

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Captor-HCT 50mg/25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains captopril 50 mg and hydrochlorothiazide 25 mg.

Excipient(s) with known effect: contains lactose monohydrate 68.7mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White octagonal tablets with a one-sided crossed score notch and the opposite convex side has the mark 'Cc' engraved on it.

The score-notch allows the tablet to be divided into equal halves or quarters.

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

CAPTOR-HCT 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 sections 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 50/25 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 25/12.5 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 25/12.5 mg once a day.

Paediatric population: There is no relevant indication for use of CAPTOR-HCT in children.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or to any other ACE inhibitor or to any other sulphonamide-derived drugs.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary/idiopathic angioneurotic oedema.
- Severe renal impairment (creatinine clearance <30 mL/min).
- Severe hepatic impairment
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of Captor-HCT with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Captor-HCT 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

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:

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 captopril. Treatment with captopril 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.

Angioedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including captopril. This may occur at any time during treatment. In such cases, captopril should be discontinued promptly 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 (0.3mL to 0.5mL) 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 Contraindications).

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).

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus): patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

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) death. 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.

Hyperkalaemia:

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function 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, hyperkalemia 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).

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 haemodynamically 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) when 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 $1000/\text{mm}^3$) 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 patients haemodialysed 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 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, CAPTOR-HCT 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.

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

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

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

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

HYDROCHLOROTHIAZIDE

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 a 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, since 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 hypochloreaemic 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.

Acute myopia and secondary angle-closure glaucoma: Sulfonamide medicinal products or sulfonamide derivative medicinal products can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. While hydrochlorothiazide is a sulfonamide, only isolated cases of acute angle-closure glaucoma without definite causal association have been reported so far with hydrochlorothiazide.

Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicinal product initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamides or penicillin allergy.

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

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

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.

CAPTOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see section 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: CAPTOR-HCT is not recommended in association with lithium due to the potentiation of lithium toxicity (see section 4.5).

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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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 captopril. 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 captopril 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 captopril 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.

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 leucopenia especially when the latter are used at higher than currently recommended doses.

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).

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

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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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) 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, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Ciclosporin

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.

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Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives: hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

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

Cardiac glycosides: enhanced possibility of digitalis toxicity associated with thiazide induced hypokalaemia.

Colestyramine resin and colestipol: 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.

Nondepolarising 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 coadministered 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.

CAPTOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

Lithium: reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased 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.

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.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

ACE-inhibitors:

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

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

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to ACE 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 foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

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 Captor-HCT 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 Captor-HCT in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

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 Captor-HCT during breastfeeding is not recommended. If Captor-HCT is used during breastfeeding doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Frequency is defined using the following convention:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data)

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

Uncommon: headache, paraesthesia

Rare: drowsiness

Very rare: cerebrovascular incidents, including stroke, cerebrovascular insufficiency and syncope.

Eye disorders:

Very rare: blurred vision.

Cardiac disorders:

Uncommon: 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 dyspnoea

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 angiodema (see section 4.4)

Very rare: glossitis, pancreatitis.

Hepatobiliary disorders:

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

Skin and subcutaneous tissue disorders:

Common: pruritus, rash, alopecia

Uncommon: angioedema (see section 4.4)

Very rare: urticaria, Stevens-Johnson syndrome, erythema multiforme, 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, gynaecomastia.

General disorders and administration site conditions:

Uncommon: chest pain, fatigue, malaise

Very rare: fever.

Investigations:

Very rare: proteinuria, eosinophilia, 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.

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Infections and infestations: sialadenitis.

"Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Non-melanoma skin cancer* (basal cell carcinoma and squamous cell carcinoma (frequency not known))

*See description of selected adverse reactions"

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

Metabolism and nutrition disorders: anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia 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, acute myopia, secondary acute angle-closure glaucoma.

Ear and labyrinth disorders: vertigo.

Cardiac disorders: postural hypotension, cardiac arrhythmias.

Vascular disorders: necrotising angitis (vasculitis, cutaneous vasculitis).

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

Gastrointestinal disorders: gastric irritation, diarrhoea, constipation, pancreatitis.

Hepato-biliary disorders: jaundice (intrahepatic cholestatic jaundice).

Skin and subcutaneous tissue disorders: photosensitivity reactions, rash, 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.

"Description of selected adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.

Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdosage are: increased diuresis, electrolyte imbalance, severe hypotension, depression of consciousness (including coma), convulsions, paresis, cardiac arrhythmias, bradycardia, renal failure.

Measures to prevent absorption (e.g. gastric lavage, administration of absorbing agents and sodium sulfate 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, 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: ACE (Angiotensin-Converting-Enzyme) inhibitors, combinations, ATC code: C09BA01. CAPTOR-HCT 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 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 1 h and 1.5 h 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.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

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

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

-Hydrochlorothiazide 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.

-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.

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

5.2 Pharmacokinetic properties

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. 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:

In the report of twelve women taking oral captopril 100mg 3 times daily, the average peak milk level was 4.7 μ g/L and occurred 3.8 hours after the dose. Based on these data, the maximum daily dosage that a nursing infant would receive is less than 0.002% of the maternal daily dosage.

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 carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Lactose Monohydrate
Pregelatinised Maize starch
Stearic Acid
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Captor-HCT tablets are packed in blisters of polypropylene and aluminium foil in packs of 30 tablets and sample packs of 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/025/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 16th October 2008

10 DATE OF REVISION OF THE TEXT

November 2019