SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-zidocapt 50/25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Captopril 50mg and Hydrochlorothiazide 25mg

Excipient with known effect: Each tablet contains 68.700mg lactose (as lactose monohydrate)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White to off white, round with an approximate diameter of 10mm,with score notch.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

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

Posology

This medicine can be administered as a single daily dose or divided into two daily doses, with or without food, in .patients whose blood pressure is not adequately controlled by captopril alone or hydrochlorothiazide alone.

The maximum daily dose should not exceed 50 mg captopril and 25 mg hydrochlorothiazide. If a satisfactory reduction in blood pressure has not been achieved, additional antihypertensive medication may be added (see sections 4.3, 4.4, 4.5 and 5.1).

Adults: Administration of the fixed combination of captopril and hydrochlorothiazide is usually recommended after dose adjustment with the individual components. The usual maintenance dose is 50 mg/25 mg once daily 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 recommended starting dose is 25 mg/12.5 mg once daily in the morning. The captopril/hydrochlorothiazide combination is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min)

Special populations: In salt/volume depleted patients, the elderly and diabetic patients, the usual starting dose is 25mg/12.5 mg once daily.

Paediatric population: Safety and effectiveness has not been established.

Method of administration:
The tablets are for oral administration. They should be taken in the morning, independently of meals, together with a generous quantity of liquid.

4.3 Contraindications

Co-zidocapt 25/12.5mg Tablets are contraindicated in the following cases:

- Hypersensitivity to captopril, any other ACE inhibitor, any sulphonamide-derived drug, or any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioneurotic oedema
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Severe hepatic impairment
- The concomitant use of Co-zidocapt 25/12mg tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR< 60mL/min/1.73m^2) (see section 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan. Co-zidocapt 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

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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.

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 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 section 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.

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.

Angioedema: Angioneurotic oedema/angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with ACE inhibitors including captopril, This reaction can occur at any time during treatment. In these cases, captopril treatment 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 (0.3 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).

Insulin Autoimmune Syndrome (IAS):
Cases of Insulin Autoimmune Syndrome (IAS), including severe hypoglycaemic events have been reported during the treatment with captopril (see section 4.8). If IAS is suspected, captopril should be discontinued, and appropriate treatment should be initiated.

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 inhibitors and receive appropriate medical follow-up.

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

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/mm³) is detected or suspected.

In most patients neutrophil counts rapidly return to normal upon discontinuing captopril.

Proteinurea: 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 lifethreatening 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, Co-zidocapt is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of lowrenin states in the black hypertensive population.

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Acute Respiratory Toxicity: Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Co-zidocapt should be withdrawn and appropriate treatment given.Hydrochlorothiazide

should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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).

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 or attack of gout may occur 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, hyponatremia and hypochloraemic 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 hyponatremia 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 analytical result in an anti-doping test.

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

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 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: Co-zidocapt is not recommended in association with lithium due to the potentiation of lithium toxicity (see section 4.5).

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

Angioneurotic oedema of the extremities, face, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE inhibitors particularly during the first week of treatment. However, in rare cases, severe angioedema may develop after months or years of long-term treatment with an ACE inhibitor.

Treatment should be discontinued promptly. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted.

Excipient warnings
Lactose: Co-zidocapt contains 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 interaction

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mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus): patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).
Potassium sparing diuretics or potassium supplements: ACE inhibitors attenuate diuretic induced potassium loss. 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 (see section 4.4).

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 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 anti-hypertensive agents(e.g. beta-blockers and long-acting calcium channel blockers).
Concomitant use of these agents may increase the hypotensive effects of captopril. 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 immuno-suppressant agents: Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia, especially when the latter are used at higher than currently recommended doses.

Sympathomimetics: 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, 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).

Co-trimoxazole (trimethoprim/sulfamethoxazole): Patients taking co-trimoxazole (trimethoprim/sulfamethoxazole) concomitantly may be at increased risk of hyperkalaemia (see section 4.4).

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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.

Cholestyramine 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 co-administered with drugs associated with torsades de pointes, e.g. some anti-arrhythmics, 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 hyponatremia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used.

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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) such as indomethacin 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.

4.6 Fertility, Pregnancy and lactation

Pregnancy
ACE-inhibitors:

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

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

Exposure to ACE inhibitor therapy during the second and third trimester is known to induce human foetotoxicity (decreased renal function, ologohydramnios, 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.
Moreover, rare cases of hypoglycaemia in neonates have been reported in case of exposure near term.

Breast-feeding

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 Co-zidocapt 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 Co-zidocapt 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 Co-zidocapt during breast feeding is not recommended. If Co-zidocapt is used during breast feeding, doses should be kept as low as possible.

Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and nuclear icterus might occur.

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: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000) and very rare (< 1/10,000).

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Undesirable effects reported for captopril and/or ACE inhibitor therapy include:

Immune System Disorder:
Frequency Not known: Insulin autoimmune syndrome

Blood and lymphatic 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:
Rare: 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 4.4) and dyspnoea
Very rare: bronchospasm, rhinitis, allergic alveolitis/ eosinophilic pneumonia
Very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4)

Gastrointestinal disorders and administration site conditions:

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

Hepato-biliary 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 with or without a rash, rash, and alopecia
Uncommon: angioedema (see section 4.4)
Very rare: urticaria, Stevens Johnson syndrome, erythema multiforme, photo-sensitivity, erythroderma, pemphigoid reactions and exfoliative dermatitis.

Musculoskeletal, connective tissue and bone 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;
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 haemo-globin, 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)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

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 and secondary acute angle-closure glaucoma, choroidal effusion (frequency not known)

Ear and labyrinth disorders:
vertigo

Cardiac disorders:
postural hypotension, cardiac arrhythmias

Vascular disorders:
necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders:
respiratory distress (including pneumonitis and pulmonary oedema)
Very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4)

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 of 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, and blood glucose is essential. In the event 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

This medication 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 each of the components separately

Captopril is an angiotensin-converting enzyme inhibitor. The angiotensin-converting enzyme (ACE) is a peptidyl dipeptidase which converts angiotensin I to angiotensin II, a substance which induces vasoconstriction that 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 in all degrees of hypertension, i.e. mild, moderate or severe. A reduction in systolic and diastolic blood pressure is observed in the supine as well as in the standing position.

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.

Treatment of hypertension with captopril results in increased arterial compliance, increased renal blood flow without significant decrease in glomerular filtration rate, and decreased left ventricular hypertrophy.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic that works by inhibiting sodium reabsorption in the cortical diluent segment

of the renal tubules. It increases the excretion of sodium and chloride in the urine and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis 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, while adverse reactions multiply. When treatment is ineffective, increasing the dose above recommended doses is not helpful, and adverse reactions often increase.

Concomitant administration of captopril and hydrochlorothiazide in clinical trials resulted in greater reductions in blood pressure than when each component was administered separately.

Administration of captopril inhibits the renin-angiotensin-aldosterone system, while tending to reduce hydrochlorothiazide-induced potassium loss.
The combination of an ACE inhibitor with a thiazide diuretic produces a synergistic effect, decreasing the risk of hypokalemia caused by the diuretic alone

Dual blockade of the renin-angiotensin-aldosterone system
Two large randomized, controlled studies (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have studied the use of combining an angiotensin-converting enzyme inhibitor with an angiotensin II receptor antagonist.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of target organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies showed no significant benefit on mortality and renal and/or cardiovascular outcomes, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension was observed compared to monotherapy.
Given the similarity of their pharmacodynamic properties, these results are also appropriate for other angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists.
Consequently, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists should 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 aliskiren group than in the placebo group

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).

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 100 mg 3 times daily, the average peak milk level was 4.7μg/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. Preclinical data reveal no other specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Stearic acid

6.2 Incompatibilities

None known

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister strips of 300 µm white opaque non-toxic polypropylene welded on to 15 µm internally film-coated aluminium semi-rigid support, packed into lithographed cardboard cartons with the relevant package leaflet.

Pack sizes of 20, 28, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

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