*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.*

# Cardace® Meto

**Ramipril & Metoprolol Succinate Extended Release Tablets**

## 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 metoprolol succinate extended release and ramipril (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 haemodynamically relevant renal artery stenosis, bilateral or unilateral in the single kidney.
- in patients with hypotensive or haemodynamically 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
- Severe bradycardia
- Second- or third-degree heart block Cardiogenic shock
- Decompensated cardiac failure
- Sick sinus syndrome (unless a permanent pacemaker is in place)

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 sulfate**.**

**WARNINGS AND PRECAUTIONS**

**<u>Ramipril</u>**

**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 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. 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 Precautions).
The use of Ramipril in combination with an AIIRA is contraindicated in patients with diabetic nephropathy. (See Contraindications and 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 "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 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. 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., 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®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 "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 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 under "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 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**.**

- **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**.**

- **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 "Adverse reactions".)

**Metoprolol**

**Ischemic heart disease**
Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Cardace®Meto, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 - 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Cardace®Meto, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized avoid abruptly discontinuing Cardace®Meto in patients treated only for hypertension.

**Heart Failure**
Worsening cardiac failure may occur during up titration of Cardace®Meto. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Cardace®Meto. It may be necessary to lower the dose of Cardace®Meto or temporarily discontinue it. Such episodes do not prelude subsequent successful titration of Cardace®Meto.

**Bronchospastic Disease**
Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative $beta_1$ cardio-selectivity, Cardace®Meto may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because$beta_1$-selectivity is not absolute, use the lowest possible dose of Cardace®Meto. Bronchodilators, including $beta_2$- agonists should be readily available or administered concomitantly

**Pheochromocytoma**
If Cardace®Meto is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta mediated vasodilation in skeletal muscle.

**Major Surgery**
Avoid initiation of a high–dose regimen of extended-release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke, and death
Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

**Diabetes and Hypoglycemia**
Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

**Hepatic Impairment**
Consider initiating Cardace®Meto therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

**Thyrotoxicosis**
Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of, beta blockade may precipitate a thyroid storm.

**Anaphylactic Reaction**

While taking beta blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

**Peripheral Vascular Disease**
Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

**Calcium Channel Blockers**
Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

## 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 "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 Contraindications and 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 “Contraindications and 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 “Precautions”, “Adverse reactions” and "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 haematological reactions (see also under "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 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 venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

***Metoprolol***

**Catecholamine Depleting Drugs**

Catecholamine depleting drugs (eg, reserpine, mono amino oxidase (MAO) inhibitors) may have an additive effect when given with beta–blocking agents. Observe patients treated with Cardace®Meto plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

**CYP2D6 Inhibitors**

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100mg and immediate release metoprolol 200mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150mg t.i.d. with immediate release metoprolol 50mg t.i.d. resulted in

two to five-fold increase in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

**Digitalis, Clonidine, and Calcium Channel blockers**
Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia.

If clonidine and a beta blocker, such as metoprolol are co-administered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine.. If replacing clonidine by beta blocker therapy, delay the introduction of beta blockers for several days after clonidine administration has stopped.

## PREGNANCY
Cardace®Meto must not be taken during pregnancy (see also under "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, haemoglobin decreased, platelet count decreased | | Bone marrow failure, pancytopenia, haemolytic anaemia |
| Nervous system disorders | Headache, dizziness (lightheadedness) | Vertigo, paraesthesia, 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, diarrhoea, 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 (maybe/become Life-threatening, rarely severe course can cause fatal obstruction); pruritus, hyperhidrosis (sweating) | Exfoliative dermatitis, urticaria, onycholysis | Photosensitivity reaction | Toxic epidermal necrolysis, 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 | | Transient | | | Gynaecomastia |

| | | | | | |
|---|---|---|---|---|---|
| system and breast disorders | | erectile impotence, libido decreased | | | |
| Psychiatric disorders | | Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence (drowsiness) | Confusional state | | Disturbance in attention |

***Metoprolol***

The following adverse reactions have been reported:

**Central Nervous System:** reversible mental depression progressing to catatonia, confusion, short term memory loss, anxiety/nervousness, hallucinations, paresthesia, headache, somnolence, nightmares, insomnia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability clouded sensorium and decreased performance on neuropsychometrics
**Cardiovascular:** cold extremities, arterial insufficiency, usually of the Raynaud type, palpitation, peripheral edema, syncope, chest pain and hypotension.
**Respiratory:** Wheezing (bronchospasm) and dyspnea
**Gastrointestinal :** Nausea, dry mouth, , constipation, flatulence, hepatitis, vomiting and heartburn.
**Hematologic:** Agranulocytosis, Nonthrombocytopenic purpura, thrombocytopenic purpura
**Hypersensitive reactions:** laryngospasm, respiratory distress, Pruritis
Musculoskeletal and connective Tissue disorders : Lupus-like Syndrome (frequency unknown)
**Miscellaneous:** Musculoskeletal pain, Arthralgia , blurred vision , decreased libido, Male impotence, tinnitus , reversible alopecia, agranulocytosis, dry eyes , worsening of psoriasis, Peyronie's disease, sweating, photosensitivity , taste disturbances

**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 $\alpha_1$-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***

Overdosage of Metoprolol succinate may lead to severe bradycardia, hypotension, and cardiogenic shock Clinical prepresentation can also include atrioventricular block, heart failure, bronchospasm, hypoxia impairment of consciousness/coma, nausea, and vomiting.

Consider treating the patients with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamically instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists.On the basis of the pharmacologic actions of metoprolol, employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

***Bradycardia*:** Evaluate the need for atropine, adrenergic-stimulating drugs or pacemaker to treat bradycardia and conduction disorders.
***Hypotension*:** Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.
***Heart Failure and shock*:** May be treated when appropriate with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon) intravenous administration of adrenergic drugs such as dobutamine, with $\alpha_1$ receptor agonistic drugs added in presence of vasodilation.
***Bronchospasm*:** Can usually be reversed by bronchodilators

**MANUFACTURED BY:**
Sanofi India Limited, L-121, Verna Industrial Estate, Verna, Goa- 403722, India

**Updated*:* October 2021**
**Source**: Ramipril CCDS Version 18 dated 09th November 2017 and Metoprolol CCDS 02 dated 15th July 2021