydrochlorothiazide is a combination of an angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide).

Losartan Potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension (high blood pressure).

2. BEFORE YOU TAKE LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE

Do not take Losartan Potassium/Hydrochlorothiazide
- 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 sulfonamide-derived substances (e.g. other diuretics, some antibiotics 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

Take special care with Losartan Potassium/Hydrochlorothiazide
- if you have previously suffered from swelling of the face, lips, throat or tongue
- if you take diuretics (water pills)
- if you are on a salt-restricted diet
- if you have or have had severe vomiting and/or diarrhoea
- if you have heart failure
- if you have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant
- if you have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function)
- if you have 'acute 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 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.

Diuretic agents such as the hydrochlorothiazide contained in Losartan Potassium/Hydrochlorothiazide may interact with other medicines. Preparations containing lithium should not be taken with Losartan Potassium/Hydrochlorothiazide without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate if you take potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines, other diuretics ("water tablets"), some laxatives, medicines for the treatment of gout, medicines to control heart rhythm or for diabetes (oral agents or insulin). It is also important for your doctor to know if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers, drugs for treatment of fungal infections, or arthritis medicines, resin used for high cholesterol, such as colestyramine, medicines which relax your muscles, sleeping tablets; opioid medicines such as morphine, ‘pressure amine’ such as adrenaline or other drugs from the same group, (oral agents for diabetes or insulin).

Please also inform your doctor when it is planned to apply iodine contrast media about taking Losartan Potassium/Hydrochlorothiazide.

Taking Losartan Potassium/Hydrochlorothiazide with food and drink
You are advised not to drink alcohol whilst taking these tablets: alcohol and Losartan Potassium/Hydrochlorothiazide tablets may increase each other's effects.

Dietary salt in excessive quantities may counteract the effect of Losartan Potassium/Hydrochlorothiazide tablets. Losartan Potassium/Hydrochlorothiazide tablets may be taken with or without food.

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

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

You must not take Losartan Potassium/Hydrochlorothiazide 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 in children. Therefore, Losartan/Hydrochlorothiazide should not be given to children.

Use in elderly patients
Losartan Potassium/Hydrochlorothiazide works equally well in and is equally well tolerated by most older and younger adult patients. Most older patients require the same dose as younger patients.

Driving and using 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.
UKPAR Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets PL 20242/0004-11

Important information about some of the ingredients of Losartan Potassium/Hydrochlorothiazide

Losartan Potassium/Hydrochlorothiazide contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE

Always take Losartan Potassium/Hydrochlorothiazide exactly as your doctor has instructed you. Your doctor will decide on the appropriate dose of Losartan Potassium/Hydrochlorothiazide depending on your condition and whether you are taking other medicines. It is important to continue taking Losartan Potassium/Hydrochlorothiazide for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

High Blood Pressure

The usual dose of Losartan Potassium/Hydrochlorothiazide for most patients with high blood pressure is 1 tablet of Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg per day to control blood pressure over the 24-hour period. This can be increased to 2 tablets once daily of Losartan / Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets or changed to 1 tablet daily of Losartan / Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets (a stronger strength) per day. The maximum daily dose is 2 tablets per day of Losartan / Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets or 1 tablet daily of Losartan / Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets.

If you take more Losartan Potassium/Hydrochlorothiazide than you should

In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. Overdose can cause a drop in blood pressure, palpitations, slow pulse, changes in blood composition, and dehydration.

If you forget to take Losartan Potassium/Hydrochlorothiazide

Try to take Losartan Potassium/Hydrochlorothiazide daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

4. POSSIBLE SIDE EFFECTS

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

If you experience the following, stop taking Losartan Potassium/Hydrochlorothiazide tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:

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

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

The following side effects have been reported:

Common (affecting less than one person in 10 but more than one person in 100):

- Cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder,
- Diarrhoea, abdominal pain, nausea, indigestion,
- Muscle pain or cramps, leg pain, back pain,
- Insomnia, headache, dizziness,
- Weakness, tiredness, chest pain,
- Increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels.

Uncommon (affecting less than one person in 100 but more than one person in 1,000):

- Anaemia, red or brownish spots on the skin (sometimes especially on the feet, legs, arms and buttocks, with joint pain, swelling of the hands and feet and stomach pain), bruising, reduction in white blood cells, clotting problems and bruising,
- Loss of appetite, increased uric acid levels or frank gout, increased blood sugar levels, abnormal blood electrolyte levels,
- Anxiety, nervousness, panic disorder (recurrent 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 heart beat, 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 (more than 1 out of 10000 patients and less than 1 out of 1000 patients):

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

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

5. HOW TO STORE Losartan Potassium/Hydrochlorothiazide

Keep out of the reach and sight of children.

Do not use Losartan Potassium/Hydrochlorothiazide after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Store below 25°C.

Keep the blister in the outer carton. Do not open the blister pack until you are ready to take the medicine.

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

6. FURTHER INFORMATION

What Losartan Potassium/Hydrochlorothiazide contains

The active substances are losartan potassium and hydrochlorothiazide.

Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide as the active ingredients.

The other ingredients are: microcrystalline cellulose (E460a), lactose monohydrate, pregelatinised maize starch, sodium starch glycolate type A, magnesium stearate (E572) in the tablet core and hydroxypropyl cellulose (E463), hypromellose 6cP(E464), titanium dioxide (E171) in the tablet coating. Each tablet contains 8.48 mg (0.216 mEq) of potassium.

What Losartan Potassium/Hydrochlorothiazide looks like and contents of the pack

White, oblong, biconvex film-coated tablets with dimensions 15.3 x 6.7 mm approximately bearing a breakline on both sides.

The tablet can be divided into equal halves.

Tablets are provided in PVC/PE/PVDC/Aluminium blisters.

Pack sizes:

7, 10, 14, 20, 28, 30, 56, 60, 90, 98, 112 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Fair-Med Healthcare GmbH
Buxtehuder Str. 112A, 21073 Hamburg, Germany

Manufacturer

Specifel S.A.
1, 2B Odoicouvi st.,
12351 Ag. Varnava
Athens, Greece

This leaflet was last approved in
UKPAR Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets PL 20242/0004-11

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets
Losartan potassium and hydrochlorothiazide

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

In this leaflet:
1. What Losartan Potassium/Hydrochlorothiazide is and what it is used for
2. Before you take Losartan Potassium/Hydrochlorothiazide
3. How to take Losartan Potassium/Hydrochlorothiazide
4. Possible side effects
5. How to store Losartan Potassium/Hydrochlorothiazide
6. Further information

1. WHAT LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE IS AND WHAT IT IS USED FOR
Losartan Potassium/Hydrochlorothiazide is a combination of an angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide).
Losartan Potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension (high blood pressure).

2. BEFORE YOU TAKE LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE
Do not take Losartan Potassium/Hydrochlorothiazide
• 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 substances (e.g. other thiazides, some antibacterial drugs such as co-trimoxazole, ask your doctor if you are not sure)
• If you are, think you may be or are planning to become pregnant (see also “Pregnancy and breast-feeding”)
• If you are breastfeeding
• 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

Take special care with Losartan Potassium/Hydrochlorothiazide
• If you have previously suffered from swelling of the face, lips, throat or tongue
• If you take diuretics (water pills)
• If you are on a salt-restricted diet
• If you have or have had severe vomiting or diarrhoea
• If you have heart failure
• If you have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant
• If you have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function)
• If you have ‘aortic or mitral valve stenosis’ (narrowing of the valves of the heart) or ‘hypertrophic cardiomyopathy’ (a disease causing thickening of heart muscle)
• If you are diabetic
• If you have had gout
• If you have or 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 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.
Diuretic agents such as the hydrochlorothiazide contained in Losartan Potassium/Hydrochlorothiazide may interact with other medicines.
Preparations containing lithium should not be taken with Losartan Potassium/Hydrochlorothiazide without close supervision by your doctor.
Special precautionary measures (e.g. blood tests) may be appropriate if you take potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines, other diuretics ("water tablets"), some laxatives, medicines for the treatment of gout, medicines to control heart rhythm or for diabetes (oral agents or insulins). It is also important for your doctor to know if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers, drugs for treatment of fungal infections, or arthritis medicines, reagents used for high cholesterol, such as colestyramine, medicines which relax your muscles, sleeping tablets; opioid medicines such as morphine, ‘pressor amines’ such as adrenaline or other drugs from the same group; (oral agents for diabetes or insulins).
Please also inform your doctor when it is planned to apply iodine contrast media taking Losartan Potassium/Hydrochlorothiazide.

Taking Losartan Potassium/Hydrochlorothiazide with food and drink
You are advised not to drink alcohol whilst taking these tablets: alcohol and Losartan Potassium/Hydrochlorothiazide tablets may increase each other’s effects.
Dietary salt in excessive quantities may counteract the effect of Losartan Potassium/Hydrochlorothiazide tablets.
Losartan Potassium/Hydrochlorothiazide tablets may be taken with or without food.

Pregnancy and breast-feeding
You should not take Losartan Potassium/Hydrochlorothiazide in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby.
If you become pregnant while on Losartan Potassium/Hydrochlorothiazide, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.
You must not take Losartan Potassium/Hydrochlorothiazide if you are breastfeeding.
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 in children. Therefore, Losartan Hydrochlorothiazide should not be given to children.

Use in elderly patients
Losartan Potassium/Hydrochlorothiazide works equally well in and is equally well tolerated by most older and younger adult patients. Most older patients require the same dose as younger patients.

Driving and using 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.
UKPAR Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets  PL 20242/0004-11

Important information about some of the ingredients of Losartan Potassium/Hydrochlorothiazide
Losartan Potassium/Hydrochlorothiazide contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE LOSARTAN POTASSIUM/HYDROCHLOROTHIAZIDE
Always take Losartan Potassium/Hydrochlorothiazide exactly as your doctor has instructed you. Your doctor will decide on the appropriate dose of Losartan Potassium/Hydrochlorothiazide depending on your condition and whether you are taking other medicines. It is important to continue taking Losartan Potassium/Hydrochlorothiazide for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

High Blood Pressure
The usual dose of Losartan Potassium/Hydrochlorothiazide for most patients with high blood pressure is 1 tablet of Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg per day to control blood pressure over the 24-hour period. This can be increased to 2 tablets once daily of Losartan / Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets or changed to 1 tablet daily of Losartan / Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets (a stronger strength) per day. The maximum daily dose is 2 tablets per day of Losartan / Hydrochlorothiazide 50 mg/12.5 mg Film-coated Tablets or 1 tablet daily of Losartan / Hydrochlorothiazide 100 mg/25 mg Film-coated Tablets.

If you take more Losartan Potassium/Hydrochlorothiazide than you should In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. Overdosing can cause a drop in blood pressure, palpitations, slow pulse, changes in blood composition, and dehydration.

If you forget to take Losartan Potassium/Hydrochlorothiazide Try to take Losartan Potassium/Hydrochlorothiazide as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Losartan Potassium/Hydrochlorothiazide tablets can cause side effects, although not everybody gets them.

If you experience the following, stop taking Losartan Potassium/Hydrochlorothiazide tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:
- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

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

The following side effects have been reported:
- Common (affecting less than one person in 10 but more than one person in 100):
  - Cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder,
  - Diarrhoea, abdominal pain, nausea, indigestion,
  - Muscle pain or cramps, leg pain, back pain,
  - Insomnia, headache, dizziness,
  - Weakness, tiredness, chest pain,
  - Increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels.
- Uncommon (affecting less than one person in 100 but more than one person in 1,000):
  - Anaemia, red or brownish spots on the skin (sometimes especially on the feet, legs, arms and buttocks, with joint pain, swelling of the hands and feet and stom- ach pain), bruising, reduction in white blood cells, clothing 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 (recurrent panic attacks), confusion, depression, abnormal dreams, sleep disorders, sleepiness, memory impair-
  - Pins and needles or similar sensations, pain in the extremities, trembling, migraine, fainting,
  - Blurred vision, burning or stinging in the eyes, conjunctivitis, worsening eye-
    sight, 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 heart-
    beat, cerebrovascular accident (TIA, “mini-stroke”), heart attack, palpitations,
- Infarction 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 (more than 1 out of 10,000 patients and less than 1 out of 1,000 patients):
- Hepatitis (inflammation of the liver), abnormal liver function tests

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

5. HOW TO STORE Losartan Potassium/Hydrochlorothiazide
Keep out of the reach and sight of children.

Do not use Losartan Potassium/Hydrochlorothiazide after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Store below 25°C. Keep the blister in the outer carton. Do not open the blister pack until you are ready to take the medicine.

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

6. FURTHER INFORMATION
What Losartan Potassium/Hydrochlorothiazide contains
The active substances are losartan potassium and hydrochlorothiazide.

Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide as the active ingredients.

The other ingredients are: microcrystalline cellulose (E460a), lactose monohy-
drate, pregelatinised maize starch, sodium starch glycolate type A, magnesium stearate (E572) in the tablet core and hydroxypropyl cellulose (E463), hypromel-
lose 6cP (E464), titanium dioxide (E171) in the tablet coating.
Each tablet contains 8.46 mg (0.216 mg) of potassium.

What Losartan Potassium/Hydrochlorothiazide looks like and contents of the pack
White, oblong, biconvex film-coated tablets with dimensions 15.3 × 6.7 mm approximately bearing a breakline on both sides.

The tablet can be divided into equal halves.

Tablets are provided in PVC/PE/PVDC/Aluminium blisters.
Pack sizes:
7, 10, 14, 20, 28, 30, 56, 60, 90, 98, 112 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Fair-Med Healthcare GmbH
Buxteheder Str. 112A, 21073 Hamburg, Germany

Manufacturer
Specifar S.A.
1, 28 Oktovriu str.,
12351 Ag. Varvara
Athens, Greece

This leaflet was last approved in
UKPAR Losartan Potassium 50mg/Hydrochlorothiazide 12.5mg and Losartan Potassium 100mg/Hydrochlorothiazide 25mg Film-Coated Tablets

Losartan Potassium/Hydrochlorothiazide
50mg/12.5mg
Film-coated tablets
Losartan and hydrochlorothiazide
Fair-Med Healthcare GmbH
Exp./Batch:

Losartan Potassium/Hydrochlorothiazide
50mg/12.5mg
Film-coated tablets
Losartan and hydrochlorothiazide
Fair-Med Healthcare GmbH
Exp./Batch:

Losartan Potassium/Hydrochlorothiazide
50mg/12.5mg
Film-coated tablets
Losartan and hydrochlorothiazide
Fair-Med Healthcare GmbH
Exp./Batch:

Losartan Potassium/Hydrochlorothiazide
50mg/12.5mg
Film-coated tablets
Losartan and hydrochlorothiazide
Fair-Med Healthcare GmbH
Exp./Batch:
Losartan Potassium/Hydrochlorothiazide

100mg/25mg film-coated tablets

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

Store below 25°C.

7 film-coated tablets

Losartan Potassium/Hydrochlorothiazide

100mg/25mg film-coated tablets

Losartan and hydrochlorothiazide

7 film-coated tablets

Losartan Potassium/Hydrochlorothiazide

100mg/25mg film-coated tablets

POM

Oral use.

Also contains lactose monohydrate.

See leaflet for further information.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Fair-Med Healthcare GmbH
Buckwieder Str. 112A
21033 Hamburg
Germany

PL 20242/0004-11