For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

Ramipril & Hydrochlorothiazide Tablets IP

Cardace®H

DESCRIPTION
Active Moiety(ies) / Active Ingredients
Ramipril and Hydrochlorothiazide.

Ramiprilat, the active metabolite of ramipril, is an inhibitor of the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme [ACE], kininase II). Hydrochlorothiazide is a thiazide diuretic.

Therapeutic or Pharmacological Class
ACE inhibitor plus diuretic. Antihypertensive.

Pharmaceutical Form(s)
Tablets.

Composition

Cardace® H 2.5 mg
Each uncoated tablet contains:
Ramipril I.P… ……2.5mg
Hydrochlorothiazide I.P…..12.5 mg
Excipients qs

Cardace ® H 5 mg
Each uncoated tablet contains:
Ramipril I.P… ……5mg
Hydrochlorothiazide I.P…..12.5mg
Colour : Red Iron Oxide, Excipients qs

Cardace ® H 10 mg
Each uncoated tablet contains:
Ramipril I.P… ……10mg
Hydrochlorothiazide I.P…..12.5 mg
Colour : Red Iron Oxide & Yellow Iron Oxide, Excipients qs

INDICATIONS
For the treatment of mild to moderate hypertension in patients (in whom combination therapy is appropriate) who have been stabilized on the individual components given in the same proportion.

Cardace® H does not represent a treatment of choice for primary hyperaldosteronism

DOSAGE AND ADMINISTRATION

Dosage

The dosage is based on the desired antihypertensive effect and on how the patient tolerates the drug.

Applies to Cardace® H 2.5 mg and Cardace® H 5 mg

The following dosage applies in the absence of special circumstances defined below:

Usual initial dosage: 2.5mg ramipril/12.5mg hydrochlorothiazide daily. If necessary, the dose may be increased at intervals of 2 to 3 weeks.

Applies to Cardace® H 10 mg

One tablet once daily in patients whose blood pressure is controlled with ramipril and hydrochlorothiazide given individually at the same doses or in patients whose blood pressure is not adequately controlled with ramipril 10mg alone.

Maximum permitted daily dose: 10 mg ramipril / 50mg hydrochlorothiazide.

Generally, it is recommended that the daily dose be administered in the morning as a single dose.

In most cases, blood pressure will fall sufficiently after 2.5 mg ramipril/12.5mg hydrochlorothiazide to 5 mg ramipril/25 mg hydrochlorothiazide.

- **Special populations**

Children

Cardace® H is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy (See Section Warnings)

Elderly

Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients (See Section Precautions).

Severe Renal Impairment:

Cardace® H is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min per 1.73 m^2 body surface) and in dialysis patients (See Section Contraindications)

Moderate Renal Impairment:

Patients with creatinine clearance 60 to 30 ml/min per 1.73 m^2 body surface area: Treatment is started with ramipril alone at a daily dose of 1.25 mg. After gradually increasing the dose of ramipril, medication with the combination preparation is started at a daily dose of 2.5 mg ramipril / 12.5 mg hydrochlorothiazide. Maximum permitted daily dose: 5 mg ramipril / 25 mg hydrochlorothiazide. Cardace® H 10 mg/12.5 mg and Cardace® H 10mg/25 mg must not be used in these patients.

Severe Hepatic Impairment

Cardace® H is contraindicated in these patients. (See Section Contraindications).

Mild or Moderate Hepatic Impairment:
In patients with mild to moderate hepatic impairment, treatment with Cardace® H must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg of ramipril. Cardace® H 5 mg/25 mg, 10 mg/12.5 mg and 10 mg/25 mg must not be used in these patients.

Patients pre-treated with diuretics
In patients pre-treated with a diuretic, consideration must be given to discontinuing the diuretic at least 2 to 3 days or (depending on the duration of action of the diuretic) longer before starting treatment with Cardace® H, or at least to reducing the diuretic dose.

Should discontinuation not be possible, it is recommended that treatment be initiated with the smallest possible dosage of ramipril (1.25 mg daily) in a free combination. It is recommended that, subsequently, a changeover be made to an initial daily dose of not more than 2.5 mg ramipril/12.5 mg hydrochlorothiazide.

Administration
Cardace® H tablets have to be swallowed with sufficient amounts of liquid (approx. ½ glass). The tablets must not be chewed or crushed.

Cardace® H may be taken before, during or after a meal.

CONTRAINDICATIONS
Cardace® H must not be used
- in patients with hypersensitivity to ramipril, any other ACE inhibitor, hydrochlorothiazide, other thiazide diuretics, sulfonamides or any of the excipients of Cardace® H.
- in patients with a history of angioedema
- concomitantly with sacubitril/valsartan therapy (see Section Interactions). Do not initiate Cardace® H until sacubitril/valsartan is eliminated from the body. In case of switch from Cardace® H to sacubitril/valsartan, do not start sacubitril/valsartan until Cardace® H is eliminated from the body.
- in patients with severe impairment of renal function with a creatinine clearance below 30 ml/min per 1.73 m² body surface area, and in dialysis patients.
- in patients with hemodynamically relevant renal artery stenosis, bilateral or unilateral in the single kidney
- in patients with clinically relevant electrolyte disturbances which may worsen following treatment with Cardace® H (e.g., hypokalemia, hyponatremia, or hypercalcemia)
- in patients with severe impairment of liver function
- with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment (creatinine clearance <60 ml/min).
- with angiotensin-II receptor antagonists (AIIRAs) in patients with diabetic nephropathy.
- during pregnancy.
- in breast-feeding women

Concomitant use of ACE inhibitors and extracorporeal treatments leading to contact of blood with negatively charged surfaces must be avoided since such use may lead to severe anaphylactoid reactions. Such extracorporeal treatments include dialysis or haemofiltration with certain high-flux (e.g. polyacrylonitril) membranes and low-density lipoprotein apheresis with dextran sulphate.

WARNINGS

Non-melanoma skin cancer:

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

Patients taking HCTZ should be informed of the risk of non-melanoma skin and lip cancer and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions.

Special attention is advised in patients with known risk factors of skin cancer such as: skin phototypes I and II (pale white and fair skin), family history of skin cancer, history of skin damage due to sun/UV radiation and radiotherapy exposure, smoking and photosensitizing treatment.

Possible preventive measures such as limited exposure to sunlight and ultraviolet rays and adequate protection when exposed to sunlight 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 non-melanoma skin and lip cancer (see Section Adverse Reactions).

Acute Respiratory Toxicity:

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, Cardace® H should be withdrawn and appropriate treatment should be given. Hydrochlorothiazide must not be administered to patients who previously experienced ARDS following intake of hydrochlorothiazide or another thiazide diuretic. [i]

Angioedema - Head, Neck or Extremities

Angioedema occurring during treatment with an ACE inhibitor necessitates immediate discontinuation of the drug**.**

Angioedema of the face, extremities, lips, tongue, glottis or larynx has been reported in patients treated with ACE inhibitors**.** Emergency treatment of life-threatening angioedema includes immediate administration of epinephrine (subcutaneous or slow intravenous injection) accompanied by monitoring of ECG and blood pressure. Hospitalization of the patient is advisable with observation for at least 12 to 24 hours and discharge only upon complete resolution of the symptoms.

Angioedema –Intestinal

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.

Insufficient experience has been gained concerning the use of Cardace® H in children, in patients with severe impairment of renal function (creatinine clearance below 20 ml/min per 1.73 m² body surface area), and in dialysis patients.Insufficient experience has been gained concerning the use of Cardace® H in children.
An increased risk of angioedema is possible with concomitant use of other drugs which may cause angioedema (see Section Contraindications and Section Interactions).

Choroidal effusion, Secondary Acute Angle-Closure Glaucoma and/or Acute Myopia : Hydrochlorothiazide is a sulfonamide. Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction, which may result in choroidal effusion with visual field defect, secondary acute angle-closure glaucoma and / or acute myopia. 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 (see Section Adverse Reactions).

Photosensitivity:
Photosensitivity reactions have been reported with the use of thiazide diuretics.
If the photosensitivity reactions occur during treatment with hydrochlorothiazide drugs, treatment should be stopped.

PRECAUTIONS
Treatment with Cardace®H requires regular medical supervision.

- **Dual blockade of the renin-angiotensin-aldosterone system (RAAS)**
  Dual blockade of the renin-angiotensin-aldosterone system by combining Cardace® H with an angiotensin-II receptor antagonist (AIIRA) or with aliskiren is not recommended since there are increased risk of hypotension, hyperkalemia and changes in renal function.
  The use of Cardace® H in combination with aliskiren is contraindicated in patients with diabetes mellitus or with renal impairment (creatinine clearance < 60 ml/min) (see section Contraindications and Section Interactions).
  The use of Cardace H in combination with an AIIRA is contraindicated in patients with diabetic nephropathy (see section Contraindications and section Interactions).

- **Patients with hyper-stimulated renin angiotensin system**
  In the treatment of patients with a hyper-stimulated renin-angiotensin system, particular caution must be exercised (see section. “Dosage and administration”). Such patients are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor is given for the first time or for the first time at an increased dose. Initial

doses or initial dose increases must be accompanied by close blood pressure monitoring until such time as no further acute reduction in blood pressure is to be anticipated.

Significant activation of the renin angiotensin system is to be anticipated, for example:

- in patients with severe, and particularly with malignant hypertension. The initial phase of treatment requires special medical supervision.

- in patients with concomitant, and particularly with severe heart failure. If heart failure is severe, the initial phase of treatment requires special medical supervision.

- in patients with haemodynamically relevant left-ventricular inflow or outflow impediment (e.g., stenosis of the aortic or mitral valve). The initial phase of treatment requires special medical supervision.

- in patients with haemodynamically relevant renal artery stenosis. The initial phase of treatment requires special medical supervision. See also under 'Monitoring of renal function' below.

- in patients pre-treated with diuretics. Where discontinuing use or reducing the dose of the diuretic is not possible, the initial phase of treatment requires special medical supervision.

- in patients in whom fluid or salt depletion exists or may develop (as a result of insufficient fluid or salt intake, or as a result of, for example, diarrhoea, vomiting or excessive sweating in cases where salt and fluid replacement is inadequate).

Generally, it is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed against the risk of volume overload). When these conditions have become clinically relevant, treatment with Cardace® H must only be started or continued if appropriate steps are taken concurrently to prevent an excessive fall in blood pressure and deterioration of renal function.

- **Patients at particular risk from a pronounced reduction in blood pressure**
  In patients who would be at particular risk from an undesirably pronounced reduction in blood pressure (e.g. patients with haemodynamically relevant stenoses of the coronary arteries or of the blood vessels supplying the brain), the initial phase of treatment requires special medical supervision**.**

- **Elderly**
  Some elderly patients may be particularly responsive to ACE inhibitors. Evaluation of renal function at the beginning of treatment is recommended (See Dosage & Administration).

- **Monitoring of renal function**

It is recommended that renal function be monitored, particularly in the initial weeks of treatment. Particularly careful monitoring is required in patients with

- heart failure

- renovascular disease, including patients with haemodynamically relevant unilateral renal artery stenosis. In the latter patient group, even a small increase in serum creatinine may be indicative of unilateral loss of renal function.
- impairment of renal function

- kidney transplant patients**.**

- **Electrolyte monitoring**
  Treatment with Cardace®H requires regular monitoring of serum sodium, potassium, calcium, uric acid, and blood glucose. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

- **Haematological monitoring**
  It is recommended that the white blood cell count be monitored to permit detection of a possible leucopenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma) or those treated with other drugs that can cause changes in the blood picture. See section "Adverse reactions".

INTERACTIONS
Food
Absorption of ramipril is not significantly affected by food.

Drug interactions
Contraindicated combinations
The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see Section Contraindications).
Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low-density lipoprotein apheresis with dextran sulfate: Risk of severe anaphylactoid reactions, see section Contraindications.

The combination of Cardace® H with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or with moderate to severe renal impairment (creatinine clearance < 60 ml/min) and is not recommended in other patients (see section Contraindications and section Precautions).

Angiotensin-II receptor antagonists (AIIRAs): The use of Cardace® H in combination with an AIIRA is contraindicated in patients with diabetic nephropathy and is not recommended in other patients (see section Contraindications and section Precautions).

Not recommended associations

Potassium salts, potassium-retaining diuretics or other medicinal products that may increase kalaemia: Rise in serum potassium concentration possible, sometimes severe. Concomitant treatment with potassium-retaining diuretics (e.g. spironolactone), potassium salts or other medicinal products that may increase kalaemia requires close monitoring of serum potassium.

Precautions for use
Antihypertensive agents and other substances with antihypertensive potential (e.g., nitrates, tricyclic antidepressants, anaesthetics): Potentiation of the antihypertensive effect is to be anticipated (concerning diuretics see also "Precautions", "Adverse reactions" and "Dosage and administration").

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of Cardace® H. Particularly close blood pressure monitoring is recommended. Furthermore, the effect of the vasopressor sympathomimetics may be attenuated by hydrochlorothiazide.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of haematological reactions (See section Precautions).

Lithium salts: Excretion of lithium may be reduced. Such reduction may lead to increased serum lithium levels and increased lithium toxicity. Lithium levels must, therefore, be monitored.

Antidiabetic agents (e.g. Insulin and sulfonylurea derivatives): ACE inhibitors may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycaemic reactions in patients concomitantly treated with antidiabetics.

Hydrochlorothiazide may attenuate the effect of antidiabetics. Particularly close blood glucose monitoring is, therefore, recommended in the initial phase of co-administration**.**

Vildagliptin: An increased incidence of angioedema was found in patients taking ACE-inhibitors and vildagliptin.

mTOR Inhibitors (e.g. temsirolimus): An increased incidence of angioedema was observed in patients taking ACE Inhibitors and mTOR Inhibitors (mammalian target of rapamycin inhibitors).

Neprilysin (NEP) inhibitors: An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitors (such as racecadotril) (see section warning)

Take into account
Nonsteroidal anti-inflammatory drugs (e.g. Indomethacin) and acetylsalicylic acid: Possible attenuation of the effect of Cardace® H as well as development of acute renal failure or an increase in serum potassium.

Heparin: Rise in serum potassium concentration possible.

Corticosteroids, carbenoxolone, large amounts of liquorice, laxatives (in case of a prolonged use), and other kaliuretic agents: Promotion of the development of hypokalaemia.

Digitalis preparations: Possible intensification of digitalis toxicity as a result of changes in electrolyte concentrations (e.g. hypokalaemia, hypomagnesaemia).

Methyldopa: Haemolysis possible**.**

Enterally administered ion exchangers such as colestyramine: Reduced absorption of hydrochlorothiazide.

Curare-type muscle relaxants: Possible intensification and prolongation of the muscular relaxing effect**.**

Alcohol: Ramipril may lead to increased vasodilation and thus potentiate the effect of alcohol.

Salt: Possible attenuation of the antihypertensive effect by increased dietary salt intake.

Desensitization therapy: The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

INTERFERENCE WITH LABORATORY AND DIAGNOSTIC TESTS
TESTS FOR PARATHYROID FUNCTION: Hydrochlorothiazide stimulates renal calcium reabsorption and may cause hypercalcaemia. This must be considered when carrying out tests for parathyroid function.

PREGNANCY
Cardace®H must not be taken during pregnancy. Therefore, pregnancy must be excluded before starting treatment.

Pregnancy must be avoided in cases where changeover to a treatment regimen without ACE inhibitors and diuretics is not possible. Otherwise there is a risk of harm to the fetus.

LACTATION
If treatment with Cardace® H is necessary during lactation, the patient must not breast-feed in order to prevent the infant from ingesting small quantities of ramipril and hydrochlorothiazide with breast milk.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
Some adverse effects (e.g. some symptoms of a reduction in blood pressure such as lightheadedness, dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:
Very common ≥10 %; Common ≥1 and <10 % ; Uncommon ≥0.1 and < 1 %;
Rare ≥0.01 and < 0.1 %; Very rare < 0.01 %, Unknown or Not known (cannot be estimated from available data).

As Cardace® H is an antihypertensive, many of its adverse reactions are effects secondary to its blood-pressure-lowering action which results in adrenergic counter-regulation or organ hypoperfusion. Numerous other effects (e.g. effects on electrolyte balance, certain anaphylactoid reactions or inflammatory reactions of the mucous membranes) are due to the ACE inhibition or to other pharmacologic actions of ramipril or hydrochlorothiazide.

The following adverse effects have been observed during therapy with Cardace® H, its constituents ramipril and hydrochlorothiazide, other ACE inhibitors, or comparable diuretics, and may, therefore, occur.
Adverse reactions frequency is defined using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Common	**Uncommon**	**Very rare**	**Not Known**
System Organ Class: Neoplasms benign, malignant and unspecified (including cysts and polyps)				Non-melanoma skin and lip cancer (Basal cell carcinoma and Squamous cell carcinoma) *Non-melanoma skin and lip cancer: Based on available data from two epidemiological studies based on Danish National cancer registries, cumulative dose-dependent association between HCTZ and non-melanoma skin and lip cancer (Basal cell carcinoma and Squamous cell carcinoma) has been observed (see section Warnings).
Cardiac disorder		Myocardial ischemia including angina pectoris , tachycardia, arrhythmia,		Myocardial infarction

		palpitations, oedema peripheral		
Blood and lymphatic system disorders		White blood cell count decreased, red blood cell count decreased, hemoglobin decreased, hemolytic anemia, platelet count decreased		Bone marrow failure, neutropenia including agranulocytosis, pancytopenia, eosinophillia, Hemoconcentration in the context of fluid depletion
Nervous system disorders	Headache, dizziness (light headedness)	Vertigo, paresthesia, tremor, balance disorder, burning sensation, dysgeusia (taste disturbances), ageusia (loss of taste),		Cerebral ischemia including ischemic stroke and transient ischaemic attack, psychomotor skills impaired (impaired reactions), parosmia (smell disturbances)
Eye disorders		Visual disturbance including blurred vision, Conjunctivitis		Xanthopsia, lacrimation decreased due to hydrochlorthiazide Secondary acute angle-closure glaucoma and/or acute myopia, choroidal effusion due to hydrochlorothiazide (See Section Warnings)
Ear and labyrinth disorders		Tinnitus		Hearing impaired
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis	Sinusitis, dyspnea, nasal congestion		Bronchospasm including asthma aggravated, Acute respiratory distress syndrome (ARDS) due to hydrochlorothiazide (See Section Warnings). Alveolitis allergic (pneumonitis), non cardiogenic pulmonary edema due to hydrochlorothiazide.
Gastrointestinal disorders		Gastrointestinal inflammation (inflammatory reactions of the gastrointestinal	Vomiting, aphtous stomatitis (inflammatory reactions	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic

		tract), digestive disturbances, abdominal discomfort, dyspepsia, gastritis, nausea, constipation Gingivitis due to hydrochlorothiazide	of the oral cavity), glossitis, diarrhea, abdominal pain upper, dry mouth	enzymes increased, small bowel angioedema Sialadenitis due to hydrochlorothiazide
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, blood urea increased, blood creatinine increased		Worsening of a pre-existing proteinuria Interstitial nephritis due to hydrochlorothiazide
Skin and subcutaneous tissue disorders		Angioedema: very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; dermatitis psoriasiform, hyperhidrosis (sweating), rash, in particular maculo-papular, pruritus, alopecia		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, Exfoliative dermatitis, photosensitivity reaction, onycholysis, pemphigoid or lichenoid exanthema or enanthema, urticaria Systemic lupus erythematosus due to hydrochlorothiazide (lupus erythematosus)
Musculoskeletal and connective tissue disorders		Myalgia		Arthralgia, muscle spasms (muscle cramps) Muscular weakness, musculoskeletal stiffness, tetany due to hydrochlorothiazide
Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Diabetes mellitus inadequate control, glucose tolerance	Anorexia, decreased appetite Blood potassium decreased, thirst due to hydrochlorothiazid	Blood potassium increased due to ramipril	Blood sodium decreased Glycosuria, metabolic alkalosis, hypochloremia, hypomagnesaemia, hypercalcemia,

	decreased, blood glucose increased, blood uric acid increased, gout aggravated, blood cholesterol and / or triglycerides increased due to hydrochlorothiazide.	e		dehydration due to hydrochlorthiazide.
Vascular disorders		Hypotension, orthostatic blood pressure decreased (disturbed orthostatic regulation), syncope, flushing		Thrombosis in the context of severe fluid depletion, vascular stenosis, hypoperfusion (exacerbation of perfusion disturbances), Raynaud's phenomenon, vasculitis.
General disorders and administration site conditions	Fatigue (tiredness), asthenia (weakness)	Chest pain, pyrexia (fever)		
Immune system disorders				Anaphylactic or anaphylactoid reactions (severe anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition) to either ramipril or anaphylactic reaction to hydrochlorothiazide, antinuclear antibody increased.
Hepatobiliary disorders		Cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional), hepatic enzyme and / or bilirubin conjugated increased.		Acute hepatic failure, jaundice cholestatic, hepatocellular damage.

		Calculous cholecystitis due to hydrochlorothiazide		
Reproductive system and breast disorders		Transient erectile impotence		Libido decreased, gynecomastia
Psychiatric disorders		Depressed mood, apathy, anxiety, nervousness, sleep disorders including somnolence (drowsiness, sleepiness)		Confusional state, restlessness, disturbance in attention (concentration problems)

OVERDOSE

Symptoms

Overdosage may cause persistent diuresis, excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, renal failure, cardiac arrhythmias, impairment of consciousness up to and including coma, cerebral convulsions, pareses, and paralytic ileus.

In patients with obstruction of urinary outflow (e.g from prostatic hyperplasia), sudden diuresis may induce acute urinary retention with overdistension of the bladder.

Management

Primary detoxification by, for example, gastric lavage, administration of adsorbants, sodium sulphate (if possible during the first 30 minutes). In the event of hypotension, administration of α_1-adrenergic agonists (e.g. norepinephrine, dopamine) or angiotensin II (angiotensinamide), which is usually available only in scattered research laboratories, must be considered in addition to volume and salt substitution. No experience is available concerning the efficacy of forced diuresis, altering urine pH, hemofiltration or dialysis in speeding up the elimination of ramipril or ramiprilat. If dialysis or hemofiltration is nevertheless contemplated, see also under "Contraindications". Hydrochlorothiazide is dialysable.

Manufactured by:

Sanofi India Limited, L-121, Verna Industrial Estate, Verna, Goa- 403722, India

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[i] Safety evaluation report - Hydrochlorothiazide and combinations, and acute respiratory distress syndrome, Mohammad Iftakhar, 23-Feb-2022

[ii] Safety evaluation report: Hydrochlorothiazide and hydrochlorothiazide combinations and choroidal effusion