CoracePlus® TABLETS

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(Lisinopril + Hydrochlorothiazide)

DESCRIPTION:
CORACE PLUS (Lisinopril and Hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.
Lisinopril, a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. It is chemically described as (S)-1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$. Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.53.
Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$. Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.72.

COMPOSITION:
Each Corace Plus 10/12.5mg Film Coated tablet contains :
Lisinopril U.S.P. 10mg
Hydrochlorothiazide U.S.P. 12.5mg
(Product Specs.: U.S.P.)

Each Corace Plus 20/12.5mg Film Coated tablet contains :
Lisinopril U.S.P. 20mg
Hydrochlorothiazide U.S.P. 12.5mg
(Product Specs.: U.S.P.)

CLINICAL PHARMACOLOGY:
Pharmacodynamic Properties:
Pharmacotherapeutic group: ACE-inhibitor and diuretic, ATC code: C09BA03

Mechanism of Action:
Lisinopril
Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration. While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Hydrochlorothiazide
Hydrochlorothiazide is a diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides do not usually affect normal blood pressure.

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

Absorption:
Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.
When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Distribution:
Lisinopril does not appear to bind to other serum proteins other than to circulating angiotensin-converting enzyme (ACE). Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Metabolism:
Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine.

Elimination:
On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril is approximately 50 ml/min. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.
At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

SPECIFIC POPULATIONS
Renal Impairment
Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. With a creatinine clearance of 30-80ml/min, mean AUC was increased by 13% only, while a 4-5 fold increase in mean AUC was observed with creatinine clearance of 5-30ml/min. Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

Hepatic Impairment.
Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30% as determined by urinary recovery) but an increase in exposure (approximately 50%).

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

THERAPEUTIC INDICATIONS:
CORACE PLUS is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake.

DOSAGE AND ADMINISTRATION:
Lisinopril monotherapy is an effective treatment of hypertension in once-daily doses of 10 mg to 80 mg, while hydrochlorothiazide monotherapy is effective in doses of 12.5 mg per day to 50 mg per day.

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

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

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

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

CONTRAINDICATIONS:
Corace Plus is contraindicated in following cases;
- Hypersensitivity to the active substances or to any of the excipients.
- Hypersensitivity to any other angiotensin converting enzyme (ACE) inhibitor.
- Hypersensitivity to any sulphonamide-derived drugs.
- History of angioedema associated with previous ACE inhibitor therapy.
- Concomitant use of Corace Plus with sacubitril/valsartan therapy. Corace Plus must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Anuria
- Severe hepatic impairment.
- The concomitant use of Corace Plus with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

WARNINGS AND PRECAUTIONS:
Fetal Toxicity
Pregnancy category D
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue CORACE PLUS as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.
In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue CORACE PLUS, unless it is considered lifesaving for the mother. Closely observe infants with histories of in utero exposure to CORACE PLUS for hypotension, oliguria, and hyperkalemia.

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. 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.

Symptomatic hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients, but is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependant hypertension. Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision. Particular consideration applies to patients with ischaemic heart or cerebrovascular disease, because an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication for further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.
In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of lisinopril-hydrochlorothiazide may be necessary.

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
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. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Renal function impairment
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below. Lisinopril/hydrochlorothiazide should not be administered to patients with renal insufficiency (creatinine clearance less than or equal to 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.
In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, renal function should be monitored during the first few weeks of lisinopril/hydrochlorothiazide therapy.
Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic.
This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or lisinopril may be required.

Prior Diuretic Therapy:
Symptomatic hypotension may occur following the initial dose of Corace Plus; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Corace Plus. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

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

Anaphylactoid reactions in haemodialytic patients
The use of lisinopril/hydrochlorothiazide is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients, undergoing certain haemodialysis procedures and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

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

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

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

Metabolic and endocrine effects
ACE inhibitor and thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemia levels should be closely monitored during the first month of treatment with an ACE inhibitor. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

Electrolyte imbalance
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting. Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not require treatment. Thiazides have been shown to increase the urinary excretions of magnesium, which may result in hypomagnesaemia.
Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Hyperkalaemia
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function, diabetes mellitus and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, other drugs associated with increase in serum potassium 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, serum potassium and renal function should be monitored.

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

Hypersensitivity/angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly in patients treated with ACE inhibitors, including lisinopril. This may occur at any time during therapy. In such cases, lisinopril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.
Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Desensitisation
Patients receiving ACE inhibitors during desensitisation treatment have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they reappeared upon inadvertent rechallenge.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported for patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

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

Anti-doping test
The hydrochlorothiazide contained in this medication could produce a positive analytic 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.

DRUG INTERACTIONS:
Antihypertensive agents
When combined with other antihypertensive agents, additive falls in blood pressure may occur. Concomitant use of glyceryl trinitrate and other nitrates or other vasodilators may further reduce the blood pressure. The combination of lisinopril with aliskiren-containing medicines should be avoided.

Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors and vildagliptin may lead to an increase in the risk of angioedema. Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.

Lithium
The combination of ACE inhibitors and lithium is generally not recommended. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and pose a high risk of lithium toxicity. The combination of lisinopril and hydrochlorothiazide with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary.

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

Tricyclic antidepressants/ antipsychotics /anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further lowering of blood pressure.

NSAIDs including acetylsalicylic acid
Chronic administration of NSAID (selective cyclooxygenase-2 inhibitors, acetylsalicylic acid >3 g/day and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of ACE inhibitors and thiazide diuretics. NSAID and ACE inhibitors may exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

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

Sympathomimetics
Sympathomimetics can reduce the antihypertensive effect of ACE inhibitors. Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Antidiabetics
Treatment with a thiazide diuretic may impair glucose tolerance. This phenomenon appeared to be more likely to occur during the first weeks of combination treatment and in patients with renal impairment. Other antidiabetic drugs including insulin requirements in diabetic patients may be increased, decreased, or unchanged. The hyperglycaemic effect of diazoxide may be enhanced by thiazides.
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives
The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by drugs associated with potassium loss and hypokalaemia. Hypokalemia may develop during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

Calcium salts
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored and the dose adjusted accordingly.

Cardiac glycosides
Hypokalemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis.

Colestyramine and colestipol
The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine. Therefore sulphonamide diuretics should be taken at least 1 hour before or 4-6 hours after intake of these agents.

Non-depolarising muscle relaxants
Thiazides may increase the responsiveness to non-depolarising skeletal muscle relaxants.

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

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

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

Ciclosporin
Concomitant administration of ACE inhibitors and ciclosporin increases the risk of renal damage and hyperkalaemia. Monitoring of serum potassium is recommended. Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Heparin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

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

Cytostatics, immunosuppressives, procainamide
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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

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

ADVERSE EFFECTS:
Common: Dizziness, headache, syncope, orthostatic effects (including orthostatic hypotension), cough, diarrhoea, vomiting, renal dysfunction,
Uncommon: Paraesthesia, vertigo, taste disturbance, sleep disturbances, mood alterations, depressive symptoms, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, palpitations, tachycardia, raynaud's syndrome, rhinitis, nausea, abdominal pain and indigestion, elevated liver enzymes and bilirubin, rash, pruritus, impotence, asthenia, fatigue, increases in blood urea, increases in serum creatinine, hyperkalaemia,
Rare: Decreases in haemoglobin, decreases in haematocrit, syndrome of inappropriate antidiuretic hormone secretion (siadh), mental confusion, olfactory disturbance, dry mouth, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx, urticaria, alopecia, psoriasis, uraemia, acute renal failure, gynaecomastia, hyponatraemia
Very Rare: Bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia, lymphadenopathy, autoimmune disease, hypoglycaemia, bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia, pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure, diaphoresis, pemphigus, toxic epidermal necrolysis, stevens-johnson syndrome, erythema multiforme, cutaneous pseudolymphoma, oliguria/anuria
Not Known: Anaphylactic/anaphylactoid reaction, hallucinations, flushing, sialadenitis, non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma), leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression, anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloremic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout, restlessness, depression, sleep disturbance, loss of appetite, paraesthesia, light-headedness, xanthopsia, transient blurred vision, acute myopia and acute angle-closure glaucoma, choroidal effusion, vertigo, postural hypotension, necrotising angiitis (vasculitis, cutaneous vasculitis), respiratory distress (including pneumonitis and pulmonary oedema), gastric irritation, diarrhoea, constipation, pancreatitis, jaundice (intrahepatic cholestatic jaundice), photosensitivity reactions, rash, systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis, muscle spasm, muscle weakness, renal dysfunction, interstitial nephritits, fever, weakness

USE IN PREGNANCY AND LACTATION:
Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy. ACE inhibitor therapy exposure during the second and third trimesters is known to induce human foetotoxicity and neonatal toxicity.
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. 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. 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 primary hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation:
lisinopril/hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of lisinopril/hydrochlorothiazide during breast feeding is not recommended. If lisinopril/hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

OVERDOSE:
The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the supine position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently. Bradycardia or extensive vagal reactions should be treated by administering atropine.

SHELF LIFE: 2.5 years

INSTRUCTION:
Store at controlled room temperature, 20° to 25°C. Protect from excessive light and humidity.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

PRESENTATION:
Corace Plus 10/12.5 mg Tablets (Lisinopril + Hydrochlorothiazide) available in cold form, cold seal blister pack of 14's.
Corace Plus 20/12.5 mg Tablets (Lisinopril + Hydrochlorothiazide) available in cold form, cold seal blister pack of 28's

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دھوپ، گرمی اور نمی سے محفوظ رکھے کے درجہ حرارت (۲۰۔۲۵ ڈگری سینٹی گریڈ) پر رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
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