

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Zesger Plus 20 mg/12.5 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

Zesger Plus 20 mg/12.5 mg Tablets are pink, round tablets marked LHZ on one side and 32.5 on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Treatment of essential hypertension.

Zesger Plus 20 mg/12.5 mg fixed dose combination (lisinopril (as dihydrate) 20 mg and hydrochlorothiazide 12.5 mg) 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/ hydrochlorothiazide will depend upon the clinical evaluation of the patient.

The usual dose is one tablet administered once daily.

The administration of a fixed combination lisinopril/ 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.

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

In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at lisinopril/hydrochlorothiazide 20 mg/12.5 mg, the dose can be increased to two tablets administered once daily.

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

#### Renal impairment

The combination of lisinopril/hydrochlorothiazide is contraindicated in patients with severe 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 (i.e. moderate or severe renal insufficiency).

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

Zesger Plus may be used in patients with creatinine clearance >30 and <80 ml/min, but only after titration of the individual components.

The recommended initial dose of lisinopril as monotherapy for these patients is 5-10 mg.

#### Previous diuretic treatment

Symptomatic hypotension may occur after the initial dose of lisinopril/hydrochlorothiazide; this occurs more often in patients that are volume and/or salt depleted as a result of previous treatment with diuretics.

The diuretic should be discontinued 2 to 3 days before the start of treatment with lisinopril/hydrochlorothiazide. If this is not possible, treatment should be started at a dose of 2.5 mg lisinopril alone.

#### Elderly

Clinical studies on the combination of lisinopril/hydrochlorothiazide have not shown that age is associated with any changes in efficacy or tolerability (see [Renal Impairment]).

#### Paediatric population

The safety and efficacy of lisinopril/hydrochlorothiazide in children has not been established.

#### Method of administration

For oral use.

As with other medicines that are taken once daily, Zesger Plus 20 mg/12.5 mg tablets should be taken at about the same time each day.

### **4.3 Contraindications**

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Hypersensitivity to any other angiotensin converting enzyme (ACE) inhibitor
- Hypersensitivity to any other sulfonamide-derived drugs
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Severe renal impairment (creatinine clearance <30ml/min)
- Severe hepatic impairment
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- The concomitant use of Lisinopril and Hydrochlorothiazide 20 mg/12.5 mg tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m<sup>2</sup>) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Lisinopril and hydrochlorothiazide must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see section 4.4 and 4.5)
- Anuria

### **4.4 Special warnings and precautions for use**

#### Renal transplantation

Lisinopril/hydrochlorothiazide 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 sulfate) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or 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 lipoproteins (LDL) apheresis with dextran sulfate have shown life-threatening anaphylactoid reactions. These symptoms can be avoided by temporary discontinuation of the treatment with ACE inhibitors before each apheresis.

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. Photosensitising 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).

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 have reappeared upon inadvertent rechallenge.

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-blacks, 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.

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.

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

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, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole, heparin and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalaemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5). Regular monitoring of serum potassium is also recommended if concomitant use of potassium supplements (including salt substitutes), heparin, aldosterone antagonists, trimethoprim or cotrimoxazole is deemed appropriate.

Hypokalaemia

Although hypokalaemia may develop through the use of thiazide diuretics, concomitant use of lisinopril may decrease diuretic-induced hypokalaemia. Regular checks of serum potassium should take place.

The possibility of hypokalaemia is strongest in patients with cirrhosis of the liver, in patients experiencing rapid diuresis, in patients having an inadequate oral intake of electrolytes and in patients concomitantly treated with corticosteroids or ACTH (see section 4.5).

#### Lithium

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

#### Metabolic and endocrine effects

##### *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. Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

##### *Cholesterol and triglycerides*

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

##### *Hyperuricaemia*

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.

#### Anti-doping test

The hydrochlorothiazide contained in this medication could produce a positive analytic result in anti-doping tests.

#### 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 normal saline. A transient hypotensive response is not a contraindication for future 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 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/minute) 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.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea levels and serum creatinine levels when lisinopril was 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.

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.

In patients with renal diseases, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the medication may occur. If a progressive renal insufficiency develops, characterized by an increase in non-protein nitrogen, careful evaluation of the therapy is necessary, and stopping the diuretics therapy should be considered (see section 4.4).

#### 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 2.5 mg dose (see section 4.2).

#### Neutropenia/agranulocytosis

The fixed-dose combination of lisinopril/hydrochlorothiazide should be withdrawn if neutropenia (neutrophils less than 1000/mm<sup>3</sup>) is detected or suspected.

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in 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.

#### 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 lisinopril and hydrochlorothiazide. Treatment with lisinopril and 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.

In patient 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.

#### 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.

#### 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 interactions**

The following interactions between lisinopril/hydrochlorothiazide, other ACE-inhibitors or products containing hydrochlorothiazide have been reported.

#### ***Lisinopril***

##### Diuretics

When a diuretic is added to the therapy of a patient receiving lisinopril the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when lisinopril is added. The possibility of symptomatic hypotension with lisinopril can be minimised by discontinuing the diuretic prior to initiation of treatment with lisinopril (see sections 4.2 and 4.4).

##### Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

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

##### Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid

Chronic administration of NSAIDs (including selective cyclooxygenase-2 inhibitors, acetylsalicylic acid > 3g/day and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of 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.

#### Other antihypertensives

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

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).

#### 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).

#### 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; patients must be monitored carefully. Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

#### Antidiabetics

Treatment with a thiazide diuretic may impair glucose tolerance. This phenomenon appeared to be more likely to occur during the first weeks of combination treatment and in patients with renal impairment. Other antidiabetic drugs including insulin requirements in diabetic patients may be increased, decreased or unchanged.

The hyperglycaemic effect of diazoxide may be enhanced by thiazides.

#### Nitrates, acetylsalicylic acid, thrombolytics and/or beta blockers

Lisinopril may be used concomitantly with acetylsalicylic acid (cardiologic doses), thrombolytics, beta blockers and/or nitrates.

#### Allopurinol

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

#### Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended. Concomitant administration of ACE inhibitors and ciclosporin increases the risk of renal damage. 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.

#### Haemodialysis

Lisinopril/hydrochlorothiazide is not indicated in patients requiring dialysis as a high incidence of anaphylactoid reactions have been reported in patients dialysed with high flux membranes and treated concomitantly with an ACE inhibitor. This combination should be avoided (see section 4.4).

Procainamide, cytostatics or immunosuppressives

Concomitant administration with ACE inhibitors can lead to an increased risk of leucopenia (see section 4.4).

Medicines 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 racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (see section 4.4).

Tissue plasminogen activators (tPA's)

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

Thiazides may increase the risk of adverse effects caused by amantadine.

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.

***Hydrochlorothiazide***

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by drugs 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 adrenocorticotrophic hormone (ACTH).

Calcium salts

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored and the dose adjusted accordingly.

Cardiac glycosides

Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Colestyramine and colestipol

The absorption of hydrochlorothiazide is reduced by colestipol or colestyramine. Therefore, sulfonamide diuretics should be taken at least one hour before or four to six hours after intake of these agents.

Non-depolarising muscle relaxants

Thiazides may increase the responsiveness to non-depolarising skeletal muscle relaxants (e.g. tubocurarine).

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.

Sotalol

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

***Lisinopril/hydrochlorothiazide***

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/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).

#### Trimethoprim

Concomitant administration of ACE inhibitors and thiazides with trimethoprim increases the risk of hyperkalaemia as trimethoprim is known to act as a potassium-sparing diuretic like amiloride.

#### Alcohol

The ability to drive and use machines may be reduced when used in combination with alcohol.

### **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 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 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. Exposure to ACE inhibitor therapy 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.

Prolonged use of hydrochlorothiazide during the third trimester may cause fetoplacental ischemia and risk of growth retardation. Following exposure near to term rare cases of neonatal hypoglycaemia and thrombocytopenia have been observed.

Hydrochlorothiazide may reduce plasma volume as well as uteroplacental blood flow.

#### Breast-feeding

##### *ACE-inhibitors:*

Because no information is available regarding the use of lisinopril/hydrochlorothiazide during breastfeeding, Zesger Plus Tablets are 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 Zesger Plus Tablets are 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 ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data) including isolated reports.

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

##### Immune system disorders

Not known: anaphylactic/anaphylactoid reaction

##### Endocrine disorders

Rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

##### Metabolism and nutrition disorders

Uncommon: gout

Very rare: hypoglycaemia

##### Psychiatric disorders

Uncommon: sleep disturbance, mood alterations, depressive symptoms

Rare: mental confusion

Not known: hallucinations

##### Nervous system disorders

Common: dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy; headache, syncope

Uncommon: paraesthesia, vertigo, taste disturbances

Rare: olfactory disturbance

##### Cardiac disorders

Uncommon: palpitation, tachycardia

#### Vascular disorders

Common: orthostatic effects (including orthostatic hypotension)

Uncommon: myocardial infarction or cerebrovascular accident, possible secondary to excessive hypotension in high risk patients (see section 4.4), Raynaud's syndrome

Not known: flushing

#### Respiratory, thoracic and mediastinal disorders

Common: dry and persistent cough (see section 4.4), which disappears after discontinuation of therapy

Uncommon: rhinitis

Very rare: bronchospasm, sinusitis, allergic, alveolitis/eosinophilic pneumonia

#### Gastrointestinal disorders

Common: diarrhoea, vomiting

Uncommon: nausea, indigestion, pancreatitis, abdominal pain, dry mouth

Very rare: intestinal 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\*\*

#### Musculoskeletal and connective tissue disorders

Uncommon: muscle spasms and muscle weakness

#### 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, chest pain

#### Investigations

Uncommon: increases in blood urea, increases in serum creatinine, hyperkalaemia

Rare: hyponatraemia

### **Findings in laboratory tests**

Changes in laboratory values have rarely been of clinical significance. Hyperglycaemia, hyperuricaemia and hyperkalaemia or hypokalaemia are seen occasionally. Mild and temporary increases in blood nitrogen urea and serum creatinine are usually seen in patients without pre-existing kidney failure. If such increases are persistent, they generally disappear when treatment is discontinued.

Bone marrow depression, manifested as anaemia and/or thrombocytopenia and/or leucopenia, has been reported.

Agranulocytosis is reported rarely, although a causal connection has not been established.

A small fall in haemoglobin and haematocrit is often reported in hypertensive patients treated with

lisinopril/hydrochlorothiazide, but it was rarely of clinical significance unless another cause of anaemia existed simultaneously.

An increase in liver enzymes and/or serum bilirubin is rarely seen, but a causal connection with lisinopril/hydrochlorothiazide has not been established. Haemolytic anaemia has been rarely reported.

\* 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 not known):***

Infections and infestations: sialadenitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)\*\*\*

Blood and lymphatic system disorders: leucopenia, 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, cardiac arrhythmias

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

Hepato-biliary 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

Musculoskeletal and connective tissue disorders: muscle spasm, muscle weakness

Renal and urinary disorders: renal dysfunction, interstitial nephritis

General disorders and administration site conditions: fever, weakness

\*\*\* 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](http://www.hpra.ie).

## 4.9 Overdose

### **Symptoms**

Lisinopril: 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.

Hydrochlorothiazide: the most common signs and symptoms are those that are due to electrolyte reduction (hypokalaemia, hyponatraemia, hypochloraemia) and dehydration due to significant diuresis.

Additional symptoms hydrochlorothiazide overdose are increased diuresis, depression of consciousness (incl. coma), convulsions, paresis, cardiac arrhythmias and renal failure. If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

### **Management**

No specific information is available on the treatment of overdose of lisinopril/hydrochlorothiazide. Treatment is symptomatic and supportive. Treatment with Lisinopril and Hydrochlorothiazide 20 mg/12.5 mg tablets should be discontinued and the patient should be monitored very closely. Therapeutic measures depend on the nature and the severity of the symptoms. Measures should be instituted to prevent absorption and to promote elimination. The recommended measures include inducing vomiting and/or gastric lavage if the drug was ingested recently, while dehydration, disturbances of the electrolyte balance and hypotension should be treated in the usual manner.

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 sulfate).

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.

Bradycardia or extensive vagal reactions should be treated by administering atropine.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and diuretics, lisinopril and diuretics, ATC code: C09B A03

Both components, lisinopril, the ACE inhibitor and hydrochlorothiazide, a diuretic, have complementary modes of action and exert an additive antihypertensive effect.

#### **Lisinopril**

##### Mechanism of action

Lisinopril is a peptidyl dipeptidase inhibitor and inhibits angiotensin converting enzyme (ACE). ACE catalyses the conversion of angiotension I to angiotension II, which has a strong vasoconstrictor effect and stimulates aldosterone secretion. Inhibition of ACE results in decreased concentrations of angiotension II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

##### Pharmacodynamic effects

The antihypertensive effect of lisinopril is mainly due to the suppression of the renin angiotensin-aldosterone system with reduction of plasma concentration of angiotension II (resulting in decreased vasopressor activity) and aldosterone. Lisinopril exerts an antihypertensive effect even in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. It remains unclear whether increased levels of bradykinin (a potent vasodilator) plays a role in the therapeutic effect of lisinopril.

Concomitant administration of lisinopril and hydrochlorothiazide gives a greater reduction in blood pressure than monotherapy. Lisinopril normally attenuates the potassium loss associated with hydrochlorothiazide.

The effects of the fixed dose combination of lisinopril/hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

#### Clinical efficacy and safety

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**

#### Mechanism of action

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive that increase the plasma-renin activity. Hydrochlorothiazide suppresses the renal reabsorption of electrolytes in the renal distal tubule and increases the excretion of sodium, chloride, potassium, magnesium, bicarbonates and water. The excretion of calcium may be reduced.

#### Pharmacodynamic effect

Thiazides do not usually affect normal blood pressure.

#### Clinical efficacy and safety

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 ( $\geq 50,000$  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 ( $\sim 25,000$  mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ( $\sim 100,000$  mg) (see also section 4.4).

## **5.2 Pharmacokinetic properties**

The combined tablet is bio-equivalent to monotherapy with each of the active ingredients.

#### Absorption

Lisinopril: Approx 25%, with an interindividual variability of 6-60% on all the tested dosages (5-80 mg). The absorption of lisinopril is not affected by food. Peak serum concentrations are reached within 6-8 hours. Effect on blood pressure was observed after 1-2 hours. The peak effect is obtained after 6 hours and lasts for at least 24 hours.

Hydrochlorothiazide: The diuretic effect is observed within 2 hours. The maximum effect is attained after 4 hours. Clinically noticeable effect will last 6-12 hours.

#### Distribution

Protein binding: Lisinopril is not bound to plasma proteins except to ACE. A reduced distribution volume may result in higher plasma concentrations in older patients than in younger patients.

#### Half-life

Lisinopril: after multiple dosing 12 hours. Hydrochlorothiazide 5½ - 15 hours.

#### Metabolism/elimination

Both active components are excreted unchanged via the kidneys. Approx. 60% of the orally administered hydrochlorothiazide is eliminated within 24 hours.

### **5.3 Preclinical safety data**

Preclinical safety data show no particular risk to humans on the basis of traditional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and toxicity in connection with reproduction.

In animal tests angiotensin converting enzyme inhibitors induce adverse effects 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 fetal renin-angiotensin system and partly due to the ischemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus (see section 4.6).

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Calcium hydrogen phosphate dihydrate  
Mannitol  
Maize starch  
Pregelatinized starch  
Magnesium stearate  
Iron oxide red (E172)

### **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**

PVC/aluminium blister: 10, 14, 28, 30, 50, 56, and 100 tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

No special requirements for disposal.

**7 MARKETING AUTHORISATION HOLDER**

McDermott Laboratories Ltd., T/A Gerard Laboratories  
35/36 Baldoyle Industrial Estate  
Grange Road  
Dublin 13  
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA0577/055/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 11<sup>th</sup> February 2005  
Date of last renewal: 9<sup>th</sup> December 2008

**10 DATE OF REVISION OF THE TEXT**

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