

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

Ramipril and Hydrochlorothiazide Capsules

Ramace® H 2.5/12.5 mg

COMPOSITION

Each capsule of Ramace H 2.5/12.5 mg contains:
Ramipril BP 2.5 mg
Hydrochlorothiazide IP 12.5 mg
Approved colours used in capsule shell.

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. Hydrochlorothiazide (HCTZ) is a thiazide diuretic and an antihypertensive. The components have quite different but complementary antihypertensive mechanisms, and the improved efficacy is not due simply to additive antihypertensive effects. Ramipril blocks the counterregulatory rise in angiotensin II triggered by diuretic therapy. Diuretics appear to enhance the antihypertensive action of ACE inhibitors particularly when the renin-angiotensin system is inactive. As a result, patients who do not respond to monotherapy often do respond to combination therapy. A further benefit is that the dosages of components in a combination can be lowered for some patients, thus reducing the risk of adverse effects. Ramipril as well as its metabolite ramiprilat has been shown to be pharmacokinetically compatible with hydrochlorothiazide, they both require once daily dosage and achieve maximum hypotensive effect approximately 4 hours after administration. Administration of Ramace® H 2.5/12.5 mg to hypertensive patients results in a reduction of blood pressure.

CLINICAL PHARMACOLOGY

Ramipril

Following oral administration of ramipril, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced.

Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%.

Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril. After oral administration of ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine, and about 40% is found in the faeces. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the 2.5-20 mg dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously.

The initial rapid decline of ramipril due to tissue distribution has a half-life of 2-4 hours. The apparent elimination phase has a half-life of 9-18 hours. The terminal elimination phase has a prolonged half-life (>50 hours). It does not contribute to the accumulation of the drug. After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations within the therapeutic range was 13-17 hours.

After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of ramipril, especially at low doses (2.5 mg), but the difference is clinically insignificant.

In patients with creatinine clearance less than 40 ml/min/1.73m², peak levels of ramiprilat are approximately doubled, and trough levels may be as much as quintupled. In multiple-dose regimens, the total exposure to ramiprilat (AUC) in these patients is 3-4 times as large as it is in patients with normal renal function who receive similar doses.

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. Compared to normal subjects, patients with creatinine clearance less than 40 ml/min/1.73m² had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations.

In patients with impaired liver function, the metabolism of ramipril to ramiprilat appears to be slowed, and plasma ramipril levels in these patients are increased about 3-fold. Peak concentrations of ramiprilat in these patients, however, are

not different from those seen in subjects with normal hepatic function, and the effect of a given dose of plasma ACE activity does not vary with hepatic function.

Hydrochlorothiazide

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium.

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.

The onset of action of thiazides occurs in 2 hours and the peak effect at about 4 hours. The action persists for approximately 6-12 hours. Hydrochlorothiazide is rapidly absorbed, as indicated by peak plasma concentrations 1-2.5 hours after oral administration. Plasma levels of the drug are proportional to dose; the concentration in whole blood is 1.6-1.8 times higher than in plasma. Thiazides are eliminated rapidly by the kidney. After oral administration of 12.5 to 100mg doses, 72-97% of the dose is excreted in the urine, indicating dose-independent absorption. Hydrochlorothiazide is eliminated from plasma in a biphasic fashion with a terminal half-life of 10-17 hours. Plasma protein binding is 67.9%. Plasma clearance is 15.9-30.0 L/hr; volume of distribution is 3.6-7.8 L/kg.

Gastrointestinal absorption of hydrochlorothiazide is enhanced when administered with food. Absorption is decreased in patients with congestive heart failure, and the pharmacokinetics are considerably different in these patients.

INDICATION

Indicated for the treatment of mild to moderate hypertension in patients (in whom combination therapy is appropriate) who have been stabilised on the individual components given in the same proportion.

CONTRAINDICATIONS

Ramace® H 2.5/12.5 mg must not be used in patients with hypersensitivity to ramipril, hydrochlorothiazide or other thiazide diuretics, sulphonamides or any of the excipients and allergy to starch. History of hereditary angioneurotic oedema. Severe impairment of renal function with a creatinine clearance below 30ml/min/1.73m² body surface area and in dialysis patients (hydrochlorothiazide ineffective). 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.

Clinically relevant electrolyte disturbances e.g. hypokalemia, hyponatremia or hypercalcemia which may worsen following treatment. Severe impairment of liver function (risk of fluid and salt imbalance). Rapid onset allergy (anaphylactoid) like hypersensitivity reactions sometimes progressing to shock have been described in the course of dialysis with certain high flux membrane (polycrilonitril membranes) during therapy with ACE inhibitors such as ramipril.

Pregnancy & Lactation

Ramace® H 2.5/12.5 mg should not be used in pregnancy as it affects development of the foetus. If the patient becomes pregnant during treatment, Ramace® H 2.5/12.5 mg must be replaced at the earliest with some other group of antihypertensive agents. If treatment with Ramace® H 2.5/12.5 mg is necessary during the lactation period, the infant should not be breastfed.

PRECAUTIONS

Treatment with Ramace® H 2.5/12.5 mg requires regular medical supervision. Generally dehydration, reduced blood volume (hypovolemia) or salt depletion should be corrected before initiating the treatment (in patients with concomitant heart failure, however, this must be carefully weighed against the risk of volume overload).

Special caution is necessary during the treatment of:

Patients with severe and particularly with malignant hypertension.

Patients with concomitant and particularly with severe heart failure.

Patients in whom fluid or salt deficiency exists or may develop (as a result of inadequate fluid or salt intake) or as a result of diarrhoea, vomiting or excessive sweating in cases where salt and fluid replacement is inadequate.

Patients with haemodynamically relevant renal artery stenosis.

Close medical supervision is also necessary in patients with haemodynamically relevant stenosis of coronary arteries or of the blood vessels supplying the brain.

In patients with pre-existing impairment of renal function or in kidney transplant patients.

Serum sodium, potassium, calcium, uric acid, and blood sugar should be monitored regularly. More frequent monitoring of potassium is necessary in patients with impaired renal function.

White blood cell count should be monitored (more frequent in the initial phase of the treatment) so that leucopenia can be detected.

Insufficient experience has been gained concerning the use of Ramace® H 2.5/12.5 mg in children.

ADVERSE REACTIONS

The following adverse effects can be observed during therapy with

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Ramace® H 2.5/12.5 mg. The adverse events are due to constituents of Ramace® H 2.5/12.5 mg i.e. ramipril and hydrochlorothiazide.

Cardiovascular

Symptomatic hypotension characterised by light-headedness sometimes accompanied by concentration disturbances as well as impaired reactions, fatigue, dizziness, weakness may occur as a result of vasodilatation after the initial dose of Ramace® H 2.5/12.5 mg. Other symptoms may include tachycardia, palpitation, orthostatic hypotension, nausea, headache, tiredness or tinnitus after excessive reduction of blood pressure.

This occurrence may be more likely in patients with:

Severe and malignant hypertension

Concomitant and particularly severe heart failure

Previous diuretic therapy

Fluid or salt deficiency

Haemodynamically relevant renal artery stenosis.

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 ischemic attacks or stroke).

Renal

During treatment with Ramace® H 2.5/12.5 mg there may be deterioration in renal function under certain circumstances progressing to life-threatening acute renal failure. This applies particularly in patients with renovascular diseases (haemodynamically relevant renal artery stenosis, in renal transplant patients and in patients of cardiac failure). In isolated cases, interstitial nephritis may develop during therapy with hydrochlorothiazide. Preexisting pronounced urinary protein excretion might increase under treatment with Ramace® H 2.5/12.5 mg. However renal protein excretion may also be reduced in patients of diabetic nephropathy.

Ramace® H 2.5/12.5 mg may lead to a decline in serum sodium concentration particularly in conjunction with restricted salt intake.

Hydrochlorothiazide may contribute to the development of hyponatremia, hypomagnesemia as well as hypercalcemia. In addition Ramace® H 2.5/12.5 mg may contribute to development or aggravation of a metabolic alkalosis.

Ramipril may contribute to an increase in concentration of serum potassium while hydrochlorothiazide may contribute to a decrease in serum potassium. Thus during the therapy with Ramace® H 2.5/12.5 mg both a decline and increase in serum potassium are possible, the latter effect being mainly encountered in patients with impaired renal function (e.g. diabetic nephropathy) or those receiving potassium sparing diuretics or potassium salts concomitantly.

Warning signs of electrolyte disturbances (e.g. changes in serum levels of sodium, potassium, calcium and magnesium) include thirst, headache, confusion, muscle cramps, tetany, muscle weakness and gastrointestinal symptoms.

Gastrointestinal

Reactions in digestive tract may develop e.g. dryness of mouth, irritation or inflammation of oral mucosa, constipation, diarrhoea, nausea and vomiting, gastritis like abdominal pain, pancreatitis, increase in hepatic enzymes and/or bilirubin, cholestatic jaundice and other forms of impaired liver function and in some instances life threatening hepatitis.

Blood picture

The following changes in blood picture may occur: a mild to severe reduction in red blood cell count and haemoglobin content, blood platelets and white blood cell count, impaired blood cell formation (bone marrow depression) and excessive reduction in number of all blood cells (pancytopenia) have been observed.

Such changes in blood picture that are sometimes life-threatening are more likely to occur in patients of impaired renal function, in patients with concomitant connective tissue disorder or in patients treated with other drugs that may cause changes in blood picture.

Others

Disturbance of balance, visual disorders, headache, nervousness, restlessness, tremor, sleep disturbances, confusion, loss of appetite, depressed mood, feeling of anxiety, abnormal sensations, taste change and muscle cramps.

Erectile impotence and reduced sexual desire (decreased libido) may occur. Inflammation of blood vessels (vasculitis), muscle and joint pains (myalgia and arthralgia), fever, eosinophilia may occur.

During treatment with hydrochlorothiazide and thus, with Ramace® H 2.5/12.5 mg increased blood concentrations of uric acid levels may occur. This may lead to gout attacks particularly in those patients whose uric acid levels are already elevated.

Hydrochlorothiazide might lower the tolerance of glucose. In patients with diabetes mellitus this may lead to deterioration of metabolic control. A latent diabetes mellitus may become manifest for the first time. Hydrochlorothiazide may cause an increase in serum cholesterol and triglycerides.

Raised titres of antinuclear antibodies have been seen with other ACE inhibitors. In temporal relationship with the use of hydrochlorothiazide, the development of lupus erythematosus has been described.

Effects on the ability to drive and operate machinery:

The antihypertensive effect in individual cases may be symptomatic. Treatment with Ramace® H 2.5/12.5 mg 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® H 2.5/12.5 mg. 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 hyperkalemia. Ramace® H 2.5/12.5 mg may weaken the effectiveness of blood sugar lowering medications (antidiabetic agents, e.g. insulin and sulphonylurea derivatives).

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. Concomitant administration of methyldopa may result in hemolysis.

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

When Ramace® H 2.5/12.5 mg is administered simultaneously with nonsteroidal antihypertensive drugs (e.g. acetyl salicylic acid or indomethacin) attenuation of antihypertensive effect and moreover acute renal failure may occur.

Ramace® H 2.5/12.5 mg may potentiate the effects of alcohol.

DOSAGE AND ADMINISTRATION

Hypertension:

The recommended initial dosage is 1 capsule of Ramace® H 2.5/12.5 mg once a day. The dose can be up titrated at intervals of 2-3 weeks to ramipril 5mg and hydrochlorothiazide 12.5mg and then to a maximum of ramipril 10 mg and hydrochlorothiazide 12.5 mg. If required another antihypertensive agent may be added. In patients pre-treated with a diuretic, consideration must be given to discontinuing the diuretic at least 2-3 days (depending on the duration of action of the diuretic) longer before initiating the treatment with Ramace® H 2.5/12.5 mg. If discontinuation is not possible the treatment should be initiated with the smallest possible dose of ramipril (1.25mg daily) in a free combination. Subsequently a changeover to an initial daily dose of Ramace® H 2.5/12.5 mg not exceeding one capsule should be made.

Dosage in patients with impaired renal function:

For patients with creatinine clearance between 60 and 30ml/min/1.73m² body surface area, treatment is initiated with ramipril alone 1.25mg. After gradually increasing the dose of ramipril, medication with Ramace® H 2.5/12.5 mg is initiated at a daily dose of 1 capsule. The maximum permitted daily dose is 2 capsules of Ramace® H 2.5/12.5 mg in such patients. When creatinine clearance cannot be measured, it can be calculated based on the serum creatinine level using Cockcroft's equation:

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

Women: Multiply the product of the above equation by 0.85

Administration

Generally, the prescribed daily dose should be taken in the morning as a single dose. The capsules must be swallowed as a whole with sufficient amounts of liquid (approx ½ glass). They may be taken before during or after a meal.

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

A blister of 10 capsules.

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AstraZeneca 

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