*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®
# Ramipril Tablets I.P.

**Description**
**Active Moiety(ies)/Active Ingredients**
The sole pharmacologically active ingredient is the prodrug ramipril. Ramiprilat, the active metabolite of ramipril, is an inhibitor of the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme [ACE], kininase II).

**Therapeutic or Pharmacological Class**
ACE inhibitor. Antihypertensive.

**Pharmaceutical Form(s)**
Tablets.

**Composition**
**Cardace® 1.25**
Each uncoated tablet contains Ramipril I.P. 1.25mg

**Cardace® 2. 5**
Each uncoated tablet contains Ramipril I.P. 2.5mg

**Cardace® 5**
Each uncoated tablet contains Ramipril I.P. 5mg

**Cardace®10**
Each uncoated tablet contains Ramipril I.P. 10mg

**THERAPEUTIC INDICATIONS**
- For reducing the risk of myocardial infarction, stroke, cardiovascular death or revascularization procedures in diabetic patients 55 years or more with one or more of the following risk factors: systolic blood pressure > 160mmHg or diastolic blood pressure > 90mmHg (or on antihypertensive treatment ); total cholesterol > 5.2mmol/L; HDL cholesterol < 0.9mmol/L; current smoker; known microalbuminuria; any evidence of previous vascular disease.
- Prevention of myocardial infarction, stroke or cardiovascular death and reduction of need for revascularization procedures in patients with an increased cardiovascular risk such as manifest coronary heart disease, a history of stroke or a history of peripheral vascular disease.
- Treatment of patients who within the first few days after an acute myocardial infarction have demonstrated clinical signs of congestive heart failure.
- Treatment of hypertension and cardiac failure.
- Treatment of non-diabetic or diabetic overt glomerular or incipient nephropathy.

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

**DOSAGE AND ADMNISTRATION**
**General**

**Dosage**
The dosage is based on the desired effect and on how the individual patient tolerates the drug.

- **Treatment of hypertension**

Recommended initial dose: 2.5 mg Cardace® once daily.

Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 2 to 3 weeks.

Usual maintenance dose: 2.5 to 5 mg Cardace® daily.

**Maximum permitted daily dose**: 10 mg Cardace®.

Instead of increasing the dose beyond 5 mg Cardace® daily, additional administration of, e.g., a diuretic or calcium antagonist may be considered.

- **Treatment of congestive heart failure**

Recommended initial dose 1.25 mg Cardace® once daily.

Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg Cardace® or more is required, this may be taken as a single dose or as two divided doses.

**Maximum permitted daily dose**: 10 mg Cardace®.

- **Treatment after myocardial infarction**

Recommended initial dose: 5 mg Cardace® daily, divided into two single doses of 2.5 mg each, with one taken in the morning and one in the evening. If the patient does not tolerate this initial dosage it is recommended that 1.25 mg be given twice daily for two days.

In either event, depending on the patient's response, the dose may - then - be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 3 days.

At a later time, the total daily dose, initially divided, may be taken as one single daily dose.

**Maximum permitted daily dose**: 10 mg Cardace®.

Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be taken to nevertheless treat these patients, it is recommended that therapy be started with the lowest possible daily dose (1.25 mg Cardace® once daily) and that particular caution be exercised in any dose increase.

- **Treatment of diabetic or non-diabetic nephropathy**

Recommended initial dose: 1.25 mg Cardace® once daily.

Depending on how the patient tolerates the drug, the dose may be increased up to a maintenance dose of 5mg Cardace® once daily.

Doses above 5 mg Cardace® once daily have not been adequately studied in controlled clinical trials.

- **Reduction in the risk of myocardial infarction, stroke, or cardiovascular death**

Recommended initial dose: 2.5 mg Cardace® once daily.

Depending on how the patient tolerates the drug, the dose may be gradually increased. It is recommended to double the dose after one week of treatment and - after another three weeks - to increase it to a usual maintenance dose of 10 mg Cardace® once daily.

Doses above 10 mg Cardace® once daily have not been adequately studied in controlled clinical trials.
Patients with severe renal impairment as defined by creatinine clearance <0.6 ml/second have not been adequately studied.

**Special Populations**

***Elderly:***
A reduced initial dose of 1.25 mg Cardace® daily must be considered

***Hepatic Impairment:***

The response to the treatment with Cardace® may be either increased or reduced. Treatment in these patients must therefore be initiated only under close medical supervision. The maximum permitted daily dose in such cases is 2.5 mg Cardace®.

***Renal Impairment:***
With a creatinine clearance between 50 and 20 ml/min per 1.73 m² body surface area, the initial daily dose is generally 1.25 mg Cardace®. The maximum permitted daily dose in this case is 5 mg Cardace®.

Patients with incompletely corrected fluid or salt depletion, in patients with severe hypertension, as well as in patients in whom a hypotensive reaction would constitute a particular risk, (e.g., with relevant stenoses of the coronary vessels or those supplying the brain). A reduced initial dose of 1.25 mg Cardace® daily must be considered.

***Patients Pre-Treated With A Diuretic:***
Consideration must be given to discontinuing the diuretic for at least 2 to 3 days or - depending on the duration of action of the diuretic - longer before starting treatment with Cardace®, or at least to reducing the diuretic dose. The initial daily dose in patients previously treated with a diuretic is generally 1.25 mg Cardace®

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

Absorption of ramipril is not significantly affected by food. Cardace® may, therefore, be taken before, during or after a meal.

**CONTRAINDICATIONS**
Cardace® must not be used:
- in patients with hypersensitivity to ramipril, to any other ACE inhibitor, or any of the excipients of Cardace®.
- in patients with a history of angioedema**.**
- concomitantly with sacubitril/valsartan therapy (see Section Interactions). Do not initiate Cardace® until sacubitril/valsartan is eliminated from the body. In case of switch from Cardace® to sacubitril/valsartan, do not start sacubitril/valsartan until Cardace® 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.

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**
**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® 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 Contraindications and Interactions).

**PRECAUTIONS**
Treatment with Cardace® requires regular medical supervision.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS) Dual blockade of the renin-angiotensin-aldosterone system by combining Cardace® 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 compared to monotherapy. The use of Cardace® in combination with aliskiren is contraindicated in patients with diabetes mellitus or with renal impairment (creatinine clearance < 60 ml/min) (see Contraindications and Section Interactions).The use of Cardace® 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 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 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® 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® 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 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 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 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".

**INTERACTIONS**

**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 haemofiltration 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 Cardace® with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or with moderate to severe renal impairment and is not recommended in other patients (see Contraindications and Precautions).

Angiotensin-II Receptor Antagonists (AIIRAs): The use of Cardace® 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, anaesthetics): 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®. 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 hypoglycaemic 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® 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® may potentiate the effect of alcohol.

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

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.

## PREGNANCY
Cardace® 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® 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**
Because insufficient information is available regarding the use of ramipril during breastfeeding, ramipril is not recommended and alternative treatment with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

**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**
As Cardace® 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.

*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 (cannot be estimated from available data).*

| | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
|---|---|---|---|---|---|
| **Cardiac disorders** | | Myocardial ischaemia 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 ischaemia including ischaemic stroke and transient ischaemic attack, |

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| | | | | | 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, dyspnoea | 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- | Exfoliative dermatitis, urticaria, onycholysis | Photosensitivity reaction | Toxic epidermal necrolysis, Stevens-Johnson |

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| | | threatening, rarely severe course can cause fatal obstruction); pruritus, hyperhidrosis (sweating) | | | 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 |

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| | | | | | exceptional) |
| **Reproductive system and breast disorders** | | Transient erectile impotence, libido decreased | | | Gynaecomastia |
| **Psychiatric disorders** | | Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence (drowsiness) | Confusional State | | Disturbance in attention |

**OVERDOSE**

**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 also under section Contraindications

**Manufactured by:**

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