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® am

Ramipril and Amlodipine Tablets

Cardace® am 10
Each uncoated tablet contains:
Ramipril IP.... 10.0 mg
Amlodipine Besylate IP equivalent to Amlodipine.....5.0 mg

Cardace® am 5
Each uncoated tablet contains:
Ramipril IP.... 5.0 mg
Amlodipine Besylate IP equivalent to Amlodipine.....5.0 mg

Cardace® am 2.5
Each uncoated tablet contains:
Ramipril IP.... 2.5 mg
Amlodipine Besylate IP equivalent to Amlodipine.....5.0 mg

THERAPEUTIC INDICATIONS

Indicated for the treatment of hypertension.

PHARMACOLOGICAL INFORMATION:

Ramipril
Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilatator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The increase in bradykinin activity probably contributes to the cardioprotective and endothelioprotective effects observed in animal experiments. It has not yet been established to what extent this is also responsible for certain unwanted effects (e.g. tickling cough).

ACE inhibitors are effective even in patients with low-renin hypertension. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker. It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle without affecting serum calcium concentrations. Direct relaxation of vascular smooth muscle forms the basis of the antihypertensive action.

DOSAGE & ADMINISTRATION

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

Recommended initial dose is one tablet of Cardace® am 2.5mg/5mg once daily. Depending on patient's response the dose may be increased. Cardace® am 5mg/5mg or Cardace® am 10mg/5mg may be used for higher dosing. It is recommended that the dose if increased should be done at intervals of 2 or 3 weeks.

Maximum permitted daily dose of ramipril is 10mg and the maximum recommended daily dose of Amlodipine is up to 10mg.

Cardace® am has to be swallowed with sufficient amount of liquid (approx. ½ glass). The tablet must not be chewed or crushed.

CONTRAINDICATIONS

Cardace® am must not be used
Related to both ramipril and amlodipine

- **in patients with hypersensitivity to ramipril, amlodipine, other ACE inhibitors, dihydropyridine derivatives or to any of the excipients**

Related to ramipril

- **in patients with a history of angioedema.**
- **concomitantly with sacubitril/valsartan therapy (see Section Interactions). Do not initiate Cardace® am until sacubitril/valsartan is eliminated from the body. In case of switch from Cardace® am to sacubitril/valsartan, do not start sacubitril/valsartan until Cardace® am 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.

Related to amlodipine

- **in patients with severe hypotension**
- **in patients with shock (including cardiogenic shock)**
- **in patients with obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)**
- **in patients with haemodynamically unstable heart failure after acute myocardial infarction**
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WARNINGS

Ramipril

- **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.

- **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.

Insufficient experience has been gained concerning the use of Cardace® am 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 Section Interactions)**.**

Related to amlodipine The safety and efficacy of amlodipine in hypertensive crisis has not been established

- **Renal impairment**

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

- **Hepatic impairment**

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

- **Cardiac failure**

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. **Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.**

PRECAUTIONS

Related to both ramipril and amlodipine

Caution is recommended in patients who are being treated concurrently with diuretics since these patients may be volume and/or salt depleted. Renal function and serum potassium should be monitored.

Related to ramipril

- **Dual blockade of the renin-angiotensin-aldosterone system (RAAS)**

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

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

- **Patients with hyper-stimulated rennin 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 dose or initial dose increases must be accompanied by close blood pressure monitoring until such time as no further acute reduction in blood pressure is 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).
- in patients undergoing major surgery or during anaesthesia with agents that produce hypotension

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® am 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 disease”.

- **Patients with liver diseases**

In patients with impaired liver function, response to the treatment with Cardace® am 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

- **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 also 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.

- **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.**

- Surgery

It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Related to amlodipine

- Elderly

In the elderly increase of the dosage should take place with care.

INTERACTIONS

Related to ramipril

Food interactions

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 Warnings).

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low-density lipoprotein apheresis with dextran sulfate: Risk of severe anaphylactoid reactions. (see Section Contraindications)

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

***Angiotensin-II Receptor Antagonists (AIIRAs):*. The use of Cardace® am in combination with an AIIRA is contraindicated in patients with diabetic nephropathy and is not recommended in other patients** (see section Contraindication 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, Anaesthetics): **Potentiation of the antihypertensive effect** is to be anticipated. **Regular monitoring of serum sodium is recommended in patients undergoing concurrent diuretic therapy.**

Vasopressor Sympathomimetics: These may reduce the antihypertensive effect of ramipril. 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 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 hypoglycaemic reactions in patients concomitantly treated with antidiabetics. Particularly close blood glucose monitoring is,** therefore, **recommended in the initial phase of co-administration.**

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

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

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

Take into account

Nonsteroidal anti-inflammatory drugs (e.g. indomethacin) and acetylsalicylic acid: Attenuation of the antihypertensive effect of Cardace®am 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® am may potentiate the effect of alcohol.

SALT: Increased dietary salt intake may attenuate the antihypertensive effect of Cardace® am

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.

Related to amlodipine Effects of other medicinal products on amlodipine

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Close clinical observation of patients is recommended and dose adjustment may thus be required.

CYP3A4 inducers:

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, **blood pressure should be monitored and dose adjustment considered both during and after concomitant medication particularly with strong CYP3A4 inducers** (e.g. rifampicin, hypericum perforatum).

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. **Due to risk of**

hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. **In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.**

Cyclosporine: No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0 – 40%) of cyclosporine were observed. **Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.**

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. **Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.**

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

PREGNANCY

Related to ramipril

Cardace® am must not be taken during pregnancy (See 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® am must be replaced as soon as possible by a treatment regimen without ACE inhibitors.** Otherwise there is a risk of harm to the fetus.
When ACE inhibitors have been administered to women in the second and third trimester of pregnancy, there have been reports of harmful effects on the fetus and newborn child, including sometimes in conjunction with oligohydramnios (presumably as an expression of impaired fetal renal function) - craniofacial deformities, pulmonary hypoplasias, fetal limb contractures, hypotension, anuria, reversible and irreversible renal failure as well as death. Prematurity, intrauterine growth retardation and persistence of Botallo's duct have also been reported in humans, although it is uncertain whether these phenomena are a consequence of exposure to ACE inhibitors.

Related to amlodipine

The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses.

Fertility:
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. **Clinical data are insufficient regarding the potential effect of amlodipine on fertility**. In one rat study, adverse effects were found on male fertility.

LACTATION

Related to both ramipril and amlodipine

Cardace am is not recommended during lactation.

Related to ramipril

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

Related to amlodipine

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

Related to ramipril

Some adverse effects (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).

Related to amlodipine

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. **Caution is recommended especially at the start of treatment.**

OVERDOSAGE

Related to amlodipine

In humans experience with intentional overdose is limited.

SIGNS AND SYMPTOMS

Related to ramipril

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

Related to amlodipine

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

MANAGEMENT

Related to ramipril

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 Section Contraindications)

Related to amlodipine

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

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.

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).

System organ class	Frequency	**Ramipril**	**Amlodipine**
Blood and lymphatic system disorders	Uncommon	**Eosinophilia**	
	Rare	**White blood cell count decreased (**including **neutropenia** or **agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased**	
	Very rare		**Leukocytopenia, thrombocytopenia**
	Not known	**Bone marrow failure, pancytopenia, haemolytic anaemia**	
Immune system disorders	Very rare		**Allergic reactions**
	Not known	**Anaphylactic or anaphylactoid reactions** (severe anaphylactic and anaphylactoid reactions to insect venoma is increased under ACE inhibition), **antinuclear antibody increased**	
Endocrine disorders	Not known	**Syndrome of inappropriate antidiuretic hormone secretion (SIADH)**	
Metabolism and nutrition disorders	Common	**Blood potassium increased**	
	Uncommon	**Anorexia, decreased appetite**	
	Very rare		**Hyperglycaemia**
	Not known	**Blood sodium decreased**	
Psychiatric disorders	Uncommon	**Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence**	**Insomnia, mood changes** (including anxiety), **depression**
	Rare	**Confusional state**	Confusion

	Not known	**Disturbance in attention**	
Nervous system disorders	Common	**Headache, dizziness** (lightheadedness)	**Somnolence, dizziness, headache** (especially at the beginning of the treatment)
	Uncommon	**Vertigo, paraesthesia, ageusia** (loss of taste), **dysgeusia** (taste disturbances)	**Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia**
	Rare	**Tremor, balance disorder**	
	Very rare		**Hypertonia peripheral neuropathy**
	Not known	**Cerebral ischemia** including **ischaemic stroke and transient ischaemic attack, psychomotor skills impaired** (impaired reactions), **burning sensation, parosmia** (smell disturbances)	**Extrapyramidal disorder**
Eye disorders	Common		**Visual disturbance** (including diplopia)
	Uncommon	**Visual disturbance** including **blurred vision**	
	Rare	**Conjunctivitis**	
Ear and labyrinth disorders	Uncommon		**Tinnitus**
	Rare	**Hearing impaired, tinnitus**	
Cardiac disorders	Common		**Palpitations**
	Uncommon	**Myocardial ischemia** including **angina pectoris** or **myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral**	**Arrhythmia,** (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare		**Myocardial infarction**
Vascular disorders	Common	**Hypotension, orthostatic blood pressure decreased** (disturbed orthostatic regulation), syncope	**Flushing**
	Uncommon	**Flushing**	**Hypotension**
	Rare	**Vascular stenosis, hypoperfusion** exacerbation of perfusion disturbances,	

		vasculitis	
	Very rare		**Vasculitis**
	Not known	**Raynaud's phenomenon**	
Respiratory, thoracic and mediastinal disorders	Common	**Non-productive tickling cough, bronchitis, sinusitis, dyspnoea**	**Dyspnoea**
	Uncommon	**Bronchospasm including asthma aggravated, nasal congestion**	**Cough, rhinitis**
Gastrointestinal disorders	Common	**Gastrointestinal inflammation** (inflammatory reactions of the gastrointestinal tract), **digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting**	**Abdominal pain, nausea, dyspepsia, altered bowel habits** (including diarrhoea and constipation)
	Uncommon	**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**	**Vomiting, dry mouth**
	Rare	**Glossitis**	
	Very rare		**Pancreatitis, gastritis, gingival hyperplasia**
	Not known	**Aphtous stomatitis** (inflammatory reactions of the oral cavity)	
Hepatobiliary disorders	Uncommon	**Hepatic enzymes and/or bilirubin conjugated increased**	
	Rare	**Jaundice cholestatic, hepatocellular damage**	
	Very rare		**Hepatitis, jaundice, hepatic enzymes increased** (mostly consistent with cholestasis).
	Not known	**Acute hepatic failure, cholestatic or cytolytic**	

		hepatitis (fatal outcome has been very exceptional)	
Skin and subcutaneous tissue disorders	Common	**Rash in particular maculo-papular**	
	Uncommon	**Angioedema with fatal outcome (maybe/become life-threatening, rarely severe course can cause fatal obstruction), pruritus, hyperhidrosis** (sweating)	**Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema urticaria**
	Rare	**Exfoliative dermatitis, urticaria, onycholysis,**	
	Very rare	**Photosensitivity reaction**	**Angioedema, erythema, multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity**
	Not known	**Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia**	**Toxic epidermal necrolysis**
Musculoskeletal and connective tissue disorders	Common	**Muscle spasms** (muscle cramps)**, myalgia**	**Ankle swelling, muscle cramps**
	Uncommon	**Arthralgia**	**Arthralgia, myalgia, back pain**
Renal and urinary disorders	Uncommon	**Renal impairment** including **renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased**	**Micturition disorder, nocturia, increased urinary frequency**
Reproductive system and breast disorders	Uncommon	**Transient erectile impotence, libido decreased**	**Impotence, gynaecomastia**
	Not known	**Gynaecomastia**	
General disorders and administration site conditions	Very common		**Oedema**
	Common	**Chest pain, fatigue**	**Fatigue, asthenia**
	Uncommon	**Pyrexia** (fever)	**Chest pain, pain,**

			malaise
	Rare	**Asthenia** (weakness)	
Investigations	Uncommon		**Weight increased, weight decreased**

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