1. NAME OF THE MEDICINAL PRODUCT

CARDIURINE®, 50 mg/25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg captopril and 25 mg hydrochlorothiazide.
Excipients: Each tablet contains 19.22 mg lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Tablets are white, round, scored on one side.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.
This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled by captopril alone or hydrochlorothiazide alone.

4.2 Posology and method of administration

Posolgy

CARDIURINE can be administered in a single or two divided doses/day with or without food in patients whose blood pressure is not adequately controlled by captopril alone or hydrochlorothiazide alone.
A maximum daily dose of 50 mg captopril/25 mg hydrochlorothiazide should not be exceeded.
If satisfactory reduction of blood pressure has not been achieved, additional antihypertensive medication may be added (see section 4.3, 4.4, 4.5 and 5.1).

Adults

The administration of the fixed combination of captopril and hydrochlorothiazide is usually recommended after dosage titration with the individual components. The usual maintenance dose is 50 mg/25 mg, once a day, in the morning. When clinically appropriate a direct change from monotherapy to the fixed combination may be considered.

Renal impairment

Creatinine clearance between 30 and 80 ml/min: the initial dose is usually 25 mg/12.5 mg once a day, in the morning.
The combination captopril/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Special populations

In salt/volume depleted patients, elderly patients, and diabetic patients, the usual starting dose is 25 mg/12.5 mg once a day.

Paediatric population

There is no relevant indication for use of CARDIURINE in children.

Method of administration

Oral route.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients mentioned in section 6.1 or to any other Angiotensin Conversion Enzyme (ACE) inhibitor or to any other sulphonamide-derived drug.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary/idiopathic angioneurotic oedema.
- The concomitant use of CARDIURINE with sacubitril/valsartan. The treatment by CARDIURINE should start at least 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- The association of CARDIURINE with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR [Glomerular Filtration Ratio] < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

CAPTOPRIL

Hypotension

Rarely hypotension is observed in uncomplicated hypertensive patients.
Symptomatic hypotension is more likely to occur in hypertensive patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, vomiting, or haemodialysis. Volume and/or sodium depletion should be corrected before the administration of an ACE inhibitor and a lower starting dose should be considered.
As with any antihypertensive agent, excessive blood pressure lowering in patients with ischaemic cardiovascular or cerebrovascular disease may increase the risk of myocardial infarction or stroke.
If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required.

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Hypersensitivity/Angioedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including Captopril. This may occur at any time during treatment. In such cases, Captopril should be discontinued immediately, and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient.
In those instances where swelling has been confined to the face and lips, the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.
Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.
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).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior

facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).
The concomitant use of CARDIURINE with sacubitril/valsartan is contraindicated due to the risk of angioedema. The treatment by CARDIURINE should start at least 36 hours after the last dose of sacubitril/valsartan. The treatment by sacubitril/valsartan should start at least 36 hours after the last dose of CARDIURINE (see sections 4.3 and 4.5).
The ACE' s concomitant use with other neutral endopeptidase (NEP) inhibitors (e.g. racecadotril), mTOR inhibitors (e.g.: sirolimus, everolimus, temsirolimus) and vildagliptine may increase the risk of angioedema (e.g. swelling air pipes or tongue, with or without respiratory involvement) (see section 4.5). Caution should be exercised when starting treatment with racecadotril, mTOR inhibitors (e.g.: sirolimus, everolimus, temsirolimus) and vildagliptine in patient already taking IEC.
Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.
Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes lethal outcome. The mechanism of this syndrome is not understood.
Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.
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 increase the risk of hypotension, hyperkalaemia and decrease 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.
Kalaemia
ACE medication can cause hyperkalaemia because they block the aldosterone liberation. This effect is not significant in patients with normal renal function. However, development of hyperkalaemia may happen in patients with renal insufficiency and/or those using potassium supplements (including potassium containing salt substitutes), concomitant potassium-sparing diuretics; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin), trimethoprim or cotrimoxazole (association trimethoprim/ sulfamethoxazole) and in particular aldosterone or angiotensin II receptor blockers. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.
Potassium-sparing diuretics and angiotensin II receptor blockers must be used with caution in patients taking ACE, with monitoring of kalaemia and renal function (see section 4.5).
Aortic and mitral valve stenosis/Obstructive hypertrophic cardiomyopathy/Cardiogenic shock
ACE inhibitors should be used with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and hemodynamically significant obstruction.
Neutropenia/Agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, including captopril. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Captopril 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 captopril is used in such patients, it is advised that white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of captopril therapy, and periodically thereafter. During treatment all patients should be instructed to report any sign of infection (e.g. sore throat, fever) and a differential white blood cell count should be performed. Captopril and other concomitant medication (see section 4.5) should be withdrawn if neutropenia (neutrophils less than 1000/mm^3) is detected or suspected.
In most patients neutrophil counts rapidly return to normal upon discontinuing captopril.
Proteinuria
Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.
Total urinary proteins greater than 1 g per day were seen in about 0.7% of patients receiving captopril. The majority of patients had evidence of prior renal disease or had received relatively high doses of captopril (in excess of 150 mg/day), or both. Nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.
Patients with prior renal disease should have urinary protein estimations (dip-stick on first morning urine) prior to treatment, and periodically thereafter.
Anaphylactoid reactions during desensitisation
Sustained life-threatening anaphylactoid reactions have been rarely reported for patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.
Anaphylactoid reactions during high-flux dialysis/lipoprotein apheresis membrane exposure
Anaphylactoid reactions have been reported in haemodialyzed patients with high-flux dialysis membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.
Surgery/Anaesthesia
Hypotension may occur in patients undergoing major surgery or during treatment with a known anaesthetic agents that are known to lower blood pressure. If hypotension occurs, it may be corrected by volume expansion.
Diabetic patients
The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.
As with other angiotensin converting enzyme inhibitors, CARDIURINE is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

HYDROCHLOROTHIAZIDE
Renal impairment
In patients with renal disease, thiazides may precipitate azotaemia. Cumulative effects of the drug may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy (see section 4.3).
Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, even minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see section 4.3).

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. In diabetic patients' dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.
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 hypochloraemia alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with captopril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).
Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.
Anti-doping test
Hydrochlorothiazide contained in this medication could produce a positive analytic result in an antidoping test.
Other
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Cases of photosensitivity reaction has been reported during thiazide therapy (see section 4.8). In case reaction appears it is recommended to discontinue the treatment. If readministration is deemed necessary it is recommended to protect areas exposed to sunlight or artificials UVA.
Choroidal effusion, acute myopia and acute angle-closure secondary glaucoma
Sulphonamides and their derivatives can cause an idiosyncratic reaction that result in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Hydrochlorothiazide being a sulphonamide, only a few isolated cases of acute angle-closure glaucoma were reported up to date, without any definite causal relation with the intake of hydrochlorothiazide.
Symptoms, including sudden appearance of decreased visual acuity or ocular pains, usually occur a few hours or a few weeks following treatment initiation. Untreated acute angle-closure glaucoma can result in definitive vision loss. The first treatment consists in stopping hydrochlorothiazide as soon as possible. Medical or surgical measures should be considered if the intraocular pressure remains uncontrolled. Risk factors of developing an acute angle-closure glaucoma could include history of allergy to penicillin or sulphonamides.
Skin cancer (non-melanoma)
A higher risk of non-melanoma skin cancer (NMSC) [Basal cell carcinoma (BC) and epidermoid carcinoma (EC)] with the increase of the cumulative exposition dose of hydrochlorothiazide

(HCTZ) has been observed in two epidemiologic studies from the cancer Danish register. Photosensitizing actions of HCTZ could be a possible mechanism of NMSC.
The patients taking HCTZ must be informed of the risk of NMSC and be advised to check regularly their skin to detect any new lesion and contact their doctor in case of any suspicious lesion. Some preventive measures as a limited exposition to UV and sunlight and the use of a good solar protection and, in case of exposition, should be advised to the patient to minimise the risk of skin cancer. The suspicious lesion must be examined quickly including eventually with a histological biopsy. The use of HCTZ can be reconsidered with a patient that have already had a NMSC (also see section 4.8).
Acute respiratory toxicity
Very rare case of acute respiratory toxicity, Acute Respiratory Distress Syndrome (ARDS) were reported after hydrochlorothiazide intake. Pulmonary oedema develop usually sets after a range a few minutes to few hours after hydrochlorothiazide intake. At first, symptoms are dyspnea, fever, pulmonary collapse and hypotension. If ARDS is suspected, CARDIURINE should be withdrawn and appropriate treatment should be administered. Hydrochlorothiazide should not be administered to patients already presenting ARDS after hydrochlorothiazide intake.

CAPTOPRIL/HYDROCHLOROTHIAZIDE COMBINATION
Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless ACE inhibitor treatment is essential, it is recommend to patients that are planning a pregnancy to modify their treatment antihypertensive to a well-established secure profile during pregnancy. When pregnancy is diagnosed, treatment should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
Risk of hypokalaemia
The combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of kalaemia should be performed.
Combination with lithium
CARDIURINE is not recommended in association with lithium due to the potentiation of lithium toxicity (see section 4.5).
Lactose
This medication contains lactose. Patients with of galactose intolerance, the lactase total deficiency or glucose-galactose malabsorption syndrome (rare hereditary problems) should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

CAPTOPRIL

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

Though kalaemia remains in the normal limit range, hyperkalaemia may occur in some patients treated with captopril/hydrochlorothiazide. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium . It is also important to be careful when the CARDIURINE is administrated with others hyperkalaemia drugs like the trimethoprim and the cotrimoxazole (trimethoprim/ sulfamethoxazole) because the trimethoprim acts like a potassium sparing diuretic. The association of CARDIURINE with the above-mentioned drugs is not recommended. If the concomitant use is indicated, it should be done with a frequent kalaemia control.

- **Eplerenone**

Marked risk of hyperkalaemia, especially in elderly patients. Strict monitoring of serum potassium and renal function during treatment association.

- **Other drugs increasing serum potassium**

Marked risk of hyperkalaemia potentially lethal.

- **Diuretics (thiazide or loop diuretics)**

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with captopril (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of captopril. However, no clinically significant drug interactions have been found in specific studies with hydrochlorothiazide or furosemide.

- **Other antihypertensive agents**

Captopril has been safely co-administered with other commonly used antihypertensive agents (e.g. beta-blockers and long-acting calcium channel blockers). Concomitant use of these agents may increase the hypotensive effects of captopril. Treatment with nitroglycerine and other nitrates, or other vasodilators, should be used with caution.

- **Alpha blocking agents**

Concomitant use of alpha blocking agents may increase the antihypertensive effects of captopril and increase the risk of orthostatic hypotension.

- **Treatments of acute myocardial infarction**

Captopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates in patients with myocardial infarction.

- **Tricyclic antidepressants/ Antipsychotics**

ACE inhibitors may enhance the hypotensive effects of certain tricyclic antidepressants and antipsychotics (see section 4.4). Postural hypotension may occur.

- **Allopurinol, procainamide, cytostatic or immunosuppressive agents**

Concomitant administration with ACE inhibitors may lead to an increased risk for leukopenia especially when the latter are used at higher doses than the currently recommended doses.

- **Sympathomimetics**

They may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored.

- **Antidiabetics**

Pharmacological studies have shown that ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in diabetics. Should this very rare interaction occur, it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with ACE inhibitors.

- **Angiotensin II receptor blockers or aliskiren**

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and altered 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).

- **Estramustine**

Risk of marked side effect angio-neurotic oedema type (angio-oedema).

- **Gliptines**

Concomitant use of ACE with vildagliptin can lead to a higher risk of angio-oedema (see section 4.4)

- **Gold**

With gold salt's administered by IV route: risk of «nitritoid» reaction when introducing ACE medication (nausea, vomiting, vasomotor effects type flush , hypotension, potentially collapses).

- **Sacubitril/ Valsartan**

Concomitant use ACE with the association sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections 4.3 and 4.4). Sacubitril/valsartan treatment should be initiated only 36 hours after the first CARDIURINE dose. CARDIURINE should only be initiated 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

- **Racecadotril**

Concomitant use ACE with a neutral endopeptidase (NEP) inhibitor (e.g. racecadotril) can lead to a major risk of angio-oedema (see section 4.4).

HYDROCHLOROTHIAZIDE

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

Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

- **Potassium sparing diuretics (monotherapy or associated)**

Rational association, useful for some patients, does not exclude the occurrence of hypokalaemia or, especially in renal deficiency and diabetic patients, occurrence of hyperkalaemia. Monitor serum potassium, eventually also ECG and, if happened, reconsider treatment.

- **Other drugs lowering serum potassium**

Intensification of hypokalaemia. Monitoring of serum potassium with correction if needed.

- **Calcium salts**

Calcium salts increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics.

- **Digitalis**

Induced hypokalaemia with thiazide can enhance the risk of digitalis toxicity .

- **Cholestyramine resin and colestipol**

They may delay or decrease absorption of hydrochlorothiazide. Sulphonamide diuretics should be taken at least one hour before or four to six hours after these medications.

- **Non-depolarising muscle relaxants (e.g. tubocurarine chloride)**

Effects of these agents may be potentiated by hydrochlorothiazide.

- **Drugs associated with torsades de pointes**

Because of the risk of hypokalaemia, caution should be used when hydrochlorothiazide is co-administered with drugs associated with torsades de pointes, e.g. some antiarrhythmics, some antipsychotics and other drugs known to induce torsades de pointes.

- **Carbamazepine**

Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatraemia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used.

- **Iodinated contrast agents**

In case of induced thiazide dehydration, intensification of acute functional renal deficiency, especially when using high doses of iodinated contrast agents.

- **Cyclosporin**

An hyperkalaemia could happen with the concomitant use of ACE and cyclosporin. An oversight of the kalaemia is recommended.

- **Heparin**

An hyperkalaemia could happen with the concomitant use of ACE and heparin. An oversight of the kalaemia is recommended.

- **Other drugs lowering serum sodium**

Intensification of hyponatremia risk.

CAPTOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

- **Lithium**

Reversible increase in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. The combination of captopril and hydrochlorothiazide with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary.

- **Non-steroidal anti-inflammatory medicinal products**

It has been described that non-steroidal anti-inflammatory medicinal products (NSAIDs) and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. The administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics.

- **Acetylsalicylic acid**

For acetylsalicylic acid anti-inflammatory doses (≥ 1 g per intake and/or ≥ 3 g daily) or for antalgics or an antipyretics (⩾ 500 mg per intake and/or < 3 g daily): acute renal deficiency in dehydrated patient, by a decrease of the secondary glomerular filtration to a renal prostaglandins synthesis decrease. There is also decrease of the antihypertensive effect. Hydrate the patient and monitor the renal function at onset of treatment.

- **Nitrates**

Intensification of hypotensive risk, especially postural. Concomitant nitrates treatment or other vasodilators should be administered with caution.

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

Concomitant use ACE with mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) can lead to a higher risk of angioedema (see section 4.4).

- **Co-trimoxazole (trimethoprim/ sulfamethoxazole)**

Patients taking concomitant treatment with cotrimoxazole (trimethoprim/ sulfamethoxazole) can present a higher risk of hyperkalaemia (see section 4.4).

- **Clinical Chemistry**

Captopril may cause a false-positive urine test for acetone. Hydrochlorothiazide may cause diagnostic interference of the bentiromide test. Thiazides may decrease serum PBI (Protein Bound Iodine) levels without signs of thyroid disturbance.

4.6 Fertility, pregnancy and lactation

Pregnancy

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Given the effects of the individual components in this combination product on pregnancy, the use of CARDIURINE is not recommended during the first trimester of pregnancy (see section 4.4). The use of CARDIURINE is contra-indicated during the 2nd and 3rd trimesters of pregnancy (see sections 4.3 and 4.4).

Available 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 congenital malformations risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see 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 feto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, only if a beneficial effect on the course of the disease is expected.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation

CAPTOPRIL
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of CARDIURINE in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.
In the case of an older infant, the use of CARDIURINE in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any undesirable effects.

HYDROCHLOROTHIAZIDE
The hydrochlorothiazide is excreted in the breast milk in small quantity. The thiazides in high dose, causing significant diuresis, could inhibit the milk production. The use of CARDIURINE is not recommended during breast-feeding. If CARDIURINE is used during lactation, the dosage should be as law as possible.

4.7 Effects on ability to drive and use machines
As with other antihypertensives, the ability to drive and use machines may be reduced, e.g. at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

4.8 Undesirable effects
Frequency is defined using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥1/1000, < 1/100), rare (≥ 1/10000, < 1/1000),very rare (< 1/10000) and unknown (frequency can't be evaluated on the available data).

CAPTOPRIL
Undesirable effects reported for captopril and/or ACE inhibitor therapy include:
Blood and lymphatic system disorders
- *Very rare*: neutropenia/agranulocytosis (see section, 4.4), pancytopenia particularly in patients with renal dysfunction (see section, 4.4), anaemia (including aplastic and haemolytic), thrombocytopenia, lymphadenopathy, eosinophilia, auto-immune diseases and/or positive ANA-titres.

Metabolism and nutrition disorders
- *Uncommon:* anorexia.
- *Very rare*: hyperkalaemia, hypoglycaemia (see section 4.4).

Psychiatric disorders
- *Common*: sleep disorders.
- *Very rare*: confusion, depression.

Nervous system disorders
- *Common*: taste impairment, dizziness.
- *Rare*: drowsiness.
- *Very rare*: cerebrovascular incidents, including stroke, cerebral vascular deficiency and syncope.
- *Unknown:* headaches, paresthesia.

Eye disorders
- *Very* rare: blurred vision.

Cardiac disorders
- *Rare*: tachycardia or tachyarrhythmia, angina pectoris, palpitations.
- *Very rare*: cardiac arrest, cardiogenic shock.

Vascular disorders
- *Uncommon*: hypotension (see section 4.4), Raynaud syndrome, flush, pallor.

Respiratory, thoracic and mediastinal disorders
- *Common*: dry, irritating, non-productive cough (see section 4.4) and dyspnea.
- *Very rare*: bronchospasm, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders
- *Common*: nausea, vomiting, gastric irritations, abdominal pain, diarrhoea, constipation, dry mouth, peptic ulcer.
- *Rare*: stomatitis/aphthous ulcerations, intestinal angioedema (see section 4.4).
- *Very rare*: glossitis, pancreatitis.

Hepatobiliary disorders
- *Very rare*: impaired hepatic function and cholestasis (including jaundice), hepatitis, eventually necrosis, elevated liver enzymes and bilirubin.

Skin and subcutaneous tissue disorders
- *Common*: pruritus, rash, and alopecia.
- *Rare*: angioedema (see section 4.4).
- *Very rare*: urticaria, Stevens Johnson syndrome, erythema multiform, photosensitivity, erythroderma, pemphigoid reactions and exfoliative dermatitis.

Musculoskeletal and connective tissue disorders
- *Very rare*: myalgia, arthralgia.

Renal and urinary disorders
- *Rare*: renal function disorders including renal failure, polyuria, oliguria, increased urine frequency.
- *Very rare*: nephrotic syndrome.

Reproductive system and breast disorders
- *Very rare*: impotence, gynecomastia.

General disorders and administration site conditions
- *Rare*: chest pain, fatigue, faintness.
- *Very rare*: fever.

Investigations
- *Very rare:* proteinuria, eosinophilia, hyperkalaemia, hyponatremia, increase of serum potassium, decrease of serum sodium, elevation of BUN, serum creatinine and serum bilirubin, decreases in haemoglobin, haematocrit, leucocytes, thrombocytes, positive ANA-titre, elevated ESR.

HYDROCHLOROTHIAZIDE

Infections and infestations
- Sialadenitis.

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

Metabolism and nutrition disorders
- Anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides.

Psychiatric disorders
- Restlessness, depression, sleep disturbances.

Nervous system disorders
- Loss of appetite, paraesthesia, light-headedness.

Eye disorders
- Xanthopsia, transient blurred vision, choroidal effusion, acute myopia, acute angle-closure secondary glaucoma.

Ear and labyrinth disorders
- Vertigo.

Cardiac disorders
- Postural hypotension, cardiac arrhythmias.

Vascular disorders
- Necrotizing angiitis (vasculitis, cutaneous vasculitis).

Respiratory, thoracic and mediastinal disorders
- Respiratory distress (including pneumonitis and pulmonary oedema).

Gastrointestinal disorders
- Gastric irritation, diarrhoea, constipation, pancreatitis.

Hepatobiliary disorders
- Jaundice (intrahepatic cholestatic jaundice).

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

Musculoskeletal and connective tissue disorders
- Muscle spasm.

Renal and urinary disorders
- Renal dysfunction, interstitial nephritis.

General disorders and administration site conditions
- Fever, weakness.

Benign tumors, malignant and non-classified (including cysts and polyps)
- "Unknown" frequency: non-melanoma skin cancer (basal cell carcinoma and epidermoid carcinoma).

Description of some undesirable effects
Non melanoma skin cancer: based on available data from epidemological studies, it was observed a cumulative dose related association between HCTZ and NMSC (see sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms of overdosage are: increased diuresis, electrolyte imbalance, severe hypotension, depression of consciousness (including coma), convulsions, paresis, cardiac arrhythmias, bradycardia and renal failure.
Measures to prevent absorption (e.g. gastric lavage, administration of absorbing agents and sodium sulphate within 30 minutes after intake) and hasten elimination should be applied if ingestion is recent.
If hypotension occurs, the patient should be placed in the shock position and sodium chloride and volume supplementation should be given rapidly. Treatment with angiotensin-II can be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. Constant monitoring of water hydration, electrolyte and acid base balance, blood glucose is essential. In case of hypokalaemia, potassium substitution is necessary. Captopril may be removed from circulation by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **captopril and diuretics, ATC code: C09BA01**
CARDIURINE is a combination of an ACE inhibitor, captopril, and an antihypertensive diuretic, hydrochlorothiazide. The combination of these agents has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

CAPTOPRIL

Captopril is an angiotensin converting enzyme (ACE) inhibitor, i.e. it inhibits ACE, the enzyme involved in the conversion of angiotensin I to angiotensin II - a vasoconstrictor which also stimulates aldosterone secretion by the adrenal cortex.
Such inhibition leads to:

- Reduced aldosterone secretion,
- Increased plasma renin activity, since aldosterone no longer exerts negative feedback,
- A drop in total peripheral resistance (with a preferential effect on muscles and kidneys) which is not accompanied by water and sodium retention or reflex tachycardia during long-term treatment. Captopril also exerts its antihypertensive effect in subjects with low or normal renin concentrations.

Captopril is effective at all stages of hypertension, i.e. mild, moderate or severe.
A reduction in supine and standing systolic and diastolic blood pressures is observed.
After a single dose, the antihypertensive effect is evident fifteen minutes post-dose and reaches a maximum between 1h and 1.5h after administration of the drug. Its duration of action is dose-dependent and varies from 6 to 12 hours.
Blood pressure becomes normalised (seated DBP < 90 mmHg) in patients after two weeks to one month of treatment and the drug retains its effectiveness over the course of time. Patients are also classified as responders if seated DBP decreased by 10% or more from baseline-BP.
Rebound hypertension does not occur when treatment is discontinued.
The treatment of hypertension with captopril leads to an increase in arterial compliance, a rise in renal blood flow without any significant drop in the glomerular filtration rate, and a decrease in left ventricular hypertrophy.

HYDROCHLOROTHIAZIDE

Hydrochlorothiazide is a thiazide diuretic which acts by inhibiting the reabsorption of sodium in the cortical diluting segment of renal tubules. It increases the excretion of sodium and chloride in urine and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urinary output and exerting an antihypertensive effect.

The time to onset of diuretic activity is approximately 2 hours. Diuretic activity reaches a peak after 4 hours and is maintained for 6 to 12 hours. Above a certain dose, thiazide diuretics reach a plateau in terms of therapeutic effect whereas adverse reactions continue to multiply. When treatment is ineffective, increasing the dose beyond recommended doses serves no useful purpose and often gives rise to adverse reactions.

Security and clinical efficacy

HYDROCHLOROTHIAZIDE

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

CAPTOPRIL AND HYDROCHLOROTHIAZIDE

The concomitant administration of captopril and hydrochlorothiazide in clinical trials led to greater reductions in blood pressure than when either of the products was administered alone.
The administration of captopril inhibits the renin angiotensin aldosterone system and tends to reduce hydrochlorothiazide-induced potassium loss.
Combination of an ACE inhibitor with a thiazide diuretic produces a synergistic effect and also lessens the risk of hypokalaemia provoked by the diuretic alone.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS): Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage.
VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (ALiskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

CAPTOPRIL

Captopril is quickly absorbed after oral administration and maximum serum concentrations are obtained around one hour after administration. Minimum mean absorption is approximately 75%. Peak plasma concentrations are reached within 60-90 minutes. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%. Approximately 25-30% of the circulating drug is bound to plasma proteins. The apparent elimination half-life of unchanged captopril in blood is about 2 hours. Greater than 95% of the absorbed dose is eliminated in the urine within 24 hours; 40-50% is unchanged drug and the remainder are inactive disulphide metabolites (captopril disulphide and captopril cysteine disulphide). Impaired renal function could result in drug accumulation. Studies in animals indicate that captopril does not cross the blood-brain barrier to any significant extent.

HYDROCHLOROTHIAZIDE

Oral absorption of hydrochlorothiazide is relatively rapid. The mean plasma half-life in fasted individuals has been reported to be 5 to 15 hours. Hydrochlorothiazide is eliminated rapidly by the kidney, and excreted unchanged (> 95%) in the urine.

LACTATION

On 12 women treated with captopril (orally) with the posology of 100mg 3 times a day, the maximum concentration of captopril in the breast milk was 4.7µg/L, 3.8 hours after the dose was taken. We can estimate, based on these data, that a breastfeeding child would receive a daily dose representing less than 0.002% of the mother daily dose.

5.3 Preclinical safety data

Animal studies performed during organogenesis with captopril and/or hydrochlorothiazide have not shown any teratogenic effect but captopril has produced foetal toxicity in several species, including foetal mortality during late pregnancy, growth retardation and postnatal mortality in the rat.
Non-clinical data reveal no other specific hazard for human based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: maize starch, lactose, microcrystalline cellulose, colloidal anhydrous silica, talc, magnesium stearate, croscarmellose sodium.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep out of the sight and reach of children.
Store in the original package, protect from heat, light and moisture.
Store below 30°C.

6.5 Nature and contents of container

PVC/Aluminium foil blisters, containing 30 scored tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines
List I

8. MARKETING AUTHORISATION HOLDER

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Zoning Industriel de Nivelles Sud, zone II - Av. Thomas Edison 105
1402 Thines (Belgium)
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9. MANUFACTURER

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10. UPDATE DATE

03/2022.