Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lisinopril/Hydrochlorothiazide 20 mg/12.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of lisinopril (as dihydrate) and 12.5 mg of hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

A white, 10.5 mm, round, biconvex, bevelled edge tablet debossed with LH2 over M on one side of the tablet and a score line on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Essential Hypertension

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

The recommended dose is one tablet administered once daily. As with other medicines that are taken once daily, Lisinopril/Hydrochlorothiazide should be taken at about the same time each day.

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.

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.

Renal Insufficiency

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 (i.e. moderate or severe renal insufficiency).

Lisinopril and hydrochlorothiazide combination is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80 ml/min, lisinopril and hydrochlorothiazide combination may be used, but only after titration of the individual components. The recommended dose of lisinopril, when used alone, in mild renal insufficiency, is 5 to 10 mg.

Prior Diuretic Therapy

Symptomatic hypotension may occur following the initial dose of lisinopril and hydrochlorothiazide combination; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with lisinopril and hydrochlorothiazide combination. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

Older People

No adjustment of dosage is required in the older people.

In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both older and younger hypertensive patients.

Lisinopril, within a daily dosage range of 20 to 80 mg, was equally effective in the older (65 years or over) and younger hypersensitive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

Paediatric Population

Safety and efficacy of Lisinopril/Hydrochlorothiazide in children has not been established.

4.3 Contraindications

- Hypersensitivity to lisinopril, to any of the excipients listed in section 6.1 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 Lisinopril/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).

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.

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.

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) 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 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. ACE inhibitor andthiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. 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 hypochloremic 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, co-trimoxazole also known as trimethoprim/sulfamethoxazole). 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).

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)
Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (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.

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).

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).

4.5 Interaction with other medicinal products and other forms of interaction

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
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).

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 antiarrhythmics, some anti-psychotics and other drugs 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, acetylsalicylic acid >3 g/day and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of an ACE inhibitors and thiazide diuretics. NSAIDs and ACE inhibitors may exert an additive effect on the increase in serum potassium and may result in a 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.

Other antihypertensives
Concomitant use of these agents 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 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 leucopoenia.

Ciclosporin
Concomitant administration of ACE inhibitors and ciclosporin 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).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)
Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Co-trimoxazole (trimethoprim/sulfamethoxazole)
Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Other concomitant therapy
Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.

Alcohol
When used with alcohol, 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 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 inhibitors 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.

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 section 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.

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.

Hydrochlorthiazide:

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 (≥10%), common (≥1%,<10%), uncommon (≥0.1%, <1%), rare (≥0.01%, <0.1%), very rare (<0.01%), 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 lymphatic system disorders:	
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.
Endocrine disorders	
Rare	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
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, depressive symptoms.
Rare	Olfactory disturbance, mental confusion.
Frequency unknown	Hallucinations.
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.
Frequency 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, intestinal angioedema.
Hepato-biliary disorders	
Uncommon	Elevated liver enzymes and bilirubin.
Very rare	Hepatitis - either hepatocellular or cholestatic, jaundice and 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.
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 elevation 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, acute myopia and acute angle-closure glaucoma.
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, systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis.
Musculo-skeletaland connective tissue disorders	Muscle spasm, muscle weakness.
Renal and urinary disorders	Renal dysfunction, interstitial nephritits.
General disorders and administration site conditions	Fever, weakness.

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,
Earlsfort Terrace,
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail:medsafety@hpra.ie.

4.9 Overdose

Limited data are available for overdose in humans. Symptoms associated with overdosage 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 normal saline 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 (incl. 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: ACE inhibitor (ACE: angiotensin converting enzyme) and thiazide diuretic, ATC-code: C09B A03

This is a fixed dose combination product containing lisinopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.

Lisinopril
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 by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease 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 antihypertensive even in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Clinical safety and efficacy
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
Hydrochlorothiazide is a diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides do not usually affect normal blood pressure.

5.2 Pharmacokinetic properties

Concomitant administration of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

Lisinopril

Absorption

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure.

Lisinopril absorption is not affected by the presence of food.

Distribution

Lisinopril does not appear to bind to other serum proteins other than to circulating angiotensin-converting enzyme (ACE).

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine.

On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/min. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30% as determined by urinary recovery) but an increase in exposure (approximately 50%) compared to healthy subjects due to

decreased clearance.

Renal impairment

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min.

Table 1 Pharmacokinetic parameters of lisinopril to different groups of renal patients after administration of a multiple 5 mg dose

Renal Function Measured by creatinine clearance	**n**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUC (0-24 hrs) (ng/hr/ml)**	**$t_{1/2}$ (hr)**
>80 ml/min	6	40.3	6	492+/-172	6.0+/-1.1
30-80 ml/min	6	36.6	8	555+/-364	11.8+/-1.9
5-30 ml/min	6	106.7	8	2228+/-938	19.5+/-5.2

With a creatinine clearance of 30-80ml/min, mean AUC was increased by 13% only, while a 4-5 fold increase in mean AUC was observed with creatinine clearance of 5-30ml/min.

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

Heart Failure

Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16% compared to healthy subjects.

Older People

Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) than younger patients.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

5.3 Preclinical safety data

Lisinopril and hydrochlorothiazide are both drugs on which extensive clinical experience has been obtained, both separately and in combination. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains:

Silica, colloidal anhydrous

Magnesium stearate

Sodium laurilsulfate

Cellulose, microcrystalline (E460)

Starch, pregelatinized

Calcium hydrogen phosphate dihydrate

Mannitol (E421)

Croscarmellose sodium

Povidone (K29/32)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blisters packs:
3 years

Bottle packs:
As packaged for sale: 3 years
After first opening: 30 days

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Alu/Alu (cold form) blister: 10, 14, 28, 30, 50, 56, 84, 90 & 100
Alu/Alu (cold form) perforated unit dose blisters: 100 x 1 tablets
PVC/PVdC/Alu blister: 10, 14, 28, 30, 50, 56, 84, 90 & 100
PVC/PVdC/Alu perforated unit dose blisters: 100 x 1 tablets
HDPE bottle: 500

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Mc Dermott Laboratories Limited t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/165/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th July 2012

10 DATE OF REVISION OF THE TEXT

May 2017