SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lisinopril and Hydrochlorothiazide 10 mg/12.5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lisinopril dihydrate 10.89 mg equivalent to lisinopril anhydrous 10 mg
Hydrochlorothiazide 12.5 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White oval shaped, slightly arched tablets, debossed “LZ 10” on one side and breakline on the other.

The score line is only there to help you break the tablet if you have difficulty swallowing it whole.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Lisinopril/hydrochlorothiazide fixed dose combination (10 mg lisinopril and 12.5 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on lisinopril alone (or hydrochlorothiazide alone).

4.2 Posology and method of administration

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

Lisinopril/hydrochlorothiazide should be taken once daily.

The administration of the fixed combination lisinopril and hydrochlorothiazide is usually recommended after dosage titration with the individual components. When clinically appropriate, a direct change from monotherapy to fixed combination may be considered.

10 mg/12.5 mg tablets may be administrated in patients whose blood pressure is not adequately controlled by 10 or 20 mg lisinopril alone.

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

Diuretic Pretreatment
The diuretic therapy should be stopped two to three days prior to the start of a treatment with lisinopril/hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 2.5 mg dose.

Renal impairment
The combination lisinopril/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). In patients with creatinine clearance between 30 and 80 ml/min it may be used only after titration of the individual components.

The recommended initial dose of lisinopril as monotherapy for these patients is 5-10 mg (see 4.4).

Elderly patients
Clinical studies on the combination of lisinopril and hydrochlorothiazide have not shown that age is associated with any changes in efficacy or tolerability. See the above section on "Renal impairment".

Children and adolescents (<18years)
Safety and efficacy of lisinopril/hydrochlorothiazide have not been established in children.

4.3 Contraindications

- History of hypersensitivity to lisinopril or to any of the excipients listed in section 6.1 or any other ACE-inhibitors
- History of hypersensitivity to hydrochlorothiazide or other sulphonamide medicinal products
- History of angioneurotic oedema relating to previous ACE-inhibitor therapy
- Hereditaryor idiopathic angioneurotic oedema.
- Severe renal insufficiency (creatinine clearance <30 ml/min)
- Severe hepatic impairment
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of Lisinopril and Hydrochlorothiazide 10 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^2) (see sections 4.5 and 5.1)

4.4 Special warnings and precautions for use

<u>Lisinopril</u>

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving lisinopril, hypotension 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 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or a 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 to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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 may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal function impairment See 4.2

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 with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal 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, they should be discontinued and renal function should be monitored during the first weeks of lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially 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.

Patients with renal transplantation

As there is no experience with lisinopril in patients with recent renal transplantation administration of lisinopril is not recommended in these patients.

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely 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 patients. 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.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Anaphylactoid reactions in haemodialysis patients
Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g with high flux membranes (e.g. 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 different class of antihypertensive agent.

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

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 re-administration of the medicinal product.

Hepatic failure
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 who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril and receive appropriate medical follow-up.

Neutropenia/agranulocytosis
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.

Race
ACE 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.

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

Lithium
The combination of lithium and lisinopril is generally not recommended (see 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

Hydrochlorothiazide
Impaired renal function
In patients with renal diseases, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the medicinal products may occur. If 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 4.3).

Impaired liver function
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 induce hepatic coma (see 4.3).

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustments of antidiabetic agents or insulin may be required. . Latent diabetic mellitus may become manifest during thiazide therapy. Increases of cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients

Electrolyte imbalances
As for any patient treated with diuretics, periodic determination of serum electrolytes at appropriate intervals should be performed.

Thiazides, including hydrochlorothiazide, may cause fluid or electrolyte imbalances (hypokalaemia, hyponatraemia and hypochloremic alkalosis). Warning signals of fluid or electrolyte imbalances are dryness mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, musclar fatigue, hypotension, oliguria, tachycardia and gastrointestinal disorders such as nausea and vomiting.

Although hypokalaemia may develop through the use of thiazide diuretics, concomitant use of lisinopril may decrease diuretic-induced hypokalaemia. The possibility of hypokalaemia is strongest in liver cirrhosis patients, in patients experiencing rapid diuresis, in patients having an inadequate oral intake of electrolytes and in patients concomitantly treated with corticosteroids or ACTH (see 4.5).

Dilutional hyponatraemia may occur in oedematous patients in hot weather Chloride deficiency is generally mild and does not need treatment.

Thiazides may decrease urinary calcium excretion and may cause a slight elevation of serum calcium levels even in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be a evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out parathyroid function tests. Thiazides have been shown to increase renal magnesium excretion, which may result in hypomagnesemia.

Anti-doping test
The hydrochlorothiazide contained in this medication could produce a positive analysis result in an anti-doping tests.

Other
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.

.

Lisinopril/hydrochlorothiazide
Hypotension and electrolyte/fluid imbalances
Symptomatic hypotension may sometimes occur following the first dose of lisinopril / hydrochlorothiazide. The odds for hypotension in hypertensive patients are greater in the presence of fluid or electrolyte imbalances, such as volume depletion, hyponatraemia, hypochloremic alkalosis, hypomagnesemia or hypokalaemia, that may occur as a result of a diuretic therapy, a low-sodium diet, dialysis or during intercurrent diarrhoea or vomiting. In such patients the serum electrolyte levels must be monitored on a regular basis. Starting the therapy and adjusting the dosage for patients who are at increased risk for symptomatic hypotension must be done under strict medical supervision.

Special attention should be given to the treatment of patients suffering from ischaemic heart disease or cerebrovascular conditions, because an excessive drop in blood pressure may trigger a myocardial infarction or cerebrovascular accident.

If severe hypotension occurs, the patient must be put into the shock position and promptly administered an intravenous infusion of a physiological saline solution. A transient hypotensive reaction is not a contraindication for future doses. If the blood volume and blood pressure have effectively been restored, therapy may likely be resumed with a lower dosage or may very well be continued simply with one of both components.

As with other vasodilators, caution must be exercised when administering lisinopril / hydrochlorothiazide to patients suffering from aortic stenosis or hypertrophic cardiomyopathy.

Impaired renal function
Thiazides are ineffective in patients with a creatinine clearance of less than 30 ml/min (i.e. a moderate or serious renal insufficiency). (see 4.3).

Lisinopril/hydrochlorthiazide should not be given to patients with a creatinine clearance of 30-80 ml/minute until dose adjustments of the separate ingredients have shown that there is a need for the doses in the combination preparation.

Some patients without a definite pre-existing renovascular disorder developed slight and transitory increases in blood urea levels and serum creatinine levels when lisinopril was given concomitantly with a diuretic. If this occurs during the use of lisinopril/ hydrochlorothiazide, the treatment should be stopped. Resuming the treatment at a reduced dosage may be possible, if appropriate, one of the components may be used on its own.

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.

Risk of hypokalaemia
The combination of an ACE-inhibitor with a thiazide does not exclude the occurrence of hypokalaemia. Regular checks of potassium should take place.

Neutropenia/agranulocytosis
The fixed-dose combination of lisinopril and hydrochlorothiazide should be withdrawn if neutropenia (neutrophils less than 1000/mm3) is detected or suspected.

4.5 Interaction with other medicinal products and other forms of interaction

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

Lisinopril
Dual blockade of the renin-angiotensin-aldosterone system
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).

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 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid = 3g/day
Chronic administration of NSAIDs (including selective cyclooxygenase-2 inhibitors) may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors may exert an additive effect on the 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.

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

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

Sympathomimetics
Sympathomimetics may reduce the hypotensive effect of ACE-inhibitors; patients must be monitored carefully.

Antidiabetics
Epidemiological studies have suggested 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 combined treatment and in patients with renal impairment.

Nitrates, acetylsalicylic acid, thrombolytics and/or beta blockers

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

Allopurinol

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

Ciclosporin

Concomitant administration of ACE inhibitors and ciclosporin increases the risk of renal failure and hyperkalaemia.

Lovastatin

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

Procainamide, cytostatics, immunosuppressive

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

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.

Hydrochlorothiazide

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropine (ACTH) or stimulating laxatives

Hydrochlorothiazide may cause electrolyte imbalances, especially hypokalaemia.

Calcium salts

Increased serum calcium levels as a result of decreased excretion may occur if concomitantly administered with thiazide diuretics.

Cardiac glycosides

There is increased risk of digitalis intoxication together with thiazide induced hypokalaemia.

Cholestyramine resin and colestipol

These may delay or reduce the 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 (i.e. tubocurarine chloride)

The effect of these medications may be potentiated by hydrochlorothiazide.

Ttorsades 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 antiarrhyttmias, some antipsychotics and other medications which are 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

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

Although in clinical trials with ACE inhibitors serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If lisinopril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see 4.4).

Trimethoprim

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

4.6 Fertility, pregnancy and lactation

Pregnancy

ACE-inhibitors:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

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.

Breast- feeding

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

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

4.7 Effects on ability to drive and use machines

As with other antihypertensives, the ability to drive and use machines may be reduced, e.g. at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.
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 Hydrochlorothiazide 20mg/12.5mg tablets with the following frequencies: very common (>1/10), common (>1/100:<1/10), uncommon (>1/1000,<1/100), rare (>1/10000;<1/1000), very rare (<1/10000) 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.

Metabolism and nutrition disorders
Uncommon: gout

Nervous system and psychiatric disorders
Common: dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy; headache, fatigue.
Uncommon: paraesthesia, asthenia

Respiratory, thoracic and mediastinal disorder
Common: dry and persistent cough, which disappears after discontinuation of therapy.

Cardiac and vascular disorders
Common: hypotension including orthostatic hypotension.
Uncommon: palpitation, chest pain, muscle spasms and muscle weakness

Gastrointestinal disorders:
Uncommon: diarrhoea, nausea, vomiting, indigestion, pancreatitis, dry mouth.

Skin and subcutaneous tissue disorders
Uncommon: rash.
Rare: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see section 4.4).

Reproductive system and genitals and breast disorders
Uncommon: impotence.

Others
Rare: a complex of symptoms, consisting of one or more of the following: fever, vasculitis, myalgia, artralgia or arthritis, positive ANA test; increased ESR, eosinophilia, leukocytosis, rash, photosensibility or other dermatologic manifestations.

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 and Hydrochlorothiazide 10mg/12.5mg and 20mg/12.5mg tablets, 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 and Hydrochlorothiazide 10mg/12.5mg and 20mg/12.5mg tablets has not been established. Haemolytic anaemia has been rarely reported.

Undesirable effects reported of the individual components:

Hydrochlorothiazide:
Infections and infestations: silaldenitis

Blood and lymphatic system disorders: leucopenia,
neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow suppression.

Metabolism and nutrition disorders: anorexia, hyperglycaemia, glucosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloremic alkalosis and hypomagnesaemia),, increases in cholesterol and triglycerides.

Psychiatric disorders: restlessness, depression, sleep disturbance

Nervous system disorders: loss of appetite, paraesthesia, light-headedness

Eye disorders: xanthopsia, transient blurred vision

Ear and labyrinth disorders: vertigo

Cardiac disorders: postural hypotension, cardiac arrhythmias

Vascular disorders: necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders: respiratory distress (including pneumonitis and pulmonatory oedema)

Gastrointestinal disorders: gastric irritation, diarrhoea, constipation, pancreatitis

Hepato-biliary disorders: jaundice (intrahepatic cholstatic jaundice)

Skin and subcutaneous disorders: photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders: muscle spasm

Renal and urinary disorders: renal dysfunction, interstital nephritis
General disorders: fever, weakness

Lisinopril and other ACE inhibitors:

Blood and the lymphatic system disorders:
Rare: decreases in haemoglobin, decreases in haematocrit.
Very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see [Special warnings and precautions for use]), haemolytic anaemia, lymphadenopathy, autoimmune disease

Metabolism and nutrition disorders
Very rare: hypoglycaemia

Nervous system and psychiatric disorders:
Common: dizziness, headache
Uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
Rare: mental confusion
Not known: depressive symptoms

Cardiac and vascular disorders:
Common: orthostatic effects (including hypotension)

uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon
Not known: flushing

Respiratory, thoracic and mediastinal disorders:
Common: cough
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, hepatitis- either hepatocellular or cholestatic, jaundice and hepatic failure (see 4.4)

Hepatobiliary disorders:
Uncommon: elevated liver enzymes and bilirubin
Very rare: hepatitis – either hepatocellular or cholestatic, jaundice, hepatic failure (see section 4.4)

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

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 4.4), urticaria, alopecia, psoriasis
Very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme , cutaneous pseudolymphoma. .

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

Renal and urinary disorders:
Common: renal dysfunction
Rare: uraemia, acute renal failure
Very rare: oliguria/anuria

Reproductive system and breast disorders:
Uncommon: impotence
Rare: gynaecomastia

Endocrine disorders:
Rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

General disorders and administration site conditions:

Uncommon: fatigue, asthenia

Investigations:
Uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
Rare: increases in serum bilirubin, hyponatraemia.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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.

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock 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 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

Hydrochlorothiazide
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 given, hypokalaemia may accentuate arrhythmia.

There is no specific information available on the treatment of a lisinopril/hydrochlorothiazide overdose. The treatment is symptomatic and supportive. Use of the medicinal product must immediately be discontinued and the patient should be observed closely. Therapeutic measures depend on the nature and severity of the symptoms. Measures should be taken to prevent absorption and accelerate elimination. Dehydration, disturbances of the electrolyte balance and hypotension should be treated in the usual manner. Gastric lavage can be considered if the overdose has been taken very recently, but this must not delay administration of activated charcoal to prevent the absorption. Passage can be speeded up using suitable laxatives such as sodium sulphate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action: Both components, the ACE inhibitor and diuretic, have complementary modes of action and exert an additive antihypertensive effect.

ACE catalyses the conversion of angiotension I to angiotension II, which has a strong vasoconstrictor effect and stimulates aldosterone secretion. The antihypertensive effect of lisinopril is mainly due to the suppression of the renin angiotensin-aldosterone system with reduction of plasma concentration of angiotension II and aldosterone. Lisinopril exerts an antihypertensive effect even in patients with low-renin hypertension. ACE is identical to 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.

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

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

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.

5.2 Pharmacokinetic properties

The combined tablet is bioequivalent 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.

Biotransformation/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 data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenic potential. In animal tests ACE inhibitors induce adverse effects on the late fetal development, resulting in fetal death and congenital effects, in particular affecting the skull. Fetotoxity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to the direct action of ACE inhibitors on the fetal renin-angiotensin system and partly due to the ischaemia resulting from maternal hypotension and decreases in fetal-placental blood flow and oxygen/nutrients delivery to the fetus (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate anhydrous

Magnesium stearate

Pregelatinised starch

Mannitol

Maize starch.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage instructions.

6.5 Nature and contents of container

PVC/PVdC-aluminium blisters, packs of 28, 30, 50, 98 and 100 tablets. Hospital packs 50 (EAV: unit dose hospital pack), 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited

Brampton Road

Hampden Park

Eastbourne

East Sussex

BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0453

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/05/2008

10 DATE OF REVISION OF THE TEXT

29/07/2015