Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lispril-Hydrochlorothiazide 10 mg/12.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of lisinopril (as dihydrate) and 12.5 mg of hydrochlorothiazide.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

The tablet is pink, round and biconvex with one-sided score notch.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.
Lisinopril/Hydrochlorothiazide fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on lisinopril alone (or hydrochlorothiazide alone).

4.2 Posology and method of administration

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

The administration of the fixed combination lisinopril and hydrochlorothiazide is usually recommended after dose 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 (see section 4.4).
20 mg/12.5 mg tablets may be administered in patients whose blood pressure is not adequately controlled by 20 mg lisinopril alone (see section 4.4).

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

As with all other medicinal products taken once daily, the tablets should be taken approximately at the same time every day.

Renal impairment
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 monotherapy for these patients is 5-10 mg (see section 4.4).

Diuretic treated patients
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/hydrochlorothiazide combination. If this is not possible, treatment should be started with lisinopril alone, in a 2.5 mg dose. Renal function and serum potassium should be monitored.

The subsequent dose of lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see sections 4.4 and 4.5).

Paediatric population
Safety and efficacy of the combination of lisinopril and hydrochlorothiazide in children have not been established. Therefore, use in children is not recommended.

Elderly
Clinical studies on the combination of lisinopril and hydrochlorothiazide have not shown that age is associated with any changes in efficacy or tolerability. However, in the elderly patients the renal function is more likely to be impaired and dose-adjustment should be made when appropriate. In the elderly patients the dose should be adjusted carefully (titration of the individual components). See the above section on 'Renal impairment'.

Method of administration
Oral use

4.3 Contraindications

- Hypersensitivity to the active substances, any other angiotensin converting enzyme (ACE) inhibitor or other sulphonamide-derived medicinal products or to any of the excipients listed in section 6.1
- History of angioedema with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Anuria
- Severe hepatic impairment
- The concomitant use of Lispril-Hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1)
- Concomitant use with sacubitril/valsartan therapy. Lispril-Hydrochlorothiazide must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Symptomatic hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients, but is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). Regular determination of serum electrolytes should be performed at appropriate intervals in such patients.

In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision.
Particular consideration applies to patients with ischaemic heart or cerebrovascular disease, because an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position, and if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication for further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dose may be possible, or either of the components may be used appropriately alone.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of lisinopril/hydrochlorothiazide may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy
As with other ACE inhibitors, lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal impairment

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (corresponds to moderate or severe renal insufficiency).

Lisinopril/hydrochlorothiazide should not be administered to patients with renal insufficiency (creatinine clearance less than or equal to 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme 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 insufficiency. 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 lisinopril/hydrochlorothiazide therapy.
Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic.

This is more likely to occur in patients with pre-existing renal impairment. Dose reduction and/or discontinuation of the diuretic and/or lisinopril may be required.

Prior diuretic therapy
The diuretic therapy should be discontinued for 2-3 days prior to initiation with lisinopril/hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

Renal transplantation
The medicinal product should not be used, since there is no experience with patients recently transplanted with a kidney.

Anaphylactoid reactions in haemodialytic patients
The use of lisinopril/hydrochlorothiazide is not indicated in patients requiring dialysis for renal failure.
Anaphylactoid reactions have been reported in patients, undergoing certain haemodialysis procedures (e.g. with the high-flux membranes AN 69 and during low-density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicinal product.

Anaphylactoid reactions related to low-density lipoproteins (LDL) apheresis
In rare occasions, patients treated with ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have shown life threatening anaphylactic reactions. These symptoms could be avoided by temporary discontinuation of the treatment with ACE inhibitors before each apheresis.

Hepatic impairment
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 (see section 4.3). Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving lisinopril/hydrochlorothiazide who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide and receive appropriate medical follow-up.

Surgery/anaesthesia
In patients undergoing major surgery or during anaesthesia with medicinal products that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Metabolic and endocrine effects
ACE inhibitor and thiazide therapy may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required. In diabetic patients treated with oral antidiabetic medicinal products or insulin, glycaemia

levels should be closely monitored during the first month of treatment with an ACE inhibitor. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.
Thiazide therapy may precipitate hyperuricaemia and/or gout in certain 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, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea or vomiting. Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not require treatment. Thiazides have been shown to increase the urinary excretions of magnesium, which may result in hypomagnesaemia.

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

Hyperkalaemia
ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function, diabetes mellitus and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride), or other medicinal products associated with increases in serum potassium (e.g. heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers), hyperkalaemia can occur. If concomitant use of the above-mentioned medicinal products is deemed appropriate, they should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be regularly monitored(see section 4.5).

Diabetic patients
In diabetic patients treated with oral antidiabetic medicinal products or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Hypersensitivity/angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. This may occur at any time during therapy. In such cases, lisinopril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema.
Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of Lispril-Hydrochlorothiazide.
Treatment with Lispril-Hydrochlorothiazide must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril,mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

The risk of angioedema may also be increased in patients concomitantly treated with ACE inhibitors and tissue plasminogen activator (see section 4.5).

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.

Desensitisation
Patients receiving ACE-inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they reappeared upon inadvertent rechallenge.

Neutropaenia/agranulocytosis
Neutropaenia/agranulocytosis, thrombocytopaenia and anaemia have been reported for patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors neutropenia occurs rarely. Neutropaenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race
Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, lisinopril may be less effective in lowering blood pressure in black patients than in non-black patients, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Lithium
The combination of ACE inhibitors and lithium is generally not recommended (see section 4.5).

Anti-doping test
The hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulphonamide or sulphonamide derivative medicinal products can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicinal product initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Lispril-Hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Medicinal products increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections 4.3 and 4.4).
Concomitant use of ACE inhibitors with neutral endopeptidase (NEP) inhibitors (e.g. racecadotril), mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus, temsirolimus), vildagliptin or tissue plasminogen activator may lead to an increased risk for angioedema (see section 4.4).

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Diuretic medicinal products and ACE inhibitors reduce the renal clearance of lithium and pose a high risk of lithium toxicity. The combination of lisinopril and hydrochlorothiazide with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary (see section 4.4).

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels
The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with lisinopril/hydrochlorothiazide. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium, particularly in patients with impaired renal function or diabetes mellitus. Care should also be taken when lisinopril is co-administered with other medicinal products that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of lisinopril/hydrochlorothiazide with the above-mentioned medicinal products is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium (see section 4.4).

Torsades de pointes-inducing medicinal products

Because of the risk of hypokalaemia the concomitant administration of hydrochlorothiazide and medicinal products that induce torsades de pointes, e.g. some antiarrhythmics, some antipsychotics and other medicinal products known to induce torsades de pointes, should be used with caution.

Tricyclic antidepressants/antipsychotics/anaesthetics:
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further lowering of blood pressure (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid
Chronic administration of NSAIDs (including selective cyclooxygenase-2 inhibitors) may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors may exert an additive effect on the deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Gold
Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Sympathomimetics
Sympathomimetics can reduce the antihypertensive effect of ACE inhibitors.
Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ACE-inhibitors, angiotensin II receptor blockers or aliskiren
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting medicinal product (see sections 4.3, 4.4 and 5.1).

Other antihypertensive medicinal products
Concomitant use of these medicinal products may increase the hypotensive effect of lisinopril/hydrochlorothiazide.
Concomitant use of glyceryl trinitrate and other nitrates or other vasodilators may further reduce the blood pressure.

Antidiabetics
Epidemiological studies indicate that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, oral hypoglycaemic medicinal products) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combination treatment and in patients with renal impairment. Treatment with a thiazide diuretic may impair glucose tolerance. Other antidiabetic medicinal products including insulin requirements in diabetic patients may be increased, decreased, or unchanged.

The hyperglycaemic effect of diazoxide may be enhanced by thiazides.

Other kaliuretic diuretics, amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.
The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).
Hypokalaemia may develop during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

Calcium salts/vitamin D
Increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics. If calcium supplements or vitamin D must be prescribed, serum calcium levels should be monitored and the dose adjusted accordingly.

Cardiac glycosides
There is increased risk of digitalis toxicity associated with thiazide induced hypokalaemia (e.g. increased ventricular irritability).

Colestyramine and colestipol
These may delay or reduce absorption of hydrochlorothiazide. Therefore sulphonamide diuretics should be taken at least 1 hour before or 4-6 hours after intake of these medicinal products.

Non-depolarizing muscle relaxants (e.g. tubocurarine chloride)
The effect of these medicinal products may be potentiated by hydrochlorothiazide.

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

Other concomitant therapy
Thiazides may increase the risk of adverse events caused by amantadine.
Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.

Allopurinol
Concomitant administration of ACE inhibitors and allopurinol increases the risk of renal damage and can lead to an increased risk of leukopaenia.

Ciclosporin
Concomitant administration of ACE inhibitors and ciclosporin increases the risk of renal damage and hyperkalaemia. Monitoring of serum potassium is recommended.
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Heparin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

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

Cytostatics, immunosuppressives, procainamide
Concomitant administration of ACE inhibitors can lead to increased risk of leukopaenia (see section 4.4).
Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Ability to drive and use machines
Lisinopril/hydrochlorothiazide combination products may have a mild to moderate effect on the ability to drive and use machines (see section 4.7).

4.6 Fertility, pregnancy and lactation

Pregnancy

ACE inhibitors

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 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. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. ACE inhibitor therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

ACE inhibitors
Because no information is available regarding the use of lisinopril/hydrochlorothiazide during breast-feeding, lisinopril/hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of lisinopril/hydrochlorothiazide during breast-feeding is not recommended. If lisinopril/hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

As with other antihypertensives, lisinopril/hydrochlorothiazide combination products may have a mild to moderate effect on the ability to drive and use machines. Especially 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. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with lisinopril and/or hydrochlorothiazide with the following frequencies:

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

The most commonly reported adverse reactions are cough, dizziness, hypotension, and headache which may occur in 1 to 10% of treated patients. In clinical studies, adverse reactions have usually been mild and transient, and in most instances have not required interruption of therapy.

Lisinopril

Blood and lymphatic system disorders	
Rare Very rare	Decreases in haemoglobin, decreases in haematocrit Bone marrow depression, anaemia, thrombocytopaenia, leukopaenia, neutropaenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease
Immune system disorders	
Not known	Anaphylactic/anaphylactoid reaction
Endocrine disorders	
Rare	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	

Very rare	Hypoglycaemia
Psychiatric disorders	
Uncommon Rare Not known	Mood alterations Mental confusion Depressive symptoms, hallucinations
Nervous system disorders	
Common Uncommon Rare	Dizziness, headache, syncope Paraesthesia, vertigo, taste disturbance, sleep disturbances Olfactory disturbance
Cardiac disorders	
Uncommon	Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia
Vascular disorders	
Common Uncommon Not known	Orthostatic effects (including orthostatic hypotension) Raynaud's syndrome Flushing
Respiratory, thoracic and mediastinal disorders	
Common Uncommon Very rare	Cough (see section 4.4) Rhinitis Bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia
Gastrointestinal disorders	
Common Uncommon Rare Very rare	Diarrhoea, vomiting Nausea, abdominal pain and indigestion Dry mouth Pancreatitis, intestinal angioedema
Hepatobiliary disorders	
Uncommon Very rare	Elevated liver enzymes and bilirubin Hepatitis – either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4)*
Skin and subcutaneous tissue disorders	
Uncommon Rare Very rare	Rash, pruritus Hypersensitivity/angioedema: angioedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis Diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, cutaneous pseudolymphoma**
Renal and urinary disorders	
Common Rare Very rare	Renal dysfunction Uraemia, acute renal failure Oliguria/anuria
Reproductive system and breast disorders	

Uncommon Rare	Impotence Gynaecomastia
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue
Investigations	
Uncommon Rare	Increases in blood urea, increases in serum creatinine, hyperkalaemia Hyponatraemia

* Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril/hydrochlorothiazide combination who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide combination and receive appropriate medical follow up.

** A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Hydrochlorothiazide

Infections and infestations	Not known	Sialadenitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Not known	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)*
Blood and lymphatic system disorders	Not known	Leukopaenia, neutropaenia/agranulocytosis, thrombocytopaenia, aplastic anaemia, haemolytic anaemia, bone marrow depression
Metabolism and nutrition disorders	Not known	Anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloraemic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout
Psychiatric disorders	Not known	Restlessness, depression, sleep disturbance
Nervous system disorders	Not known	Loss of appetite, paraesthesia, light-headedness
Eye disorders	Not known	Xanthopsia, transient blurred vision, choroidal effusion, acute myopia, acute angle-closure glaucoma
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Postural hypotension
Vascular disorders	Not known	Necrotising angiitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory distress (including pneumonitis and pulmonary oedema)
	Very rare	Acute respiratory distress syndrome (ARDS) (see section 4.4)
Gastrointestinal disorders	Not known	Gastric irritation, diarrhoea, constipation, pancreatitis.
Hepatobiliary disorders	Not known	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Not known	Photosensitivity reactions, rash, cutaneous lupus erythematosus, systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Not known	Muscle spasm, muscle weakness
Renal and urinary disorders	Not known	Renal dysfunction, interstitial nephritis
General disorders and administration site conditions	Not known	Fever, weakness

*Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Limited data are available for overdose in humans. Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the supine position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

Additional symptoms of hydrochlorothiazide overdose are increased diuresis, depression of consciousness (including coma), convulsions, paresis, cardiac arrhythmias and renal failure.
Bradycardia or extensive vagal reactions should be treated by administering atropine.
If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, combinations, ACE inhibitors and diuretics, ATC code: C09B A03.

Lisinopril/hydrochlorothiazide consists of a combination of lisinopril, an inhibitor of angiotensin converting enzyme, and hydrochlorothiazide, a thiazide diuretic. Both components have complimentary modes of action, and exert an additive antihypertensive effect.

Lisinopril is a peptidyl dipeptidase inhibitor. It 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 in adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II in plasma resulting in decreased vasopressor activity and reduced aldosterone secretion. The latter may result in an increase in serum potassium concentration.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is shown also to have an antihypertensive effect in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Bradykinin is a potential vasodepressive peptide, and to which extent the increased level plays a role in the therapeutic effects of lisinopril has not been elucidated yet.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Hydrochlorothiazide is a diuretic and an antihypertensive medicinal product. It affects the distal renal tubular effect in the kidneys to reabsorb electrolytes and to increase the excretion of sodium and chloride in approximately equivalent amounts. The loss of sodium may be followed by a loss of potassium and sodium hydrogen carbonate. The antihypertensive mode of action of thiazides is unknown.

Thiazides do not usually affect normal blood pressure.
When combined with other antihypertensives, an additive fall in blood pressure may occur.

Lisinopril may attenuate potassium loss induced by hydrochlorothiazide.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

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.

Biotransformation/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.

Half-life: Lisinopril: On multiple dosing 12 hours. Hydrochlorothiazide 5½ – 15 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In animal tests angiotensin converting enzyme inhibitors induce adverse reactions on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to the ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate Dihydrate
Croscarmellose Sodium
Mannitol
Maize Starch
Magnesium Stearate
Iron Oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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.

Pack sizes: 14, 28, 30, 50, 56, 98, 100 and 400 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/051/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 January 2004
Date of last renewal: 7 March 2009

10 DATE OF REVISION OF THE TEXT

March 2022