

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: Lisinopril dihydrate 10.89mg equivalent to lisinopril 10 mg and hydrochlorothiazide 12.5 mg

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pink, round, biconvex, one-sided score notch.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension. Lispril-Hydrochlorothiazide fixed dose combination (10mg lisinopril and 12.5mg 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.

Lispril-Hydrochlorothiazide 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.

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

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

A maximum daily dose of 40mg lisinopril/25mg 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 Lispril-Hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 2.5mg dose. These patients should be carefully monitored for objective and subjective symptoms of hypotension after the first dose of Lispril-Hydrochlorothiazide (*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 < 30mg/min). In patients with creatinine clearance between 30 and 80ml/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 5-10mg (*see 4.4 Special warning 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 Lispril-Hydrochlorothiazide in children has not been established.

4.3 Contraindications

- Hypersensitivity to lisinopril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor
- Hypersensitivity to hydrochlorothiazide or other sulphonamide-derived drugs
- 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 m²) (see sections 4.5 and 5.1).

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 rennin-dependant 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 normal saline. A transient hypotensive response is not a contraindication for further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage 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 function 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. Dosage 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

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 agent.

Anaphylactoid reactions related to low-density lipoproteins (LDL) aphaeresis

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

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 (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 agents 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

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemia levels should be closely monitored during the first month of treatment with an ACE inhibitor. Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

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

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the abovementioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents 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 anti-histamines 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).

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.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported for patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors neutropenia occurs rarely. Neutropenia 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 medication 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 anti-hypertensive 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.

Acute myopia and secondary angle-closure glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in 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 drug 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 sulfonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Diuretic agents 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:

The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes, particularly in patients with impaired renal function or diabetes mellitus, may lead to a significant increase in serum potassium. If concomitant use of lisinopril/hydrochlorothiazide and any of these agents is required, 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 antiarrhythmias, some anti-psychotics and other drugs known to induce torsades de pointes, should be used with caution.

Tricyclic antidepressants / antipsychotics / anesthetics:

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 / anti-rheumatic drugs (NSAID):

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 effects of ACE inhibitors.

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 agent (see sections 4.3, 4.4 and 5.1).

Other antihypertensives:

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

Antidiabetics:

Epidemiological studies indicate that concomitant administration of ACE inhibitors and anti-diabetic medicinal products (insulins, oral hypoglycaemic agents) 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.

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

Calcium salts:

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

Cardiac glycosides:

There is increased risk of digitalis toxicity associated with thiazide induced hypokalaemia.

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 agents.

Non-depolarizing muscle relaxants (e.g. tubocurarine chloride):

The effect of these agents may be potentiated by hydrochlorothiazide.

Trimethoprim:

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

Sotalol:

Thiazide induced hypokalaemia can increase the risk of sotalol induced arrhythmia.

Allopurinol:

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

Cyclosporine:

Concomitant administration of ACE inhibitors and cyclosporine increases the risk of renal damage and hyperkalaemia.

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 leucopenia (see section 4.4).

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 contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4)

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. 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 also 5.3). Should exposure to ACE inhibitors 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 also 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.

Lactation

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 breastfeeding 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 affects 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 (≥ 1/1000 to < 1/100)
- Rare (≥ 1/10.000 to < 1/1000)
- Very rare (< 10.000)
- Not known (cannot be estimated from the available data).

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

Lisinopril:

Blood and the lymphatic system disorders:
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Rare	Decreases in haemoglobin, decreases in haematocrit.
Very rare	Bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease
Metabolism and nutrition disorders:	
Very rare	Hypoglycaemia
Nervous system disorders and psychiatric disorders	
Common	Dizziness, headache, syncope
Uncommon	Paraesthesia, vertigo, taste disturbance, sleep disturbances, mood alterations
Rare	Mental confusion
Frequency unknown	Depressive symptoms
Cardiac and vascular disorders	
Common	Orthostatic effects (including orthostatic hypotension)
Uncommon	Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia, Raynaud's syndrome
Unknown	
	Flushing
Respiratory, thoracic and mediastinal disorders	
Common	Cough (see section 4.4)
Uncommon	Rhinitis
Very rare	Bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia
Gastrointestinal disorders	
Common	Diarrhoea, vomiting
Uncommon	Nausea, abdominal pain and indigestion
Rare	Dry mouth
Very rare	Pancreatitis, instestinal angioedema
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes and bilirubin
Very rare	Hepatitis – either hepatocellular or cholestatic, jaundice, hepatic failure (see section 4.4). *

Skin and subcutaneous tissue disorders	
Uncommon	Rash, pruritus
Rare	Hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis
Very rare	Diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma. **
Renal and urinary disorders	
Common	Renal dysfunction
Rare	Uraemia, acute renal failure
Very rare	Oliguria/anuria
Reproductive system and breast disorders	
Uncommon	Impotence
Rare	Gynaecomastia
Endocrine Disorders	
Rare	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue
Investigations	
Uncommon	Increases in blood urea, increases in serum creatinine, hyperkalaemia
Rare	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 (frequencies unknown):

Infections and infestations	Sialadenitis
Blood and lymphatic system disorders	Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloremic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout

Psychiatric disorders	Restlessness, depression, sleep disturbance
Nervous system disorders	Loss of appetite, paraesthesia, light-headedness
Eye disorders	Xanthopsia, transient blurred vision
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Postural hypotension
Vascular disorders	Necrotising angiitis (vasculitis, cutaneous vasculitis).
Respiratory, thoracic and mediastinal disorders	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders	Gastric irritation, diarrhoea, constipation, pancreatitis.
Hepatobiliary disorders	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis
Musculo-skeletal, connective tissue and bone disorders	Muscle spasm, muscle weakness
Renal and urinary disorders	Renal dysfunction, interstitial nephritis
General disorders	Fever, weakness

4.9 Overdose

No specific information is available regarding overdose with Lispril-Hydrochlorothiazide. 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 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 agent. 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.

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 administered 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 Hydrogen Phosphate Dihydrate
Croscarmellose Sodium
Mannitol
Maize Starch
Magnesium Stearate
Red Ferric Oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD

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

May 2016