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 & Metoprolol Succinate Extended Release Tablets
Cardace® Meto

COMPOSITION

Cardace® Meto 2.5
Each uncoated bilayer tablet contains:
Ramipril I.P. ….2.5mg
Metoprolol Succinate IP…….23.75mg
(equivalent to Metoprolol tartrate 25mg)
(as extended release)
Colour : Yellow Ferric Oxide

Cardace® Meto 5
Each uncoated bilayer tablet contains:
Ramipril I.P. ….5mg
Metoprolol Succinate IP…….47.5mg
(equivalent to Metoprolol tartrate 50mg)
(as extended release)
Colour : Red Ferric Oxide

THERAPEUTIC INDICATIONS

For the treatment of essential hypertension in adults.

DOSAGE AND ADMNISTRATION

Metoprolol succinate extended release and ramipril tablets are intended for once-a-day administration in patients with hypertension.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The dosage should be individualized and titration may be needed in some patients. As the therapeutic response, adverse effects and relative cardioselectivity are related to plasma concentration, poor metabolisers may require lower than normal doses.

The usual initial dosage is one tablet of Cardace Meto 2.5 (25mg/2.5mg) daily. If blood pressure remains uncontrolled after about 2-3 weeks of therapy, the dose may be increased to metoprolol succinate extended release and ramipril (50mg/5mg) daily, depending on severity of blood pressure. Further increases may be done until the desired therapeutic response is achieved, adverse effects become intolerable or a usual maximum adult dosage of 10mg of ramipril and 100mg of metoprolol succinate extended release daily is attained.

Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

SPECIAL POPULATIONS

Elderly patients and patients with renal or hepatic impairment:

The lowest effective dose is recommended for patients with hepatic dysfunction or renal impairment and for elderly patients. Since the initial dose of ramipril in these patients is 1.25mg, this fixed dose combination is not suitable for initial therapy. The combination may be used later on when the patient requires at least 2.5mg of ramipril. In such patients, the maximum total daily dose of ramipril should not exceed 5mg.

Administration
Tablets have to be swallowed with sufficient amounts of liquid (approx. ½ glass). The tablets must not be chewed or crushed and can be taken before, during or after a meal.

CONTRAINDICATIONS

This product must not be used:

- in patients with hypersensitivity to ramipril, metoprolol, to any beta blocker, to any other ACE inhibitor, or any of the excipients of this product.
- in patients with a history of angioedema**.**
- concomitantly with sacubitril/valsartan therapy (see Section Interactions). Do not initiate Cardace® Meto until sacubitril/valsartan is eliminated from the body. In case of switch from Cardace® Meto to sacubitril/valsartan, do not start sacubitril/valsartan until Cardace® Meto is eliminated from the body.
- in patients with hemodynamically relevant renal artery stenosis, bilateral or unilateral in the single kidney.
- in patients with hypotensive or hemodynamically unstable states**.**
- 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
- Second- or third-degree heart block
- Cardiogenic shock
- For concomitant intravenous administration of calcium channel blockers of verapamil or diltiazem type;
- Unstable decompensated heart failure (pulmonary edema, hypo-perfusion or hypotension) and continuous or regular therapy increasing heart contractility (with beta receptor agonist);
- Clinically significant sinus bradycardia (<50/min);
- Sick sinus syndrome;
- Severe disorder of peripheral perfusion associated with pain or trophic changes;
- Hypotension (systolic BP below 100 mmHg);
- Sinoatrial block;
- Bronchial asthma and chronic obstructive bronchopulmonary disease of severe degree;
- Untreated pheochromocytoma;
- Metabolic acidosis;
- Patients with suspected acute myocardial infarction if the pulse rate is lower than 50 bpm, PQ interval is longer than 0.24 s, or systolic blood pressure lower than 100 mmHg.

Patients with decompensated heart failure who are optimally treated with other drugs may use a special titration schedule for doses of metoprolol.

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 hemofiltration with certain high-flux (e.g. polyacrylonitril) membranes and low-density lipoprotein apheresis with dextran sulfate**.**

WARNINGS AND PRECAUTIONS

Ramipril

Angioedema - Head, Neck or Extremities
Angioedema can occur immediately after starting treatment with an ACE inhibitor, however severe angioedema may also occur at any time during long-term treatment with an ACE inhibitor. In case of angioedema, ramipril must be discontinued immediately**.**

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. Healthcare professionals should review the response to treatment noting standard therapies for histamine-mediated angioedema may be ineffective for bradykinin-mediated angioedema. 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 Ramipril 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.

An increased risk of angioedema is possible with concomitant use of other drugs which may cause angioedema (see Section Contraindication and Section Interactions)**.**

Treatment with Ramipril requires regular medical supervision.

- **Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with aliskiren-containing medicines.**

Dual blockade of the renin-angiotensin-aldosterone system by combining Ramipril with an angiotensin-II receptor antagonist (AIIRA) or aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia and changes in renal function compared to monotherapy.

The use of Ramipril in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (creatinine clearance < 60 mL/min) (see Contraindications and Section Precautions).

The use of Ramipril in combination with an AIIRA is contraindicated in patients with diabetic nephropathy. (See Contraindications and Section Precautions)

- **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 also under 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 or a concomitant diuretic 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 heart failure**,** particularly if severe or if treated with other substances having antihypertensive potential. If heart failure is severe, the initial phase of treatment requires special medical supervision.

- in patients with hemodynamically 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 hemodynamically relevant renal artery stenosis. The initial phase of treatment requires special medical supervision. Discontinuation of diuretic therapy may be required. 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 exist or may develop (as a result of insufficient fluid or salt intake, or as a result of, e.g., diarrhea, vomiting or excessive sweating in cases where salt and fluid replacement is inadequate).

Generally, it is recommended that dehydration, hypovolemia 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®Meto 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

See also under 'Patients with liver diseases'.

- **Patients with liver diseases**

In patients with impaired liver function, response to the treatment with Cardace®Meto may be either increased or reduced. In addition, in patients in whom severe liver cirrhosis with oedema and/or ascites is present, the renin angiotensin system may be significantly activated; therefore, particular caution must be exercised in treating these patients (see also above and under Section Dosage and Administration).

- **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 hemodynamically 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 under Section Dosage and Administration).

- **Monitoring of renal function**

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

- heart failure
- renovascular disease, including patients with hemodynamically 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**.**

- **Electrolyte monitoring**

It is recommended that serum potassium and serum sodium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function**.**

- **Hematological 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 dverse reactions.)

Metoprolol

In chronic obstructive disease, metoprolol may cause increased resistance in the respiratory tract (especially with doses over 200 mg). Patients with bronchospastic diseases should not use beta blockers. With regard to relative beta-1 selectivity, metoprolol may be used with caution in patients who do not respond to other antihypertensives or do not tolerate them. Because beta-1 selectivity is not absolute, beta-2 stimulants (in the form of tablets or aerosol) and the lowest possible doses of metoprolol (up to 200 mg) should be administered concomitantly. If dyspnea or bronchospasm occur, beta-2 stimulants must be administered, and the treatment must be terminated.

While on therapy with metoprolol, the risk of affecting the metabolism of sugars or masking hypoglycemia is lower compared to non-selective beta blockers. In diabetes, it is necessary to optimally adjust the antidiabetic therapy and to warn the diabetic patient about masking hypoglycemia manifested by increased sweating.

Severe hypoglycemia may result in seizures, especially in the context of an overdose.

In some patients, metoprolol may exacerbate the symptoms of heart failure. Sympathetic stimulation is an important vital component supporting the circulatory function in congestive heart failure and beta blocker inhibition may carry the potential risk of additionally reducing myocardial contractility and speeding up heart failure. Beta-adrenergic block brings the potential risk of additionally reducing myocardial contractility and exacerbating heart failure.

Very rarely, an existing AV conduction disorder may become worse and may result in an AV block of a higher degree. The medicinal product may only be administered to patients with a first-degree A-V block with extra caution.

If bradycardia develops while administering metoprolol, the dose of metoprolol should be reduced, or it should be discontinued entirely.

Metoprolol may, as a result of its antihypertensive effect, exacerbate the symptoms of severe peripheral perfusion disorder.

For pheochromocytoma, metoprolol may be used only after starting treatment with an alpha blocker.

Metoprolol therapy should not be discontinued suddenly but gradually, over 10–14 days, down to 25 mg once daily in the course of the last 6 days (applicable for metoprolol 50 and 100 mg). During this period, patients with ischemic heart disease should be monitored with extra caution. The risk of a coronary accident, including sudden death, may be elevated while discontinuing beta blocker therapy. Increased caution is necessary especially in patients with Prinzmetal's angina pectoris because beta-1 selective substances may increase the number and duration of angina pectoris attacks.

Metoprolol therapy may sometimes mask the symptoms of thyrotoxicosis. Metoprolol should therefore be administered with caution to patients who have thyrotoxicosis or are expected to develop it, while their thyroid and heart function must be carefully monitored.

Before administering general anesthesia, the anesthesiologist should be informed that the patient is using metoprolol. Inhalation anesthetics may increase the cardiodepressant effects of beta blockers. Discontinuing metoprolol in the course of a surgical intervention is not recommended. Continuing beta blockers reduces the risk of arrhythmia and myocardial ischemia during a surgical intervention and after it. If therapy continues, caution must be taken with the use of some anesthetics. It is necessary to avoid high doses of metoprolol in patients undergoing a non-cardiological surgical intervention because it would be associated with bradycardia and hypotension in patients with a cardiovascular risk.

Dosage may need to be adjusted in patients with severe liver function disorder because metoprolol undergoes biotransformation in the liver.

Anaphylactic shock has a more severe course in patients treated with beta blockers and may be resistant to regular doses of adrenaline.

Patients with a history of severe allergic reaction may be administered metoprolol only with extra caution. Extra caution is also necessary in allergic patients treated with vaccines (desensitization therapy).

The risk/benefit ratio of the therapy must also be considered in patients with myasthenia gravis, psoriasis, and depression disorder.

INTERACTIONS

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

Drug interactions

Contra-indicated 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 hemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low-density lipoprotein apheresis with dextran sulfate: Risk of severe anaphylactoid reactions; see also under Section Contraindications.

The combination of Ramipril with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or 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 combination of Cardace® Meto with AIIRAs is not recommended. The use of Ramipril 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, sometimes severe, is to be anticipated. 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 (e.g. diuretics) and other substances with antihypertensive potential (e.g. nitrates, tricyclic antidepressants, anesthetics): Potentiation of the antihypertensive effect is to be anticipated (concerning diuretics see also under SectionPrecautions", Section Adverse reactions" and Section Dosage and administration). Regular monitoring of serum sodium is recommended in patients undergoing concurrent diuretic therapy.

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of Cardace®Meto. Particularly close blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of hematological reactions (see also under Section Precautions).

Lithium salts: Excretion of lithium may be reduced by ACE inhibitors. 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 hypoglycemic reactions in patients concomitantly treated with anti-diabetics. 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 Warnings)

Take into account:
Nonsteroidal anti-inflammatory drugs (e.g. indomethacin) and acetylsalicylic acid: Attenuation of the antihypertensive effect of Cardace®Meto is to be anticipated. Furthermore, concomitant treatment of ACE

inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium.

Heparin: Rise in serum potassium concentration possible.

Alcohol: Increased vasodilatation. Cardace®Meto may potentiate the effect of alcohol.

Salt: Increased dietary salt intake may attenuate the antihypertensive effect of Cardace®Meto.

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

Metoprolol
Increased medical supervision is required for all patients who concomitantly use other drugs containing beta-1 sympathetics (e.g. eye drops) and ganglioplegics.

Monoamine oxidase inhibitors (I-MAO)
Concomitant use of MAO inhibitors is not recommended due to the danger of reinforcing the hypotension effect of metoprolol as well as the risk of developing a hypertension crisis which may occur up to 14 days after discontinuing I-MAO.

Ergotamine
Due to the fact that beta blockers may affect peripheral circulation, caution is necessary with concomitant administration of drugs with a similar effect, e.g. ergotamine.

Clonidine
Beta blockers may accentuate the "rebound hypertension" that may occur after clonidine discontinuation. With scheduled discontinuation of clonidine therapy, beta blocker therapy must be discontinued several days before the expected clonidine discontinuation.

Alpha blockers
Patients using alpha blockers, such as prazosin, tamsulosin, doxazosin and terazosin, have an elevated risk of hypotension, especially severe orthostatic hypotension.

Calcium channel blockers
It is necessary to keep in mind the negative inotropic and negative chronotropic effect of metoprolol in cases when it is used concomitantly with calcium channel blockers of verapamil and diltiazem type and/or antiarrhythmics. Patients treated with beta blockers should not have intravenous administration of drugs containing calcium antagonists of verapamil type, due to the risk of hypotension, AV conduction disorders, and left ventricular insufficiency. Concomitant therapy of beta blockers with dihydropyridines (such as nifedipine and amlodipine) may increase heart rhythm and the risk of hypotension, and patients with latent heart insufficiency may develop heart failure as the final consequence.

Class I antiarrhythmics and amiodarone
Beta blockers may increase the negative inotropic and negative dromotropic effect of antiarrhythmics of quinidine type and amiodarone.

Cardiac glycosides
Concurrent administration with cardiac glycosides may result in deepening the negative chronotropic effect and extending the AV conduction.

Nitrates
Nitrates may increase the hypotension effect of metoprolol.

Enzyme inductors and inhibitors
Metoprolol is a CYP2D6 substrate, and therefore enzyme inhibitors may affect metoprolol plasma concentrations. Metoprolol plasma concentration is reduced by rifampicin. Metoprolol concentration may be elevated with the concomitant administration of antiarrhythmics (e.g. propafenone), antiretrovirals (e.g. ritonavir), antihistamines (e.g. diphenhydramine), fungicides (e.g. terbinafine), cimetidine, antimalarials (e.g. hydroxychloroquine or quinidine), alcohol and hydralazine, antipsychotics (e.g. thioridazine, celecoxib), and with the concomitant administration of antidepressants such as bupropion, or with selective serotonin reuptake inhibitors (SSRI), i.e. paroxetine, fluoxetine and sertraline.

Non-steroidal anti-inflammatory drugs
Concomitant administration of indomethacin or other prostaglandin synthesis inhibitors may reduce the antihypertensive effect of beta blockers.

Skeletal muscle relaxants
The hypotension effect of beta blockers may be elevated in the presence of baclofen and tizanidine. Concomitant administration of beta blockers with tizanidine may increase bradycardia.

Drugs with a known antihypertensive effect
Caution is necessary if metoprolol is combined with other drugs that may reduce blood pressure, such as tricyclic antidepressants, barbiturates or phenothiazines.

Sympathomimetics
Concomitant administration with sympathomimetics results in a mutual inhibition effect. Metoprolol antagonizes the beta-1 effect of sympathomimetics.

Xanthines
Aminophylline, theophylline may increase the pressure response thus resulting in hypertension due to the mutual inhibition of treatment effects.

Parasympathomimetics
Concomitant administration with parasympathomimetics (neostigmine, pyridostigmine) may result in hypotension and extended bradycardia.

Insulin and oral antidiabetics
The effect of insulin and oral antidiabetics on reducing the blood glucose level may be reinforced by beta blockers. Oral anti-diabetic dosage in patients using beta blockers must sometimes be adjusted.

General anesthetics
Some inhalation anesthetics may increase the cardiodepressant effects of beta blockers.

Adrenaline
Severe hypertension and bradycardia were reported many times in patients treated with non-selective beta receptor blockers who were administered adrenaline (epinephrine). It is not expected that metoprolol as a selective beta blocker will cause a hypertension response after adrenaline, but it cannot be eliminated.

Phenylpropanolamine
A single administration of phenylpropanolamine to healthy volunteers and patients with hypertension

using beta blockers resulted in elevating blood pressure in both. However, the administration of a repeated dose of phenylpropanolamine concomitantly with beta blockers did not change the blood pressure level. Caution and careful monitoring is necessary when starting concomitant administration of phenylpropanolamine and beta blockers.

Lidocaine
Metoprolol may reduce the elimination (reduce clearance) of lidocaine.

Antacids
In concomitant administration of metoprolol with antacid, elevated metoprolol plasma concentrations were observed.

Alcohol
Concomitant use of alcohol and metoprolol increases the level of blood alcohol and protracts its effect.

Diltiazem

An increased risk of depression has been observed when beta-blockers are co-administered with diltiazem.

Sinus arrest may occur when beta blockers, including Cardace®Meto, are used in combination with other drugs known to induce sinus arrest such as amiodarone, digoxin, diltiazem, verapamil, flecainide, ivabradine.

REPRODUCTION

PREGNANCY
Cardace®Meto must not be taken during pregnancy (see also under Section Contraindications). Therefore, pregnancy must be excluded before starting treatment. Pregnancy must be avoided in cases where treatment with ACE inhibitors is indispensable.

If the patient intends to become pregnant, treatment with ACE inhibitors must be discontinued, i.e. replaced by another form of treatment.

If the patient becomes pregnant during treatment, medication with Cardace®Meto must be replaced as soon as possible by a treatment regimen without ACE inhibitors. Otherwise there is a risk of harm to the fetus.

LACTATION
Cardace® Meto is not recommended during lactation. Consider possible infant exposure.

PAEDIATRIC POPULATION
Safety and efficacy in pediatric population has not been established.

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

Ramipril

As ramipril 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 this drug class

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	Rare	Very rare	Not known
Cardiac disorders		Myocardial ischemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, hemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, hemolytic anemia
Nervous system disorders	Headache, dizziness (lightheadedness)	Vertigo, paresthesia, ageusia (loss of taste), dysgeusia (taste disturbances)	Tremor, balance disorder		Cerebral ischemia including ischemic stroke and transient ischemic attack, psychomotor skills impaired (impaired reactions), burning sensation, parosmia (smell

					disturbances)
Eye disorders		Visual disturbance including blurred vision	Conjunctivitis		
Ear and labyrinth disorders			Hearing impaired, tinnitus		
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation (inflammatory reactions of the gastrointestinal tract), digestive disturbances, abdominal discomfort, dyspepsia, diarrhea, nausea, vomiting	Fatal pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphtous stomatitis (inflammatory reactions of the oral cavity)
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased			
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular	Angioedema with fatal outcome	Exfoliative dermatitis, urticaria,	Photosensitivity reaction	Toxic epidermal necrolysis,

		(maybe/become Life-threatening, rarely severe course can cause fatal obstruction); pruritus, hyperhidrosis (sweating)	onycholysis		Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective tissue disorders	Muscle spasms (muscle cramps), myalgia	Arthralgia			
Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite			Blood sodium Decreased
Vascular disorders	Hypotension, orthostatic blood pressure decreased (disturbed orthostatic regulation), syncope	Flushing	Vascular stenosis, hypoperfusion (exacerbation of perfusion disturbances, vasculitis		Raynaud's Phenomenon
General disorders and administration site conditions	Chest pain, fatigue	Pyrexia (fever)	Asthenia (weakness)		
Immune system disorders					Anaphylactic or anaphylactoid reactions (severe anaphylactic and anaphylactoid reactions to insect venoma is increased

					under ACE inhibition), antinuclear antibody increased
Hepatobiliary disorders		Hepatic enzymes and/or bilirubin conjugated increased	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional)
Reproductive system and breast disorders		Transient erectile impotence, libido decreased			Gynecomastia
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence (drowsiness)	Confusional state		Disturbance in attention

Metoprolol

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%; Not known (cannot be estimated from available data).

MedDRA system organ classes	**frequency**	**Type of effect**
Blood and lymphatic system disorders	very rare	thrombocytopenia
Metabolism and nutrition disorders	rare	masking hypoglycemia symptoms
Psychiatric disorders	common	sleepiness, insomnia
	uncommon	nightmares
	rare	depression, concentration disorders
	very rare	memory disorders, confusion, hallucinations, nervousness, anxiety
Nervous system disorders	uncommon	dizziness, headache
	rare	paresthesia

	very rare	taste disorders
Eye disorders	very rare	vision disorders, dry eye, conjunctivitis*
Ear and labyrinth disorders	very rare	tinnitus
Cardiac disorders	uncommon	bradycardia
	rare	temporary exacerbation of symptoms of heart failure, palpitation, heart arrhythmia
	very rare	cardiac impulse conduction disorders
	not known	sinus arrest in predisposed patients (e.g., elderly patients or patients with pre-existing bradycardia, sinus node dysfunction or atrioventricular block)
Vascular disorders	rare	postural hypotension (very rarely accompanied by syncope), Raynaud's syndrome
	very rare	claudications, gangrene in patients with an existing severe disorder of peripheral perfusion
Respiratory, thoracic and mediastinal disorders	uncommon	exertion dyspnea
	rare	bronchospasm
	very rare	cold
Gastrointestinal disorders	common	nausea, vomiting, abdominal pain
	rare	diarrhea, constipation, dyspepsia
	very rare	dry mouth
Hepatobiliary disorders	very rare	hepatitis
Skin and subcutaneous tissue disorders*	rare	urticaria, rash (in the form of psoriasiform and dystrophic skin lesions)
	very rare	light sensitivity, exacerbation of psoriasis, increased sweating, alopecia
Musculoskeletal and connective tissue disorders	rare	muscle cramps
	very rare	arthralgia
	Not known	Lupus-like syndrome
Reproductive system and breast disorders	rare	erectile dysfunction/sexual dysfunction
General disorders and administration site conditions	very common	fatigue
	rare	peripheral edema
Investigations	rare	elevated levels of triglycerides and cholesterol
	very rare	weight gain, abnormal liver function tests

*The incidence of undesirable effects such as skin reactions or eye irritation is low and, in most cases, the symptoms disappear after therapy is terminated.

OVERDOSAGE

Ramipril

Signs and Symptoms:

Overdosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Management:

Primary detoxification by, for example, gastric lavage, administration of adsorbents, sodium sulfate; (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, alteration in urine pH, haemofiltration, or dialysis in speeding up the elimination of ramipril or ramiprilat. If dialysis or haemofiltration is nevertheless considered, see under "Contraindications".

Metoprolol

Signs and Symptoms

Severe hypotension, sinus bradycardia, hypoglycemia, hypoglycemic seizures, AV-block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, unconsciousness and even coma, cramps, nausea, vomiting, cyanosis and sinus arrest.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may exacerbate the patient's condition.

Management:

There is no specific known antidote; overdose therapy is symptomatic. Care should be provided in a facility that can provide the corresponding supportive measuring, monitoring and supervision.
If justified, gastric lavage may be done and/or activated charcoal administered.
Severe bradycardia and hypotension should be treated with atropine. If the desired effect has not been reached, noradrenaline and dopamine may be used. As metoprolol is a competitive isoproterenol antagonist, high doses of this active ingredient may reverse many effects of excess doses of metoprolol.
Hypotension, acute heart failure and shock should be treated with an adequate increase in volume, glucagon injection (50 µg/kg), and if necessary, followed by an intravenous infusion of glucagon (2 5 mg/h).

Hypoglycemia / hypoglycemic seizures: Administer oral / IV glucose

MANUFACTURED BY:

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

Updated*:* Mar 2026

Source: Ramipril CCDS Version 19 dated 15-Jan-2026 and Metoprolol CCDS 03 dated 2nd March 2023