Lisinopril +HCT 10/12.5MG TABLETS
PL 32019/0042
Lisinopril +HCT 20/12.5MG TABLETS
PL 32019/0043

UKPAR

TABLE OF CONTENTS

Lay Summary .................................................................................................................. Page 2
Scientific discussion ......................................................................................................... Page 3
Steps taken for assessment ............................................................................................... Page 10
Steps taken after authorisation – summary ..................................................................... Page 11
Summary of Product Characteristics ................................................................................ Page 12
Product Information Leaflet ............................................................................................ Page 27
Labelling .......................................................................................................................... Page 29
Lisinopril + Hydrochlorothiazide Tablets 10/12.5mg & 20/12.5mg

LAY SUMMARY

The MHRA granted Marketing Authorisations (licences) for medicinal products containing Lisinopril + Hydrochlorothiazide in combination on 19th April 2010.

The names of the active ingredients in these products are lisinopril and hydrochlorothiazide. Throughout this report, hydrochlorothiazide will be shortened to ‘HCT’.

The products have been approved in two different combinations of strengths. One strength contains lisinopril 10mg and HCT 12.5mg. The other strength contains lisinopril 20mg and HCT 12.5mg.

These medicines are only available from your doctor on a prescription. They are used to treat or prevent high blood pressure.

A Patient Information Leaflet containing important information on how to use these products in order to benefit from them is attached at the end of this report.

The remainder of this report contains more detailed technical information about how the medicines were approved by MHRA.

No new or unexpected safety concerns arose during review of information provided by the company and it was, therefore, judged that the benefits of taking Lisinopril + HCT Tablets (10/12.5mg and 20/12.5mg) outweigh the risks, hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>8</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>9</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>10</td>
</tr>
</tbody>
</table>
INTRODUCTION

The UK granted a marketing authorisation for the medicinal products Lisinopril +HCT 10/12.5mg Tablets and Lisinopril +HCT 20/12.5mg Tablets (PL 32019/0042-3) to Tillomed Laboratories Limited on 19th April 2010. The product is available as a prescription-only medicine (POM).

The application was submitted as a simple abridged, according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to previously granted applications for Lisinopril +HCT 10/12.5mg Tablets and Lisinopril +HCT 20/12.5mg Tablets (PL 11311/0235-6), which were originally approved on 7th March 2004 to Tillomed Laboratories Limited.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to that of previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PAR was generated for it.

The active ingredients are lisinopril dihydrate and hydrochlorothiazide.

Lisinopril dihydrate belongs to a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors. The mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system. Lisinopril inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion.

Hydrochlorothiazide is a thiazide diuretic. These affect the tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases rennin activity and increases aldosterone secretion, with consequential 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 ACE inhibitor tends to reverse the associated potassium loss.
PHARMACEUTICAL ASSESSMENT

LICENSE NO: PL 32019/0042-3

PROPRIETARY NAMES: Lisinopril + HCT 10/12.5mg and 20/12.5mg Tablets

ACTIVE(S): Lisinopril dihydrate and hydrochlorothiazide

COMPANY NAME: Roger Oakes Limited


LEGAL STATUS: POM

1. INTRODUCTION

These are simple, piggyback applications for Lisinopril + HCT 10/12.5mg and 20/12.5mg Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Roger Oakes Ltd, Allstoe House, Church Lane, Greetham, Rutland, LE15 7NF.

The applications cross-refer to Lisinopril + HCT 10/12.5mg Tablets and Lisinopril + HCT 20/12.5mg Tablets (PL 11311/0235-6), which were originally approved on 7th March 2004 to Tillomed Laboratories Limited.

The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Lisinopril + HCT 10/12.5mg and Lisinopril + HCT 20/12.5mg Tablets. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain lisinopril dihydrate, equivalent to 10 or 20mg, and hydrochlorothiazide, equivalent to 12.5mg. They are to be stored in polyvinylchloride/aluminium blisters in pack sizes of 14, 28, 30, 50, 56, 98, 100 and 400 tablets. The marketing authorisation holder has stated that not all pack sizes are to be marketed, but has committed to submitting mock-ups of any new pack sizes to the regulatory authorities for approval before marketing. The proposed shelf-life (2 years) and storage conditions (no special storage instructions) are consistent with the details registered for the cross-reference products.

2.3 Legal status

On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

Roger Oakes Ltd, Allstoe House, Church Lane, Greetham, Rutland, LE15 7NF.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.
2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
It has been declared that none of the excipients are sourced from animal or human origin. These details are consistent with those for the cross-reference products.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME AND APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summaries are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference products. PIL user testing has been submitted and the results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In-line with current legislation, the applicant has also included the name of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.
7. CONCLUSIONS
The data submitted with the applications are acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

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

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the cross-reference products and as such have been judged to be satisfactory.

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

EFFICACY
These applications are identical to previously granted applications for Lisinopril +HCT 10/12.5mg Tablets and Lisinopril +HCT 20/12.5mg Tablets (PL 11311/0235-6), which were originally approved on 7th March 2004 to Tillomed Laboratories Limited.

No new or unexpected safety concerns arise from these applications.

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

RISK: BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with lisinopril dihydrate and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The risk:benefit is, therefore, considered to be positive.
**Lisinopril + HCT 10/12.5mg Tablets**  
*PL 32019/0042*  
**Lisinopril + HCT 20/12.5mg Tablets**  
*PL 32019/0043*

**Steps Taken for Assessment**

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<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 29/12/2008.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 03/04/2009.</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on 03/07/2009 and 19/11/2009.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 19/10/2009 and 01/12/2009.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 19/04/2010</td>
</tr>
</tbody>
</table>
Lisinopril + HCT 10/12.5 and 20/12.5mg Tablets

Lisinopril + HCT 10/12.5mg Tablets
PL 32019/0042

Lisinopril + HCT 20/12.5mg Tablets
PL 32019/0043

Steps Taken After Assessment

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lisinopril + HCT 10 mg/12.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains: Lisinopril dihydrate 10.9 mg equivalent to lisinopril 10 mg and hydrochlorothiazide 12.5 mg.

excipients
see point 6.1

3 PHARMACEUTICAL FORM
Tablet
pink, round, biconvex, one-sided score notch

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension. Lisinopril + HCT 10mg/12.5 mg tablets fixed dose combination (10 mg lisinopril and 12.5 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on lisinopril alone (or hydrochlorothiazide alone).

4.2 Posology and method of administration
The selection of a suitable antihypertensive dose of lisinopril and hydrochlorothiazide will depend upon the clinical evaluation of the patient.

Lisinopril + HCT 10mg/12.5 mg tablets should be taken once daily.

The administration of the fixed combination lisinopril and hydrochlorothiazide is usually recommended after dosage titration with the individual components.

When clinically appropriate a direct change from monotherapy to fixed combination may be considered.

10 mg/12,5 mg tablets may be administered in patients whose blood pressure is not adequately controlled by 10 mg lisinopril alone.

20 mg/12,5 mg tablets may be administered in patients whose blood pressure is not adequately controlled by 20 mg lisinopril alone.

A maximum daily dose of 40 mg lisinopril/25 mg hydrochlorothiazide should not be exceeded.

Previous diuretic treatment:
Symptomatic hypotension may occur following the initial dose; this is more likely in patients who are volume and/or salt depleted because of diuretic therapy.

Diuretics should be discontinued for 2-3 days before starting Lisinopril + HCT 10 mg/12.5 mg tablets. If this is not possible, treatment should be started with lisinopril alone, in a 2,5 mg dose. These patients should be carefully monitored for objective and subjective symptoms of hypotension after the first dose of Lisinopril + HCT 10 mg/12.5 mg tablets (see 4.4 Special warnings and precautions for use, hypotension and electrolyte/fluid imbalance).

Renal impairments:
The combination lisinopril/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). In patients with creatinine clearance between 30 and 80 ml/min it may be used only after titration of the individual components.
The recommended initial dose of lisinopril as mono-therapy for these patients is 5-10 mg (see 4.4 Special warnings and special precautions for use).
**Elderly patients:**
Clinical studies on the combination of lisinopril and hydrochlorothiazide have not shown that age is associated with any changes in efficacy or tolerability. See the above section on “Renal impairment”.

**Children:**
The safety and efficacy of Lisinopril + HCT 10 mg/12.5 mg tablets in children has not been established.

### 4.3 Contraindications
- History of hypersensitivity to lisinopril or to any of the excipients or any other ACE inhibitor
- History of hypersensitivity to hydrochlorothiazide or other sulphonamide-derived medicinal product
- Angioneurotic oedema relating to previous treatment with an ACE inhibitor
- Hereditary/idiopathic angioneurotic oedema
- Severe renal- and liver insufficiency
- Stenosis of the renal arteries
- Second and third trimester of pregnancy (see 4.6 Pregnancy)
- Lactation (see 4.6 Lactation)

### 4.4 Special warnings and precautions for use

**Hypotension and electrolyte/fluid imbalance:** Symptomatic hypotension is rare in uncomplicated hypertension, but is more likely in the presence of fluid or electrolyte imbalance, e.g. salt depletion, hyponatraemia, hypochloraeic alkalosis, hypomagnesaemia or hypokalaemia which may occur from prior diuretic therapy, salt restriction, dialysis, vomiting, diarrhoea.

Regular monitoring of serum electrolytes should be performed at appropriate intervals in such patients.

Particular consideration should be given when therapy is administered to patients with ischaemic heart disease or cerebrovascular disease because an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular event.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of physiological saline. A transient hypotensive response is usually not a contraindication to continued therapy. Following restoration of plasma volume and pressure, re-institution of therapy may be possible; or either of the components may be used alone, as appropriate.

As with other vasodilators, Lisinopril + HCT 10 mg/12.5 mg tablets should be given with caution to patients with aortic stenosis, mitral stenosis or hypertrophic cardiomyopathy.

**Renal function impairment:** Thiazides are ineffective in patients with creatinine clearance values < 30 ml/min (i.e. moderate or severe renal insufficiency).

Lisinopril + HCT 10 mg/12.5 mg tablets should not be administered to patients with creatinine clearance 30-80 ml/minutes until titration of the individual components has shown the need for the doses present in the combination tablet.

Some patients with no apparent pre-existing renovascular disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic. If this occurs during therapy with Lisinopril + HCT 10 mg/12.5 mg tablets, the treatment should be discontinued. Re-institution of therapy at reduced dosage may be possible, or either of the components may be used alone, as appropriate.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine usually reversible upon discontinuation of therapy, have been seen. This is
especially likely in patients with renal insufficiency. If renovascular hypertension is also present, there is an increased risk of severe hypotension and renal failure. In these patients treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, renal function should be monitored during the first few weeks of treatment.

*Hepatic disease:* Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of the syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

*Surgery/Aneesthesia:* In patients undergoing major surgery or during anaesthesia with agents that cause hypotension, lisinopril may block angiotensin formation secondary to compensatory renin release. This can be corrected by plasma volume expansion.

*Metabolic and endocrine effects:* Thiazide therapy may impair glucose tolerance and may increase cholesterol and triglyceride levels. The glycaemic levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor. Dosage adjustment of antidiabetic agents, including insulin, may be required.

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

Thiazide therapy may precipitate hyperuricaemia and/or gout in some patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

*Electrolyte imbalance:* As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraeamic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea or vomiting (see section 4.8).

*Angioedema:* Angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with ACE inhibitors particularly during the first weeks of treatment. However, in rare cases, severe angioedema may develop after long-term treatment with an ACE inhibitor. Treatment should be discontinued promptly. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

*Hypersensitivity, anaphylactic reactions:* 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.

Anaphylactic reactions during desensitization: Sustained life-threatening anaphylactic reactions have been rarely reported for patients undergoing desensitizing treatment with hymenoptera venom while receiving an ACE-inhibitor. In the same patients these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon
inadvertent rechallenge. Therefore, caution should be used in patients treated with an ACE inhibitors undergoing such desensitization.

Anaphylactic reactions during high-flux dialysis/lipoprotein apheresis membrane exposure: Anaphylactic reactions have been reported in patients haemodialysed with high-flux dialysis membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

Serum potassium: The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. During treatment with ACE inhibitor the following group of patients are at an increased risk of hyperkalaemia: patients with impaired renal function, diabetes mellitus, patients who are using potassium sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Frequent monitoring of serum potassium is recommended (see 4.5 Interaction with other medicinal products and other forms of interaction). The combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of kalaemia should be performed.

Cough: As ACE-inhibitors can cause a persistent cough they should be given cautiously to patients who are coughing.

Neutropenia/Agranulocytosis: The risk of neutropenia appears to be dose- and type-related and is dependent on the patient’s clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus (SLE), scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

Proteinuria: Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Ethnic differences: ACE inhibitors cause a higher rate of angioedema in black than in non-black patients. When lisinopril, a component of the fixed dose combination, is given, Afro-Caribbean patients may show a reduced therapeutic response.

4.5 Interaction with other medicinal products and other forms of interaction

Potassium-sparing diuretics, potassium supplements and salt substitutes: The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. The use of potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use of Lisinopril + HCT 10 mg/12.5mg tablets and any of these agents is required, then they should be used cautiously and with frequent monitoring of serum potassium.

Lithium: Lithium generally should not be given with diuretics or with an ACE inhibitor. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity. Careful monitoring of serum lithium should be performed if the combination proves necessary.

Anti-diabetics: Concomitant administration of ACE inhibitors and anti-diabetic medicines may cause an increased blood glucose lowering effect with an increased risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of treatment, and in patients with renal impairment.

NSAID (non-steroidal anti-inflammatory drugs): Concomitant administration with NSAID (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of ACE inhibitors and thiazide diuretics. In patients with renal dysfunction who are treated with NSAIDs, coadministration of lisinopril may result in a further deterioration of renal function including possible acute renal failure and an increase in serum potassium. 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.

Allopurinol: Concomitant administration of ACE inhibitors and allopurinol increases the risk
of renal failure.

Cyclosporin: Concomitant administration of ACE inhibitors and cyclosporin increases the risk
of renal failure and hyperkalaemia.

Lovastatin: Concomitant administration of ACE inhibitors and lovastatin increases the risk of
hyperkalaemia.

Probenecid: Concomitant administration may increase thiazide serum concentrations.

Trimethoprim: Concomitant administration of ACE inhibitors and thiazides with trimethoprim
increases the risk of hyperkalaemia.

Digitalis glycosides: Hypokalaemia induced by thiazide treatment can increase the effect of
digitalis glycosides.

Sotalol: Thiazide-induced hypokalaemia can increase the risk of sotalol-induced arrhythmias.

Colestyramin, colestipol: Concomitant administration of colestyramin or colestipol, reduces
the elimination of thiazide by 85% and 43% respectively. If concomitant administration of
these agents and the combination product is indicated, administration should be separated by
several hours.

Tricyclic antidepressants/antipsychotics: May enhance the hypotensive effects of ACE-
inhibitors.

Torsades de pointes-inducing drugs: Should not be combined with HCTZ.

Corticosteroids, amphotericin B (parenteral), carbenoxolone, corticotropin (ACTH) or
stimulant laxatives: HCTZ may intensify electrolyte imbalance, in particular hypokalaemia.

Other antihypertensive agents: Additive effects may occur.

Sympathomimetics: May reduce the antihypertensive effects of ACE inhibitors, patients
should be carefully monitored to confirm that the desired effects are being obtained.

Allopurinol, procainamide, cytostatic or immunosuppressive agents: Concomitant
administration with ACE inhibitors may lead to an increased risk of leucopenia.

Calcium salts: Increased serum calcium levels due to decreased excretion may occur when
administered concurrently with thiazide diuretics.

Other agents: Thiazides may increase the response to tubocurarine.

Haemodialysis:
Lisinopril + HCT 10 mg/12.5mg tablets is not indicated in patients requiring dialysis as a high
incidence of anaphylactic reactions have been reported in patients dialysed with high flux
membranes and treated concomitantly with an ACE inhibitor. This combination should be
avoided.
4.6 Pregnancy and lactation

Pregnancy
Lisinopril + HCT 10 mg/12.5 mg tablets is not recommended during the first trimester of pregnancy. When a pregnancy is planned or confirmed, an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but limited number of cases of first trimester exposure has not shown malformations.

Lisinopril + HCT 10 mg/12.5 mg tablets is contraindicated during the second and third trimesters of pregnancy. Prolonged lisinopril exposure during the second and third trimesters is known to induce toxicity in foetuses (decreased renal function, oligohydramnious, skull ossification retardation) and in neonates (neonatal renal failure, hypotension, hyperkalaemia).

Hydrochlorothiazide in case of prolonged exposure during the third trimester of pregnancy may cause a foeto-placental ischaemia and risk of growth retardation. Moreover, rare case of hypoglycaemia and thrombocytopenia in neonates has been reported in case of exposure near the term.

Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.

Should exposure to Lisinopril + HCT 10 mg/12.5 mg tablets have occurred from the second trimester of pregnancy ultrasound check of renal function and skull is recommended.

Lactation
Lisinopril + HCT 10 mg/12.5 mg tablets is contraindicated in the lactation period. Both lisinopril and hydrochlorothiazide are excreted in human milk. Thiazides during breastfeeding by lactating mothers have been associated with a decrease or even suppression of the milk lactation. Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and jaundice in foetus or neonate might occur. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of this therapy to the mother.

4.7 Effects on ability to drive and use machines

As with other antihypertensives, the ability to drive and use machines may be reduced, e.g. at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these effects depend on the individual’s susceptibility. The risk of hypotension, dizziness and fainting should be considered.

4.8 Undesirable effects

In clinical studies, side effects are the same as those reported previously with lisinopril or hydrochlorothiazide administered separately.

Common (>1/100, < 1/10)
General: Dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy. Headache, fatigue.
Respiratory: Dry and persistent cough, that disappears after discontinuation of therapy.
Cardiovascular: Hypotension including orthostatic hypotension.

Uncommon (> 1/1000, < 1/100)
Gastro-intestinal: Diarrhoea, nausea, vomiting, indigestion, pancreatitis, dry mouth.
Skin: Rash
Metabolic: Gout
Cardiovascular: Palpitation, chest pain, muscle cramps and muscle weakness.
Nervous system: Paraesthesia, asthenia
Urogenital: Impotence

Rare (> 1/10,000, <1/1,000)
Hypersensitivity reactions: Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see 4.4, Special warnings and special precautions for use).
**Others:** A symptom complex which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, leucocytosis, rash, photosensitivity or other dermatological manifestations.

**Laboratory test values:** Alterations of laboratory values have rarely been of clinical importance. Occasional hyperglycaemia, hyperuricaemia, hyperkalaemia or hypokalaemia have been noted. Increase in blood cholesterol and triglyceride concentration can be observed with thiazide treatment. Usually minor increases in blood urea and serum creatinine have been seen in patients without evidence of pre-existing renal impairment. If such increases persist, they are usually reversible upon discontinuation of the treatment. Bone marrow depression, manifest as anaemia and/or thrombocytopenia and/or leucopenia has been reported. Agranulocytosis has been rarely reported, but a causal relationship to the combination medicinal product has not been established. Small decreases in haemoglobin and haematocrit have been reported frequently in hypertensive patients but were rarely of clinical importance unless other causes of anaemia co-existed. Rarely, elevations of liver enzymes and/or serum bilirubin have occurred, but a causal relationship to Lisinopril + HCT 10 mg/12.5 mg tablets has not been established. Haemolytic anaemia has rarely been reported.

**Undesirable effects reported with the individual components:**

**Hydrochlorothiazide**
Anurexia, gastric irritation, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance including hyponatraemia, muscle spasm, restlessness, transient blurred vision, renal failure, renal dysfunction, cardiac arrhythmias, cutaneous lupus-erythematosus-like reactions, toxic epidermal necrolysis and interstitial nephritis.

**Lisinopril:**
Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, tachycardia, angina pectoris, syncope, flush, anaphylactic reactions, Raynaud syndrome, proteinuria, photosensitivity, abdominal pain and indigestion, mood alterations, mental confusion, vertigo have occurred; as with other angiotensin converting enzyme inhibitors, taste disturbance and sleep disturbance have been reported; bronchospasm, rhinitis, sinusitis, alopecia, urticaria, diaphoresis, pruritus, psoriasis and severe skin disorders, (including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme), have been reported; hyponatraemia, uraemia, oligaemia/anuria, renal dysfunction, acute renal failure, hepatitis (hepatocellular or cholestatic), jaundice and haemolytic anaemia.

### 4.9 Overdose

No specific information is available regarding overdose with Lisinopril + HCT 10 mg/12.5 mg tablets. Treatment is symptomatic with correction of dehydration, electrolyte disturbance and hypotension. Emptying of stomach and gastric lavage after recently administration. Patients should be kept under close supervision.

**Lisinopril:**
**Symptoms of overdose:** Severe hypotension, electrolyte disturbances and renal failure. After overdose, the patients should be kept under close supervision.

**Treatment of overdose:** The treatment is determined by the symptoms severity and nature. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, the patients should be placed in the shock position and an intravenous infusion of physiological saline should be given rapidly. Treatment with angiotensin II (if available) may be considered. ACE inhibitors may be removed from the general circulation by haemodialysis. The use of high-flux polyacrylonitrile dialysis membranes should be avoided. Serum electrolytes and creatinine should be monitored frequently.
Hydrochlorothiazide:
Symptoms of overdose: Symptoms are caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor (ACE: angiotensin converting enzyme) and thiazide diuretic, ATC-Code: C09B A03.

Mechanism of action: Both components, the ACE inhibitor and diuretic, have complementary modes of action and exert an additive antihypertensive effect. ACE catalyses the conversion of angiotensin I to angiotensin II, which has strong vasoconstrictor effect and stimulates aldosterone secretion. The antihypertensive effect of Lisinopril is mainly due to the suppression of the renin-angiotensin-aldosterone system with reduction of plasma concentration of angiotensin II and aldosterone. Lisinopril exerts an antihypertensive effect even in patients with low-renin hypertension. ACE is identical to kinase II, an enzyme that degrades bradykinin. It remains unclear whether increased levels of bradykinin (a potent vasodilator) plays a role in the therapeutic effect of lisinopril.

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive that increases the plasma-renin activity. Hydrochlorothiazide suppresses the renal reabsorption of electrolytes in the renal distal tubule and increases the excretion of sodium, chloride, potassium, magnesium, bicarbonates and water. The excretion of calcium may be reduced. Concomitant administration of lisinopril and hydrochlorothiazide gives a greater reduction in blood pressure than monotherapy. Lisinopril normally attenuates the potassium loss associated with hydrochlorothiazide.

5.2 Pharmacokinetic properties

The combination tablet is bioequivalent with separate administration of each of the active substances.

Absorption: Lisinopril: Approximately 25% with interpatient variability (6-60%) at all doses tested (5-80 mg). The absorption of lisinopril is not influenced by food. Maximal serum concentration is reached after 6-8 hours. Effect on blood pressure is observed after 1-2 hours. The effect is maximal after 6 hours and lasts for at least 24 hours.

Hydrochlorothiazide: Diuretic effect is seen within 2 hours. Maximal effect is reached after 4 hours. Clinically adequate diuretic effect lasts for 6-12 hours.

Distribution: Protein binding: Lisinopril is not bound to plasma proteins other than ACE. Reduced volume of distribution in elderly can give a higher plasma concentration than in younger patients.

Half-life: Lisinopril: On multiple dosing 12 hours. Hydrochlorothiazide 5.5 - 15 hours.

Metabolism/elimination: Both of the active substances are eliminated unchanged via the kidneys. Approximately 60% of hydrochlorothiazide that is administrated orally is eliminated within 24 hours.

5.3 Preclinical safety data

In animal studies ACE inhibitors gives harmful injury on the foetal development in the last phase of gestation (see 4.6 Pregnancy and lactation).

Available preclinical data indicate no other potential hazards than effects caused by the pharmacological mechanisms of action of the two compounds.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- calcium hydrogenphosphate dihydrate
- croscarmellose sodium
- mannitol
- maize starch
- magnesium stearate
- ferric oxide red (E 172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
The tablets are packed in polyvinylchloride /aluminium blisters and inserted into a carton. Package sizes: 14, 28, 30, 50, 66, 98, 100, 400. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Roger Oakes Ltd
Allstoe House
Church Lane
Greetham
Rutland
LE15 7NF

8 MARKETING AUTHORISATION NUMBER(S)
PL32019/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/04/2010

10 DATE OF REVISION OF THE TEXT
19/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Lisinopril + HCT 20 mg/12.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains: Lisinopril dihydrate 21.78 mg equivalent to lisinopril 20 mg and hydrochlorothiazide 12.5 mg.

excipients
see point 6.1

3 PHARMACEUTICAL FORM
Tablet
pink, round, biconvex, one-sided score notch

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension. Lisinopril + HCT 20mg/12.5 mg tablets fixed dose combination (20 mg lisinopril and 12.5 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on lisinopril alone (or hydrochlorothiazide alone).

4.2 Posology and method of administration
The selection of a suitable antihypertensive dose of lisinopril and hydrochlorothiazide will depend upon the clinical evaluation of the patient.

Lisinopril + HCT 20mg/12.5 mg tablets should be taken once daily.

The administration of the fixed combination lisinopril and hydrochlorothiazide is usually recommended after dosage titration with the individual components.

When clinically appropriate a direct change from monotherapy to fixed combination may be considered.

10 mg/12.5 mg tablets may be administered in patients whose blood pressure is not adequately controlled by 10 mg lisinopril alone.

20 mg/12.5 mg tablets may be administered in patients whose blood pressure is not adequately controlled by 20 mg lisinopril alone.

A maximum daily dose of 40 mg lisinopril/25 mg hydrochlorothiazide should not be exceeded.

Previous diuretic treatment:
Symptomatic hypotension may occur following the initial dose; this is more likely in patients who are volume and/or salt depleted because of diuretic therapy.

Diuretics should be discontinued for 2-3 days before starting Lisinopril + HCT 20 mg/12.5 mg tablets. If this is not possible, treatment should be started with lisinopril alone, in a 2.5 mg dose. These patients should be carefully monitored for objective and subjective symptoms of hypotension after the first dose of Lisinopril + HCT 20 mg/12.5 mg tablets (see 4.4 Special warnings and precautions for use, hypotension and electrolyte/fluid imbalance).

Renal impairments:
The combination lisinopril/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). In patients with creatinine clearance between 30 and 80 ml/min it may be used only after titration of the individual components. The recommended initial dose of lisinopril as mono-therapy for these patients is 5-10 mg (see 4.4 Special warnings and special precautions for use).
Elderly patients:
Clinical studies on the combination of lisinopril and hydrochlorothiazide have not shown that age is associated with any changes in efficacy or tolerability. See the above section on “Renal impairment”.

Children:
The safety and efficacy of Lisinopril + HCT 20 mg/12.5 mg tablets in children has not been established.

4.3 Contraindications
- History of hypersensitivity to lisinopril or to any of the excipients or any other ACE inhibitor
- History of hypersensitivity to hydrochlorothiazide or other sulphonamide-derived medicinal product
- Angioneurotic oedema relating to previous treatment with an ACE inhibitor
- Hereditary/idiopathic angioneurotic oedema
- Severe renal- and liver insufficiency
- Stenosis of the renal arteries
- Second and third trimester of pregnancy (see 4.6 Pregnancy)
- Lactation (see 4.6 Lactation)

4.4 Special warnings and precautions for use
Hypotension and electrolyte/fluid imbalance: Symptomatic hypotension is rare in uncomplicated hypertension, but is more likely in the presence of fluid or electrolyte imbalance, e.g. salt depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur from prior diuretic therapy, salt restriction, dialysis, vomiting, diarrhoea.

Regular monitoring of serum electrolytes should be performed at appropriate intervals in such patients.

Particular consideration should be given when therapy is administered to patients with ischaemic heart disease or cerebrovascular disease because an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular event.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of physiological saline. A transient hypotensive response is usually not a contraindication to continued therapy. Following restoration of plasma volume and pressure, reinstitution of therapy may be possible; or either of the components may be used alone, as appropriate.

As with other vasodilators, Lisinopril + HCT 20 mg/12.5 mg tablets should be given with caution to patients with aortic stenosis, mitral stenosis or hypertrophic cardiomyopathy.

Renal function impairment: Thiazides are ineffective in patients with creatinine clearance values < 30 ml/min (i.e. moderate or severe renal insufficiency).

Lisinopril + HCT 20 mg/12.5 mg tablets should not be administered to patients with creatinine clearance 30-80 ml/minutes until titration of the individual components has shown the need for the doses present in the combination tablet.

Some patients with no apparent pre-existing renovascular disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic. If this occurs during therapy with Lisinopril + HCT 10 mg/12.5 mg tablets, the treatment should be discontinued. Reinstitution of therapy at reduced dosage may be possible, or either of the components may be used alone, as appropriate.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine usually reversible upon discontinuation of therapy, have been seen. This is
especially likely in patients with renal insufficiency. If renovascular hypertension is also present, there is an increased risk of severe hypotension and renal failure. In these patients treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, renal function should be monitored during the first few weeks of treatment.

Hepatic disease: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of the syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Surgery/Antiesthesia: In patients undergoing major surgery or during anaesthesia with agents that cause hypotension, Lisinopril may block angiotensin formation secondary to compensatory renin release. This can be corrected by plasma volume expansion.

Metabolic and endocrine effects: Thiazide therapy may impair glucose tolerance and may increase cholesterol and triglyceride levels. The glycaemic levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor. Dosage adjustment of antidiabetic agents, including insulin, may be required.

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

Thiazide therapy may precipitate hyperuricaemia and/or gout in some patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

Electrolyte imbalance: As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea or vomiting (see section 4.8).

Angioedema: angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with ACE inhibitors particularly during the first weeks of treatment. However, in rare cases, severe angioedema may develop after long-term treatment with an ACE inhibitor. Treatment should be discontinued promptly. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Hypersensitivity, anaphylactic reactions: 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.

Anaphylactic reactions during desensitization: Sustained life-threatening anaphylactic reactions have been rarely reported for patients undergoing desensitizing treatment with hymenoptera venom while receiving an ACE-inhibitor. In the same patients these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon
An inadvertent rechallenge. Therefore, caution should be used in patients treated with an ACE inhibitors undergoing such desensitization.

Anaphylactic reactions during high-flux dialysis/lipoprotein apheresis membrane exposure: Anaphylactic reactions have been reported in patients haemodialysed with high-flux dialysis membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

Serum potassium: The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. During treatment with ACE inhibitor the following group of patients are at an increased risk of hyperkalaemia: patients with impaired renal function, diabetes mellitus, patients who are using potassium sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Frequent monitoring of serum potassium is recommended (see 4.5 Interaction with other medicinal products and other forms of interaction). The combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of kalaemia should be performed.

Cough: As ACE-inhibitors can cause a persistent cough they should be given cautiously to patients who are coughing.

Neutropenia/Agranulocytosis: The risk of neutropenia appears to be dose- and type-related and is dependent on the patient’s clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus (SLE), scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

Proteinurea: Proteinurea may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Ethnic differences: ACE inhibitors cause a higher rate of angioedema in black than in non-black patients. When lisinopril, a component of the fixed dose combination, is given, Afro-Caribbean patients may show a reduced therapeutic response.

4.5 Interaction with other medicinal products and other forms of interaction

Potassium-sparing diuretics, potassium supplements and salt substitutes: The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. The use of potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use of Lisinopril + HCT 20 mg/12.5mg tablets and any of these agents is required, then they should be used cautiously and with frequent monitoring of serum potassium.

Lithium: Lithium generally should not be given with diuretics or with an ACE inhibitor. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity. Careful monitoring of serum lithium should be performed if the combination proves necessary.

Anti-diabetics: Concomitant administration of ACE inhibitors and anti-diabetic medicines may cause an increased blood glucose lowering effect with an increased risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of treatment, and in patients with renal impairment.

NSAID (non-steroidal anti-inflammatory drugs): Concomitant administration with NSAID (i. e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of ACE inhibitors and thiazide diuretics. In patients with renal dysfunction who are treated with NSAIDs, coadministration of lisinopril may result in a further deterioration of renal function including possible acute renal failure and an increase in serum potassium. 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.

*Allopurinol:* Concomitant administration of ACE inhibitors and allopurinol increases the risk of renal failure.

*Cyclosporin:* Concomitant administration of ACE inhibitors and cyclosporin increases the risk of renal failure and hyperkalaemia.

*Lovastatin:* Concomitant administration of ACE inhibitors and lovastatin increases the risk of hyperkalaemia.

*Probenecid:* Concomitant administration may increase thiazide serum concentrations.

*Trimethoprim:* Concomitant administration of ACE inhibitors and thiazides with trimethoprim increases the risk of hyperkalaemia.

*Digitalis glycosides:* Hypokalaemia induced by thiazide treatment can increase the effect of digitalis glycosides.

*Sotalol:* Thiazide-induced hypokalaemia can increase the risk of sotalol-induced arrhythmias.

*Colestyramin, colestipol:* Concomitant administration of colestyramin or colestipol, reduces the elimination of thiazide by 85% and 43% respectively. If concomitant administration of these agents and the combination product is indicated, administration should be separated by several hours.

*Tricyclic antidepressants/antipsychotics:* May enhance the hypotensive effects of ACE-inhibitors.

*Torsades de pointes-inducing drugs:* Should not be combined with HCTZ.

*Corticosteroids, amphotericin B (parenteral), carbenoxolone, corticotropin (ACTH) or stimulant laxatives:* HCTZ may intensify electrolyte imbalance, in particular hypokalaemia.

*Other antihypertensive agents:* Additive effects may occur.

*Sympathomimetics:* May reduce the antihypertensive effects of ACE inhibitors, patients should be carefully monitored to confirm that the desired effects are being obtained.

*Allopurinol, procainamide, cytostatic or immunosuppressive agents:* Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia.

*Calcium salts:* Increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics.

*Other agents:* Thiazides may increase the response to tubocurarine.

*Haemodialysis:* Lisinopril + HCT 20 mg/12.5 mg tablets is not indicated in patients requiring dialysis as a high incidence of anaphylactic reactions have been reported in patients dialysed with high flux membranes and treated concomitantly with an ACE inhibitor. This combination should be avoided.
4.6 Pregnancy and lactation

Pregnancy

Lisinopril + HCT 20 mg/12.5 mg tablets is not recommended during the first trimester of pregnancy. When a pregnancy is planned or confirmed, an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but limited number of cases of first trimester exposure has not shown malformations.

Lisinopril + HCT 20 mg/12.5 mg tablets is contraindicated during the second and third trimesters of pregnancy. Prolonged lisinopril exposure during the second and third trimesters is known to induce toxicity in foetuses (decreased renal function, oligohydramnios, skull ossification retardation) and in neonates (neonatal renal failure, hypotension, hyperkalaemia).

Hydrochlorothiazide in case of prolonged exposure during the third trimester of pregnancy may cause a foeto-placental ischaemia and risk of growth retardation. Moreover, rare case of hypoglycaemia and thrombocytopenia in neonates has been reported in case of exposure near the term.

Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.

Should exposure to Lisinopril + HCT 20 mg/12.5 mg tablets have occurred from the second trimester of pregnancy ultrasound check of renal function and skull is recommended.

Lactation

Lisinopril + HCT 20 mg/12.5 mg tablets is contraindicated in the lactation period. Both lisinopril and hydrochlorothiazide are excreted in human milk. Thiazides during breastfeeding by lactating mothers have been associated with a decrease or even suppression of the milk lactation. Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and jaundice in foetus or neonate might occur. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of this therapy to the mother.

4.7 Effects on ability to drive and use machines

As with other antihypertensives, the ability to drive and use machines may be reduced, e.g. at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these effects depend on the individual’s susceptibility. The risk of hypotension, dizziness and fainting should be considered.

4.8 Undesirable effects

In clinical studies, side effects are the same as those reported previously with lisinopril or hydrochlorothiazide administered separately.

Common (>1/100, < 1/10)

- General: Dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy. Headache, fatigue.
- Respiratory: Dry and persistent cough, that disappears after discontinuation of therapy.
- Cardiovascular: Hypotension including orthostatic hypotension.

Uncommon (> 1/1000, < 1/100)

- Gastro-intestinal: Diarrhoea, nausea, vomiting, indigestion, pancreatitis, dry mouth.
- Skin: Rash
- Metabolic: Gout
- Cardiovascular: Palpitation, chest pain, muscle cramps and muscle weakness.
- Nervous system: Paraesthesia, asthenia
- Urogenital: Impotence

Rare (> 1/10,000, <1/1,000)

- Hypersensitivity reactions: Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see 4.4, Special warnings and special precautions for use).
Others: A symptom complex which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, leucocytosis, rash, photosensitivity or other dermatological manifestations.

Laboratory test values: Alterations of laboratory values have rarely been of clinical importance. Occasional hyperglycaemia, hyperuricaemia, hyperkalaemia or hypokalaemia have been noted. Increase in blood cholesterol and triglyceride concentration can be observed with thiazide treatment. Usually minor increases in blood urea and serum creatinine have been seen in patients without evidence of pre-existing renal impairment. If such increases persist, they are usually reversible upon discontinuation of the treatment. Bone marrow depression, manifest as anaemia and/or thrombocytopenia and/or leucopenia has been reported. Agranulocytosis has been rarely reported, but a causal relationship to the combination medicinal product has not been established. Small decreases in haemoglobin and haematocrit have been reported frequently in hypertensive patients but were rarely of clinical importance unless other causes of anaemia co-existed. Rarely, elevations of liver enzymes and/or serum bilirubin have occurred, but a causal relationship to Lisinopril + HCT 20 mg/12.5 mg tablets has not been established. Haemolytic anaemia has rarely been reported.

Undesirable effects reported with the individual components: Hyrochlorothiazide

Anurexia, gastric irritation, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonia and pulmonary oedema, anaphylactic reactions, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance including hyponatraemia, muscle spasm, restlessness, transient blurred vision, renal failure, renal dysfunction, cardiac arrhythmias, cutaneous lupus-erythematosus-like reactions, toxic epidermal necrolysis and interstitial nephritis.

Lisinopril: Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, tachycardia, angina pectoris, syncope, flush, anaphylactic reactions, Raynaud syndrome, proteinuria, photosensitivity, abdominal pain and indigestion, mood alterations, mental confusion, vertigo have occurred; as with other angiotensin converting enzyme inhibitors, taste disturbance and sleep disturbance have been reported; bronchospasm, rhinitis, sinusitis, alopecia, urticaria, diaphoresis, pruritus, psoriasis and severe skin disorders, (including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme), have been reported; hyponatraemia, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, hepatitis (hepatocellular or cholestatic), jaundice and haemolytic anaemia.

4.9 Overdose

No specific information is available regarding overdose with Lisinopril + HCT 20 mg/12.5 mg tablets. Treatment is symptomatic with correction of dehydration, electrolyte disturbance and hypotension. Emptying of stomach and gastric lavage after recently administration. Patients should be kept under close supervision.

Lisinopril: Symptoms of overdose: Severe hypotension, electrolyte disturbances and renal failure. After overdose, the patients should be kept under close supervision.

Treatment of overdose: The treatment is determined by the symptoms severity and nature. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, the patients should be placed in the shock position and an intravenous infusion of physiological saline should be given rapidly. Treatment with angiotensin II (if available) may be considered. ACE inhibitors may be removed from the general circulation by haemodialysis. The use of high-flux polyacrylonitrile dialysis membranes should be avoided. Serum electrolytes and creatinine should be monitored frequently.
**Hydrochlorothiazide:**
Symptoms of overdose: Symptoms are caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

5  PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* ACE inhibitor (ACE: angiotensin converting enzyme) and thiazide diuretic, ATC-Code: C09B A03.

*Mechanism of action:* Both components, the ACE inhibitor and diuretic, have complementary modes of action and exert an additive antihypertensive effect. ACE catalyses the conversion of angiotensin I to angiotensin II, which has strong vasoconstrictor effect and stimulates aldosterone secretion. The antihypertensive effect of Lisinopril is mainly due to the suppression of the renin-angiotensin-aldosterone system with reduction of plasma concentration of angiotension II and aldosterone. Lisinopril exerts an antihypertensive effect even in patients with low-renin hypertension. ACE is identical to kinase II, an enzyme that degrades bradykinin. It remains unclear whether increased levels of bradykinin (a potent vasodilator) plays a role in the therapeutic effect of lisinopril.

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive that increases the plasma-renin activity. Hydrochlorothiazide suppresses the renal reabsorption of electrolytes in the renal distal tubule and increases the excretion of sodium, chloride, potassium, magnesium, bicarbonates and water. The excretion of calcium may be reduced. Concomitant administration of lisinopril and hydrochlorothiazide gives a greater reduction in blood pressure than monotherapy. Lisinopril normally attenuates the potassium loss associated with hydrochlorothiazide.

5.2 Pharmacokinetic properties

The combination tablet is bioequivalent with separate administration of each of the active substances.

*Absorption:* Lisinopril: Approximately 25% with interpatient variability (6-60%) at all doses tested (5-80 mg). The absorption of lisinopril is not influenced by food. Maximal serum concentration is reached after 6-8 hours. Effect on blood pressure is observed after 1-2 hours. The effect is maximal after 6 hours and lasts for a least 24 hours.

*Hydrochlorothiazide:* Diuretic effect is seen within 2 hours. Maximal effect is reached after 4 hours. Clinically adequate diuretic effect lasts for 6-12 hours.

*Distribution:* Protein binding: Lisinopril is not bound to plasma proteins other than ACE. Reduced volume of distribution in elderly can give a higher plasma concentration than in younger patients.

*Half-life:* Lisinopril: On multiple dosing 12 hours. Hydrochlorothiazide 5.5 - 15 hours.

Metabolism/elimination: Both of the active substances are eliminated unchanged via the kidneys. Approximately 60% of hydrochlorothiazide that is administrated orally is eliminated within 24 hours.

5.3 Preclinical safety data

In animal studies ACE inhibitors gives harmful injury on the foetal development in the last phase of gestation (see 4.6 Pregnancy and lactation).

Available preclinical data indicate no other potential hazards than effects caused by the pharmacological mechanisms of action of the two compounds.
6  PHARMACEUTICAL PARTICULARS
6.1  List of excipients
    calcium hydrogenphosphate dihydrate
    croscarmellose sodium
    mannitol
    maize starch
    magnesium stearate
    ferric oxide red (E 172)

6.2  Incompatibilities
    Not applicable

6.3  Shelf life
    2 years

6.4  Special precautions for storage
    This medicinal product does not require any special storage conditions.

6.5  Nature and contents of container
    The tablets are packed in polyvinylchloride /aluminium blisters and inserted into a carton.
    Package sizes: 14, 28, 30, 50, 56, 98, 100, 400.
    Not all pack sizes may be marketed.

6.6  Special precautions for disposal
    None

7  MARKETING AUTHORISATION HOLDER
    Roger Oakes Ltd
    Allstoe House
    Church Lane
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    Rutland
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8  MARKETING AUTHORISATION NUMBER(S)
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9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
    19/04/2010
UKPAR Lisinopril + HCT 10/12.5 and 20/12.5mg Tablets

PL 32019/0042-3

**How to use**

Lisinopril + HCT Tablets can cause side effects, although not everybody gets them.

Stop taking Lisinopril + HCT Tablets and seek medical advice immediately if you develop any of the following symptoms:

- Severe allergic reaction (e.g., itching, rash, swelling of hands, face, lips, throat, mouth, or tongue)

Common side effects (affects 1-10% of users in 100):

- Dizziness (Vertigo)
- Headache
- Feeling tired (Fatigue)
- Dry and persistent cough
- Low blood pressure (Hypotension)

Uncommon side effects (affects 1-10% users in 1000):

- Dizziness (Vertigo)
- Feeling sick (Nausea)
- Being sick (Vomiting)
- Irritation (Ophthalmia)
- Information of the pancreas (Pancreatitis)
- Dry mouth (Xerostomia)
- Skin rash
- Feeling your heartbeat (Papistasthenia)
- Chest pain
- Muscular strain
- Tingling or numbness in the hands or feet (Parasthesia)
- General weakness (Asthenia)
- Inability to maintain an erection (Impotence)

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

**Further information**

What Lisinopril + HCT contains:

The active substances are Lisinopril Hydrochlorothiazide and Hydrochlorothiazide.

Other ingredients are:

- Calcium hydrogen phosphat dishydrate, croscarmellose sodium, mannitol, mastic starch, magnesium stearate and ferric oxide red (E 172).

What Lisinopril + HCT looks like and contains in the pack:

Lisinopril + HCT Tablets are pink, round, and scored. Lisinopril + HCT Tablets are scored on one side.

Lisinopril + HCT are available in:

- Lisinopril + HCT Tablets are available in packs of 14, 28, 30, 50, 66, 98, 100, 400.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**

Roger Cödker UAB
Altoше House, Church Lane
Greetland, Huddersfield
LE15 7NF

**Manufacturer:**

Solutus Pharma GmbH, Otto-Von-Guericke-Allee 1, 30173 Barletta, Germany

**Product Licence Number:**

Lisinopril + HCT 10/12.5mg Tablets PL 32019/0034 Lisinopril + HCT 20/12.5mg Tablets PL 32019/0043

The leaflet was last reviewed in February 2010.