Drugfield **PHARMACEUTICALS LIMITED**

SUMMARY OF PRODUCT CHARACTERISTICS

Kuinopril Plus® Tablet

1. NAME OF THE MEDICINAL PRODUCT

Kuinopril (Lisinopril 10mg + Hydrochlorotiazide 12.5mg) plus tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Lisinopril 10mg as dihydrate and Hydrochlorothiazide 12.5mg
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solid-Tablet

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Lisinopril/ hydrochlorothiazide is indicated in the management of mild to moderate hypertension in patients who have been stabilized on the individual components given in the same proportions.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Primary Hypertension

The usual dosage is one tablet, administered once daily. As with all other medication taken once daily, lisinopril/hydrochlorothiazide should be taken at approximately the same time each day.
In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dose can be increased to two tablets administered once daily.

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 Tablets are not to be used as initial therapy in any patient with renal insufficiency.
In patients with creatinine clearance of >30 and <80 ml/min, Lisinopril/hydrochlorothiazide may be used, but only after titration of the individual components. The recommended dose of lisinopril, when used alone, in mild renal insufficiency, is 5 to 10mg.

Prior Diuretic Therapy

Symptomatic hypotension may occur following the initial dose of lisinopril/ hydrochlorothiazide; this is more likely inpatients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be

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

Elderly
No adjustment of dosage is required in the elderly.
In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both older people and younger hypertensive patients.
Lisinopril, within a daily dosage range of 20 to 80mg, was equally effective in the elderly (65 years or over) and non-elderly hypersensitive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

Paediatric population
Safety and effectiveness in children have not been established

Method of administration
Swallow the tablet with a drink of water

4.3. CONTRAINDICATIONS

- Hypersensitivity to hydrochlorothiazide or other sulphonamide-derived drugs
- History of angioedema associated with previous ACE inhibitor therapy
- Concomitant use of lisinopril & hydrochlorothiazide with sacubitril/valsartan therapy. Lisinopril/ hydrochlorothiazide must not be initiated earlier than 36 hours after the last dose of zsacubitril/valsartan (see sections 4.4 and 4.5).
- Hereditary or idiopathic angioedema
- Severe renal impairment (creatinine clearance <30ml/min)
- Anuria
- Severe hepatic impairment
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- The concomitant use of Lisinopril and hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.
Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of

exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Symptomatic Hypotension

Symptomatic hypotension is seen rarely 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 section 4.5 and section 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. A 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 to further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

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

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

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

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Renal Function Impairment

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

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

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, renal function should be monitored during the first weeks of lisinopril/hydrochlorothiazide therapy.

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

Prior Diuretic Therapy

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

Renal transplantation

Should not be used, since there is no experience with patients recently transplanted with a kidney.

Anaphylactoid reactions in Haemodialytic Patients

The use of lisinopril/hydrochlorothiazide is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients, undergoing certain

haemodialysis procedures (e.g. with the high-flux membranes AN 69 and during low-density lipoproteins (LDL) apheresis with dextran 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 during low-density lipoproteins (LDL) apheresis

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

Hepatic impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see section 4.3). Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving lisinopril/hydrochlorothiazide who develop jaundice or marked elevations of hepatic enzymes should discontinue Lisinopril/hydrochlorothiazide and receive appropriate medical follow-up.

Surgery/Anaesthesia

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

Metabolic and Endocrine Effects

ACE inhibitor and thiazide therapy may impair glucose tolerance. Dosage adjustment of anti-diabetic agents, including insulin, may be required. In diabetic patients treated with oral anti-diabetic agents or insulin, glycaemia levels should be closely monitored during the first month of treatment with an ACE inhibitor. Latent diabetes mellitus may become manifest during thiazide therapy.

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

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

Electrolyte imbalance

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and 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 hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function, diabetes mellitus and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics (e.g.spironolactone, triamterene or amiloride), other drugs associated with increase in serum potassium (e.g. heparin,trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists orangiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, serum potassium and renal function should be monitored (see section 4.5).

Diabetic patients

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

Hypersensitivity/angioedema

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

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

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

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

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

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 &Hydrochlorothiazide. Treatment with Lisinopril & Hydrochlorothiazide must not be initiated earlier than 36 hours after thelast 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)

Patients taking concomitant ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)and vilda liptin may lead to an increased risk for 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.

Desensitisation

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

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported for patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors neutropenia occurs rarely. Neutropenia andagranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious

infections, which in a few instances did not respond to intensive antibiotic therapy. If lisinopril

is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race

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

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

Cough

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

Lithium

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

Anti-doping test

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

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative 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).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

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

Acute Respiratory Toxicity

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERATION

Antihypertensive Agents

When combined with other antihypertensive agents, additive falls in blood pressure may occur. Concomitant use of glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

The combination of lisinopril with aliskiren-containing medicines should be avoided (see section 4.3 and 4.4)

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).

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. temsirolimus, sirolimus, everolimus) and vildagliptin may lead to an increase in the risk of angioedema (see section 4.4).

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

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Diuretics agents and ACE inhibitors reduce the renal clearance of lithium and pose a high risk of lithium toxicity. The combination of Lisinopril and hydrochlorothiazide with lithium is therefore not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section4.4).

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels

The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with lisinopril. Use of 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 a significant increase in serum potassium. Care should also be taken when lisinopril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) astrimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of lisinopril &hydrochlorothiazide with the above-mentioned drugs is not recommended. If concomitant use oflisinopril/hydrochlorothiazide and any of these agents is required, they should be used with caution and with frequent monitoring of serum potassium (see section 4.4).

Torsades de pointes-inducing medicinal products

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

Tricyclic antidepressants/ antipsychotics /anaesthetics

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

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

Chronic administration of NSAIDs (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 exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Gold

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude effectiveness of the press or 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.

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 acidderivatives).

Hypokalemia may develop during concomitant use of steroids or adrenocorticotropic 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

Hypokalemia 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 cholestyramine. Therefore sulphonamide diuretics should be taken at least 1 hour before or 4-6 hours after intake of these agents.

Non-depolarizing muscle relaxants

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

Trimethoprim

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

Sotalol

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

Allopurinol

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

Ciclosporin

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

Monitoring of serum potassium is recommended.

Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin.

Monitoring of serum potassium is recommended.

Lovastatin

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

Cytostatics, immunosuppressives, procainamide

Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) andpotentiate their myelosuppressive effects (see section 4.4).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Co-trimoxazole (trimethoprim/sulfamethoxazole)

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

Amantadine

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

Alcohol, Barbiturates or Anaesthetics

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

Ability to drive and use machines

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

4.6 FERTILITY, PREGNANCY, LACTATION

PREGNANCY

ACE inhibitors:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4)
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE 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.
ACE inhibitor therapy exposure during the second and third trimesters is known to induce human foeto toxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also section 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and4.4).

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 hypo perfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding
ACE inhibitors:
Because no information is available regarding the use of Lisinopril/hydrochlorothiazide during breast feeding, lisinopril/hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new born 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 combination during breast feeding is not recommended. If lisinopril &

hydrochlorothiazide combination is used during breast feeding, doses should be kept as low as possible**.**

4.7 EFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other anti hypertensives, 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/orhydrochlorothiazide with the following frequencies.
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).
The most commonly reported ADRs are cough, dizziness, hypotension, and headache which may occur in 1 to 10% of treated patients. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy.

4.9 OVERDOSE

Symptoms
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. Additional symptoms of 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
The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the supine position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g.,emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vitalsigns, 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 PHARACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitor and thiazide diuretic,

ATC-code: C09B A03.
Lisinopril/hydrochlorothiazide Tablets are a fixed dose combination product containing lisinopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.

Lisinopril
Mechanism of action
Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

Pharmacodynamic effects
Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Clinical safety and efficacy

Renin-angiotensin system (RAS)-acting agents
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 2diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2diabetes 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.

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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 diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of the thiazides is unknown.

Pharmacodynamic effects

Thiazides do not usually affect normal blood pressure.

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 populations controls, respectively. High HCTZ use (≥ 50,000mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95%CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 PHARMACOKINETIC PROPERTIES

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

Lisinopril:
Absorption

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients.
Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with inter-patient variability of 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure.
Lisinopril absorption is not affected by the presence of food.

Distribution
Lisinopril does not appear to be bound to serum proteins other than to circulating angiotensin converting enzyme (ACE).
Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

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

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

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

Heart failure

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

Elderly

Elderly patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) compared with younger subjects.

Hydrochlorothiazide:

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

At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within2 hours, peaks in about 4 hours and lasts 6 to 12 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Calcium phosphate dibasic
FD & C blue
Tartrazine yellow
PVP (K-30)
Isopropyl alcohol
Sodium starch glycolate
Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTION FOR STORAGE

Store in a cool dry place, below 30^0C

6.5 NATURE AND CONTENT OF CONTAINER AND SPECIAL EQUIPMENT FOR USE ADMINISTRATION OR IMPLANTATION

Kuinopril plus is available as 10mg lisinopril and 12.5mg hydrochlorotiazide in blister packs of 3 x 10's

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirement

7 APPLICANT/MANUFACTURER

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