

Others :

Dry cough and in rare cases, muscular cramps, chest pain, tingling, depression, taste disturbances and impotence have been reported in isolated cases. Vasculitis myalgia, arthralgia, fever, eosinophilia and raised titres of antinuclear antibodies have been reported in rare instances with other ACE inhibitors, and may occur with Ramipril.

Laboratory test findings :

The serum sodium level may decrease. Elevation of serum potassium may occur, since **RAMACE** leads to a decrease in aldosterone secretion; potassium-sparing diuretics or potassium supplements should therefore be avoided. Increases in serum bilirubin and/or liver enzymes have been observed. Leukopenia and decreases in haemoglobin and platelets have been observed with ACE inhibitors (see 'precautions').

Effects on the ability to drive and operate machinery :

The antihypertensive effect in individual cases may be symptomatic. Treatment with **RAMACE** may therefore, affect the ability to drive, cross the road safely or operate machinery, especially at the start of treatment or when changing over from other preparations, or during concomitant use of alcohol.

Interactions :

Combination with diuretics or other antihypertensive agents or nitrates and tricyclic antidepressants may potentiate the antihypertensive response to **RAMACE**. Patients previously treated with diuretics may experience a marked drop in blood pressure.

Potassium-sparing diuretics such as spironolactone, amiloride and triamterene or potassium supplements may increase the risk of hyperkalaemia. ACE inhibitors have been reported, in rare instances, to augment the hypoglycaemic action of sulphonylureas and insulin.

As with other ACE inhibitors, the antihypertensive effects of **RAMACE** may be decreased in patients taking non-steroidal anti-inflammatory drugs (e.g., acetylsalicylic acid, phenylbutazone, indomethacin).

A high intake of dietary salt may decrease the effects of antihypertensive medication.

Leukopenia may be aggravated in patients undergoing treatment with immunosuppressants, cytostatic agents, systemic corticosteroids or allopurinol.

Since ACE inhibitors decrease the excretion of lithium salts, lithium concentrations in the blood should be monitored in patients undergoing such therapy.

General anaesthetics or anaesthetics with an antihypertensive action may cause the blood pressure to drop further in patients taking **RAMACE**. Appropriate counter measures, such as increasing the blood volume or, if necessary, administering angiotensin II, should be taken before or during surgery, ACE inhibitors may potentiate the effects of alcohol.

STORAGE

Store in a cool dry place.

EXPIRY DATE

Do not use later than the date of expiry.
Keep medicines out of reach of children.

PRESENTATION

RAMACE 1.25 : Strip of 10 Capsules
RAMACE 2.5 : Strip of 10 Capsules
RAMACE 5 : Strip of 10 Capsules
RAMACE 10 : Strip of 10 Capsules

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® Regd. Trade Mark

For further information:

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

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

Ramipril Capsules
Ramace®

COMPOSITION

RAMACE 1.25

Each capsule contains: Ramipril BP 1.25 mg.

RAMACE 2.5

Each capsule contains: Ramipril BP 2.5 mg.

RAMACE 5

Each capsule contains: Ramipril BP 5 mg.

RAMACE 10

Each capsule contains: Ramipril BP 10 mg.

PROPERTIES

Ramipril is a potent and long-acting inhibitor of the angiotensin converting enzyme (ACE). It is a prodrug which is hydrolyzed in the liver after absorption from the gastro-intestinal tract to form the active angiotensin converting enzyme inhibitor, ramiprilat. Administration of **RAMACE** to hypertensive patients results in a reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours of drug intake, the peak effect occurs 3-6 hours after drug intake and has been shown to be maintained for at least 24 hours at recommended doses.

INDICATIONS

- Hypertension
- Cardiac failure
- Reduction of mortality in patients after myocardial infarction

DOSAGE AND ADMINISTRATION

Hypertension :

The recommended initial dosage is 2.5 mg **RAMACE** once a day: Depending upon the patient's response, the dosage may then be increased at intervals of 2-3 weeks, first to 5 mg and then to a maximum of 10 mg once daily. If required another antihypertensive agent may be added.

Occasionally, in patients already taking diuretics, an undesirable sudden fall in blood pressure may occur after the first dose of **RAMACE**. If possible, therefore, treatment with a diuretic should be discontinued 2-3 days before starting treatment with **RAMACE**. If this is not possible, initial treatment with **RAMACE** should start at a dose of 1.25 mg once daily and then be adjusted to the patient's needs.

RAMACE capsules should be swallowed whole during or after meals with a generous amount of fluid.

Cardiac failure :

The recommended initial dose is **RAMACE** 1.25 mg once daily along with diuretics and/or digitalis. For non-responders, the dose may be increased to 2.5 mg once daily which may further be stepped up if required to 5 mg once daily, upto a maximum of 10 mg daily as a single dose or in two divided doses. Therapy should be started under close medical supervision.

Myocardial Infarction :

Recommended initial dose : 5 mg **RAMACE** daily divided into two single doses of 2.5 mg each, one 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.

Later, the total daily dose, initially divided, may be taken as one single daily dose. Maximum permitted daily dose; 10 mg **RAMACE**. Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be made to nevertheless treat these patients, it is recommended that therapy be started with the lowest possible daily dose (1.25 mg **RAMACE** once daily) and that the dosage be increased only with particular caution.

125 mm

34-180-50

190 mm

Dosage in patients with impaired renal function :

For patients with creatinine clearance levels of 50 ml/min and above (serum creatinine < 1.5 mg/dl), dosage adjustment is not required.

For patients with creatinine clearance levels between 20 and 50 ml/min (serum creatinine between 1.5 and 3 mg/dl), the initial dose is 1.25 mg **RAMACE** once daily and the maximum dose is 5 mg **RAMACE** once daily.

There is insufficient experience to recommend **RAMACE** in patients with very severe degrees of renal impairment where the creatinine clearance is <20 ml/min (serum creatinine >3 mg/dl) and in patients undergoing dialysis.

If facilities for estimation of creatinine clearance are not available, the levels can be calculated from the serum creatinine values using the following formula (Cockcroft's equation):

$$\text{Men : Creatinine clearance (ml/min) = } \frac{\text{Body weight (kg) x (140-age in years)}}{72 \text{ x serum creatinine (mg/dl)}}$$

Women : Multiply the product of the above equation by 0.85.

Dosage in patients with impaired liver function :

In patients with impaired liver function, the metabolism of Ramipril - and therefore the formation of the bioactive metabolite ramiprilat - is delayed due to diminished activity of the esterases in the liver, resulting in elevated plasma Ramipril levels. Treatment with **RAMACE**, should therefore be initiated under close medical supervision and should not exceed 2.5 mg daily.

Dosage in other special patient groups :

Where fluid or salt deficiency has not been completely corrected, as well as in patients in whom a sudden hypotensive event would constitute a particular risk, e.g., patients with coronary or cerebral arteriosclerosis, a reduced initial dose of 1.25 mg **RAMACE** must be considered.

In patients pretreated with a diuretic, consideration must be given to discontinuing the diuretic at least 2 to 3 days (depending on the duration of action of the diuretic) before starting treatment with **RAMACE**, or at least to reducing the diuretic dose. The physician will decide in each individual case whether such discontinuation or dose reduction is possible and for how long. The initial dose in patients previously treated with a diuretic is generally 1.25 mg **RAMACE**.

CONTRAINDICATIONS

Hypersensitivity to Ramipril. Allergy to starch. Hereditary angioneurotic oedema. Haemodynamically relevant unilateral or bilateral renal artery stenosis, mitral stenosis, aortic stenosis, and in patients with low blood pressure (hypotensive patients) or in patients with an unstable circulatory situation (haemodynamically unstable patients) where there might be a risk of life-threatening fall in blood pressure and renal failure.

Pregnancy & Lactation :

As with all ACE inhibitors, **RAMACE** should not be used in pregnancy as it affects development of the foetus. If the patient becomes pregnant during treatment, **RAMACE** must be replaced at the earliest with some other group of antihypertensive agents. If treatment with **RAMACE** is necessary during the lactation period, the infant should not be breast-fed.

PRECAUTIONS**History of hereditary angioneurotic oedema :**

Patients should be questioned for a history of angio-oedema of the face, extremities, lips, tongue, glottis and/or larynx. If there is a suspicion that the patient may have hereditary angioneurotic oedema, treatment with **RAMACE** must not be given.

Impaired renal function :

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin aldosterone system, treatment with angiotensin converting enzyme inhibitors, including **RAMACE**, may be associated with progressive renal impairment. Renal function should therefore be checked before and during treatment.

In patients with renovascular disease, e.g., renal artery stenosis that is still haemodynamically irrelevant or haemodynamically relevant unilateral renal artery stenosis, as well as after renal transplantation, increases in blood urea nitrogen and serum creatinine may occur. Experience with other angiotensin converting enzyme inhibitors suggests that these increases are usually reversible upon discontinuation of **RAMACE** and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when **RAMACE** has been given concomitantly with a diuretic.

This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of **RAMACE** and/or discontinuation of the diuretic may be required. **RAMACE** is not suitable for the treatment of patients requiring haemodialysis for end stage renal failure since only negligible amounts are dialysable. On rare occasions, life-threatening anaphylactoid reactions have also been reported in course of dialysis with certain high flux membranes (e.g., polyacrylonitrile membranes) during therapy with ACE inhibitor. Concomitant use of **RAMACE** with such membranes must be avoided.

Impaired liver function :

As **RAMACE** is a prodrug metabolised in the liver to its active moiety, particular caution and close monitoring should be ensured in patients with impaired liver function. (see 'Dosage and administration')

Congestive heart failure :

Patients with heart failure given **RAMACE** may experience some reduction in B.P., especially with the first dose, but discontinuation of therapy is usually not necessary when the patient is initiated on treatment with the lowest dose and if the patient is not having salt depletion due to diuretic use. Therapy should however be initiated under close medical supervision, especially in patients with oliguria or azotaemia.

Children :

The safety and effectiveness of **RAMACE** have not yet been established in children.

Symptomatic hypotension :

Severe symptomatic hypotension and in isolated cases syncope have been rarely observed in malignant hypertension and after the initial dose of **RAMACE** and after increasing the dose of **RAMACE**. This is more likely to occur in patients with volume and salt depletion caused by prolonged diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with **RAMACE**. It is recommended that blood pressure be therefore monitored for a few hours after the initial dose as well as after every incremental dose of ACE inhibitors. This precaution should be observed if a diuretic is added to the treatment regimen. If hypotension occurs, the patient should be placed in a supine position with legs slightly raised and, if necessary, receive an intravenous infusion of physiological saline. Treatment with **RAMACE** may usually be continued following restoration of effective blood volume and blood pressure. Care should be exercised to prevent a sudden undesirable fall in blood pressure in patients with significant coronary or cerebral ischaemia.

Leukopenia :

ACE inhibitors have caused agranulocytosis and even generalised bone marrow depression, rarely in otherwise healthy hypertensive patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease, such as lupus erythematosus and scleroderma, and are under treatment with drugs, such as corticosteroids and antimetabolites. The white blood cell count and protein levels in the urine should be monitored regularly in the latter group of patients.

Adverse reactions :

The frequency of adverse reactions associated with **RAMACE** was low in clinical trials. Generally, adverse reactions are mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

Cardiovascular :

Symptomatic hypotension characterised by dizziness, weakness, nausea, headache, palpitation, tiredness or tinnitus may occur after the initial dose of **RAMACE** and after increasing the dose of **RAMACE** (see 'Precautions'). Isolated cases of syncope have been observed. In patients with pre-existing coronary artery disease or cerebrovascular disease, a sudden fall in blood pressure may cause perfusion disturbances to the heart (angina pectoris or myocardial infarction) or the brain (transient ischaemic attacks or stroke).

Renal :

See 'Precautions'

Gastrointestinal :

Nausea, vomiting, abdominal pain and diarrhoea may occur, but these reactions are often transient. In very rare cases, taste disturbances may occur.

Allergic :

Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of **RAMACE**. Occasionally hair loss (alopecia) and precipitation of Raynaud's phenomenon with ACE inhibitors may be observed.

Angioneurotic oedema :

In very rare cases, angioneurotic oedema has occurred during therapy with ACE inhibitors, including **RAMACE**. If laryngeal stridor or angio-oedema of the face, tongue or glottis occurs, treatment with **RAMACE** must be discontinued and appropriate therapy started immediately.

125 mm

190 mm