SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril/Hydrochloorthiazide STADA 10/12,5 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lisinopril/Hydrochlorothiazide <...> 10 mg/12.5 mg; each tablet contains: lisinopril dihydrate equivalent to lisinopril 10 mg and hydrochlorothiazide 12.5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

10 mg /12.5 mg
White, round, biconvex scored tablets with imprint C 10 on one side.

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

Posology
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 tablets should be administered every day at roughly the same time.

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 mg lisinopril alone.

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

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

Diuretic Pre-treatment
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 5 mg dose.

Renal impairments:
The combination lisinopril/hydrochlorothiazide is contraindicated in patients with severe renal impairments (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 are 5-10 mg (see 4.4).

Older people
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”.

Paediatric population
Safety and efficacy of lisinopril/hydrochlorothiazide have not been established in children.

Method of administration
For oral use.

4.3 Contraindications

- Hypersensitivity to lisinopril or to any of the excipients listed in section 6.1 or to any other angiotensin converting enzyme (ACE) inhibitors
- Hypersensitivity to hydrochlorothiazide or other sulphonamide-derived medicinal products
- History of angioedema relating to previous treatment with an ACE-inhibitor
- Hereditary or idiopathic angioedema.
- Severe renal insufficiency (creatinine clearance <30 ml/min)
- Anuria
- Severe hepatic impairment
- 2nd or 3rd trimesters of pregnancy (see section 4.4 and 4.6).
- The concomitant use of lisinopril/hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Symptomatic hypotension
Symptomatic hypotension may sometimes occur following the first dose of lisinopril / hydrochlorothiazide and is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril, hypotension is more likely to occur in the presence of fluid or electrolyte imbalances, such as volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia, that may occur as a result of diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, electrolyte imbalances, such as hyponatraemia, hypochloraemic alkalosis or has severe renin-dependent hypertension (see 4.5 and 4.8). Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. 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 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 may be necessary.

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

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

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

In patients with renal diseases, thiazides may precipitate azotaemia. In patients with impaired renal function, cumulative effects of the medication may occur. If a progressive renal insufficiency develops, characterised by an increase in non-protein nitrogen, careful evaluation of the therapy is necessary, and stopping the diuretics therapy should be considered (see section 4.3).

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 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, 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.

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.

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.

Anaphylactoid reactions in haemodialysis 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 high flux membranes AN 69 and during low-density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis
Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

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

Metabolic and endocrine effects
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5). Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. Latent diabetic 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 imbalances
As for any patient treated with diuretics, periodic determination of serum electrolytes in appropriate intervals should be performed.
Thiazides, including hydrochlorothiazide, may cause fluid and electrolyte imbalances (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signals of fluid or electrolyte imbalances are dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, myalgia or muscle cramps, muscle 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 diuretics-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).

In hot weather hyponatraemia may occur is oedematous patients. The chloride deficiency is generally mild and does not need treatment.
Thiazides may reduce calcium excretion via the urine and cause a slight intermittent increase in serum calcium levels even in the absence of known disorders in the calcium metabolism. Distinct hypercalcaemia may be a hint of hidden hyperparathyroidism. Thiazides should be discontinued before parathyroid function tests are performed. Thiazides have shown to increase the renal magnesium excretion, which may result in hypomagnesaemia.

Serum potassium
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 and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole 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).

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
Hypersensitivity/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 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.

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

Desensitisation
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re- administration of the medicinal product.

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.
The fixed-dose combination of lisinopril and hydrochlorothiazide should be withdrawn if neutropenia (neutrophils less than 1,000/mm^3) is detected or suspected.

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.

Lithium
The combination of lithium and Lisinopril is generally not recommended (see section 4.5).

Pregnancy and lactation
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).

Use of lisinopril/HCT is not recommended during breast-feeding.

Anti-doping test
Hydrochlorothiazide present in this medication may give a positive analysis result in anti-doping tests.

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.

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 (HCT) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCT could act as a possible mechanism for NMSC.

Patients taking HCT 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 HCT may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

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, Lisinopril/Hydrochlorothiazide <...> 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 interaction

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, syncope, 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). Closely monitor blood pressure, renal function, and electrolytes in patients on lisinopril and other agents that affect the RAAS. Do not co-administer aliskiren with lisinopril in patients with diabetes. Avoid use of aliskiren with lisinopril in patients with renal impairment (GFR < 60 ml/min/1.73m^2) (see section 4.3).

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 and enhance the already increased lithium toxicity with ACE inhibitors. Use 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 section 4.4).

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).

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

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. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes 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.

Medications associated with torsades de pointes
Because of the risk of hypokalaemia, care should be taken if hydrochlorothiazide is administered concomitantly with medications associated with torsades de pointes, f.i. some antiarrhythmics, some antipsychotics and other medications which are known to induce torsades de pointes.

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 section 4.4)

Nonsteroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (doses from 3 g/day)
Chronic administration of NSAIDs (including selective cyclooxygenase-2 inhibitors) may reduce the antihypertensive effect of an ACE inhibitor. 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 hypotensive effect of ACE-inhibitors; patients must be monitored carefully.

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

Antidiabetics
Epidemiological studies 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.

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (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
Increased risk of digitalis intoxication together with thiazide induced hypokalaemia.

Colestyramine resin and colestipol
These may reduce or slow down the absorption of hydrochlorothiazide. Therefore, sulphonamide diuretics should be taken at least one hour before or four to six hours after these drugs.

Non-depolarising muscle relaxants (i.e. tubocurarine chloride)
The effect of these medications may be increased by hydrochlorothiazide.

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

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

Allopurinol
Concomitant administration of ACE inhibitors and allopurinol increases the risk of renal damage and may lead to an increased risk of leukopenia.

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

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.

Procainamide, cytostatic or immunosuppressive agents
Concomitant administration with ACE inhibitors may lead to an increased risk of leukopenia (see section 4.4).

Thrombolytics and/or beta blockers
Lisinopril may be used concomitantly with thrombolytics and beta blockers.

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.

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. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

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 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4)

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative 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 foetoplacental 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.

Breastfeeding
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 breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of lisinopril-hydrochlorothiazide during breast feeding is not recommended. If lisinopril-hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.
Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and nuclear icterus have also been observed.

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

Clinical studies have shown that the undesirable effects of the combination preparation are similar to the ones already reported with lisinopril and hydrochlorothiazide separately.

The following undesirable effects have been observed and reported during treatment with lisinopril/hydrochlorothiazide 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) including isolated reports, not known (cannot be estimated from the available data).

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 disappeared 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 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, arthralgia or arthritis, positive ANA test; increased ESR, eosinophilia, leukocytosis, rash, photosensitivity or other dermatologic manifestations.

Laboratory test values
Fluctuations in laboratory values were rarely of clinical importance. Hyperglycaemia, hyperuricaemia, hyperkalaemia or hypokalaemia have been reported incidentally. Increases in blood cholesterol and triglyceride concentrations may be observed in thiazide treatment. A slight increase in blood urea level and serum creatinine are usually found in patients without a history of decreased renal function. When an increase is observed, this will usually disappear after stopping the treatment. Bone marrow depression, which manifests itself as anaemia and/or thrombocytopenia and/or leukopenia, has been reported. Agranulocytosis is reported in rare cases, but a clear relation to the combination preparation could not be determined. Small decreases in haemoglobin and haematocrit values are frequently reported in patients with hypertension, but were rarely of clinical significance unless other anaemia causes existed. Increases in liver enzymes and/or serum bilirubin have been noted rarely, but a causal link to lisinopril/hydrochlorothiazide has not been determined.
Haemolytic anaemia has been reported rarely.

Undesirable effects reported of the individual components:

Hydrochlorothiazide (frequencies not known):

Infections and infestations: sialadenitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps):
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

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

Metabolism and nutrition disorders: anorexia, hyperglycaemia, glucosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloraemic 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, choroidal effusion, 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)
Acute respiratory distress syndrome (ARDS) (see section 4.4) (frequency very rare)

Gastrointestinal disorders: gastric irritation, diarrhoea, constipation, pancreatitis

Hepato-biliary disorders: jaundice (intrahepatic cholestatic 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, muscle weakness

Renal and urinary disorders: renal dysfunction, interstitial nephritis

General disorders: fever, weakness

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCT and NMSC has been observed (see also sections 4.4 and 5.1).

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, leukopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease

Metabolism and nutrition disorders
very rare: hypoglycaemia

Nervous system and psychiatric disorders:
common: dizziness, headache, syncope
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 (see section 4.4)
uncommon: rhinitis
very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:
common: diarrhoea, vomiting
uncommon: nausea, abdominal pain and indigestion
rare: dry mouth
very rare: pancreatitis, intestinal angioedema

Hepatobiliary disorders:
uncommon: elevated liver enzymes and bilirubin

very rare: hepatitis- either hepatocellular or cholestatic, jaundice and 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 section 4.4), urticaria, alopecia, psoriasis
very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

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 leukocytosis, 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 national reporting system listed in Appendix V.

4.9 Overdose

There is no specific information available on the treatment of a lisinopril/hydrochlorothiazide overdose. The treatment is symptomatic and supportive. Use of the medication 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. The recommended measures include inducing vomiting and/or pumping the stomach if the drug was ingested recently, while dehydration, disturbances of the electrolyte balance and hypotension should be treated in the usual manner.

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
Symptoms of hydrochlorothiazide overdose are increased diuresis, depression of consciousness (incl. coma), convulsions, paresis, cardiac arrhythmias and renal failure. Bradycardia or extensive vagal reactions should be treated by administering atropine. If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 angiotensin I to angiotensin 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 angiotensin 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) play a role in the therapeutic effect of lisinopril.

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. 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 and 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.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCT 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 HCT use (≥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 HCT: 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
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.

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 angiotensin converting enzyme inhibitors induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Fetotoxicity, 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 foetal renin-angiotensin system and partly due to the ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus (see 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate (E341)
Magnesium stearate (E470b)
Maize starch
Mannitol (E421)
Colloidal anhydrous silica (E551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Lisinopril/Hydrochlorothiazide <...> 10/12.5 mg: 4 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Lisinopril/Hydrochlorothiazide <...> 10/12.5 mg
PVC/PVDC/aluminium blisters in cardboard pack; 10, 14, 15, 20, 28, 30, 40, 50, 56, 60, 70, 80, 90, 98, 100, 200, 250, 400, 500 and 1000 tablets per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2 – 18
61118 Bad Vilbel
Duitsland

8. MARKETING AUTHORISATION NUMBERS

RVG 29993

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 22/08/2003

Datum van hernieuwing van de vergunning: 14/01/2009

10. DATE OF REVISION OF THE TEXT

Laatst gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8; 13 maart 2022