Ramipace®

(R a m i p r i l BP)

ریمی پیس

COMPOSITION

Ramipace 1.25 mg Tablet
Each tablet contains:
Ramipril……1.25mg
Ramipace 2.5 mg Tablet
Each tablet contains:
Ramipril……..2.5mg
Ramipace 5 mg Tablet
Each tablet contains:
Ramipril……..….5mg
Ramipace 10 mg Tablet
Each tablet contains:
Ramipril……..10mg
(BP Specs.)

WARNING: FETAL TOXICITY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and death to the developing fetus. When pregnancy is detected, Ramipril should be discontinued as soon as possible.

DESCRIPTION

Ramipace contains Ramipril an orally active inhibitor of the Angiotensin converting enzyme (ACE) employed in the treatment of hypertension and some other cardiovascular disorders. It is chemically designated as (2S, 3aS, 6aS)-1[(S)-N[(S)-1-Carboxy-3-phenylpropyl]alanyl]octa hydrocyclopenta[b]pyrrole-2-carboxylic acid, 1ethyl ester. Its molecular formula is $C_{23}H_{32}N_2O_5$

CLINICAL PHARMACOLOGY

Mechanism of Action
Ramipril and its active metabolite ramiprilat inhibit ACE (Angiotensin Converting Enzyme). Angiotensin converting enzyme is a peptidyldipeptidase that catalyzes the conversion of angiotensin I to the potent vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decrease aldosterone secretion resulting in decreased water retention. Reduced vasoconstriction and decreased water retention contribute towards the antihypertensive effects of Ramipril. The decrease in aldosterone secretion due to Ramipril may also result in a small increase of serum potassium.
The effect of Ramipril on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma.

Pharmacokinetics

Absorption
Following oral administration Ramipril is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of Ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract.
The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg ramipril is 45 %. Peak plasma concentrations of ramiprilat, are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution
The serum protein binding of Ramipril is about 73 % and that of ramiprilat about 56%.

Metabolism
Ramipril is almost completely metabolized to its active diacid metabolite ramiprilat via cleavage of the ester group (primarily in the liver), which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive.

Excretion
Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline, which represents distribution of the drug into a large peripheral compartment and subsequent binding to both plasma and tissue ACE, has a half-life of 2–4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of 9–18 hours. The terminal elimination phase has a prolonged half-life (>50 hours) and probably represents the binding/dissociation kinetics of the ramiprilat/ACE complex. It does not contribute to the accumulation of the drug. After multiple daily doses of Ramipril 5 mg-10 mg, the half-life of ramiprilat concentrations within the therapeutic range was 13–17 hours.
Excretion of the metabolites is primarily renal. 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 feces. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

INDICATIONS

Treatment of hypertension
Ramipril is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
Ramipril may be used alone or in combination with thiazide diuretics.

Reduction in risk of myocardial infarction, stroke and death from cardiovascular causes
Ramipril is indicated in patients 55 years or older at high risk of developing a major cardiovascular event due to a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), in order to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes.
Ramipril can be used in addition to other required treatments (such as antihypertensive, antiplatelet, or lipid-lowering therapy).

Heart failure occurring post myocardial infarction
Ramipril is indicated in stable patients who demonstrate clinical signs of congestive heart failure within the first few days after sustaining an acute myocardial infarction. Administration of Ramipril to such patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure.

DOSAGE AND ADMINISTRATION

Hypertension

Starting dose:
The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. The dose should be adjusted later according to blood pressure response.
For patients being treated with diuretics, hypotension may occur following addition of Ramipril to therapy. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Ramipril. In hypertensive patients in whom the diuretic is not discontinued, therapy with Ramipril should be initiated with a 1.25 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Ramipril should be adjusted according to response.
Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood pressure following the initial dose. A starting dose of 1.25 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

Maintenance dose:
The starting dose can be doubled at interval of two to four weeks in order to gradually achieve target blood pressure.
The usual maintenance dosage range is 2.5 mg to 20 mg per day administered as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with Ramipril alone, other antihypertensive drugs can be added.
Reduction in risk of myocardial infarction, stroke and death from cardiovascular causes

Reduction in risk of myocardial infarction, stroke and death from cardiovascular causes

Starting dose:
In clinically and hemodynamically stable patients, the starting dose should be 2.5 mg once daily for 1 week.

Titration and Maintenance dose:
The starting dose should be doubled to 5 mg once daily for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg once daily. If the patient is hypertensive or has recently sustained a myocardial infarction, a divided dose can be given.

Heart failure occurring post myocardial infarction

Starting dose:
For the treatment of post-myocardial infarction patients who have shown signs of congestive heart failure, the recommended starting dose of Ramipril is 2.5 mg twice daily (5 mg per day). A patient who becomes hypotensive at this dose may be switched to 1.25 mg twice daily.
After the initial dose of Ramipril, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced as this will diminish the likelihood of hypotension.

Titration and maintenance dose:
After one week at the starting dose, the dose can be increased (if tolerated) towards a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart.
Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. If a decision is taken to treat these patients, it is recommended that therapy be started at 1.25 mg once daily and that particular caution be exercised in any dose increments.

Dosing considerations and dosage adjustment in special populations

Renal Impairment
The baseline renal function must be established in patients starting Ramipril. No dosage adjustment is required in patients with estimated creatinine clearance > 40 mL/min. In patients with moderate or severe renal impairment (creatinine clearance < 40 ml/min and < 15 ml/min respectively), the dose of Ramipril must be adjusted as described below.
Ramipril is slightly dialyzable and if administered to a hemodialysis patient, it should be given few hours after hemodialysis is performed.

Hypertension
For patients with hypertension and moderate or severe renal impairment as described above, the recommended initial dose is 1.25 mg once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg.

Heart Failure Post-Myocardial Infarction
For patients with heart failure and moderate/severe renal impairment, the recommended initial dose is 1.25 mg once daily. The dose may be increased to 1.25 mg twice daily, and up to a maximum dose of 2.5 mg twice daily depending on clinical response and tolerability.

Patients with Volume Depletion or Renal Artery Stenosis
Blood pressure decreases associated with any dose of Ramipril depend, in part, on the presence or absence of volume depletion (e.g., past and current diuretic use) or the presence or absence of renal artery stenosis. If such circumstances are suspected to be present, initial dose should be 1.25 mg once daily. Further dosage is to be adjusted according to blood pressure response.

Patients with Hepatic impairment
In patients with hepatic impairment, treatment with Ramipril should be initiated only under close medical supervision and the maximum daily dose is 2.5 mg

Administration requirements
Ramipace tablets should be swallowed whole before, during or after meals with a generous amount of fluid.

CONTRAINDICATIONS

• Hypersensitivity to Ramipiril or other ACE inhibitors
• History of angioedema with an ACE inhibitor or Angiotensin-II receptor blocker (such as telmisartan, valsartan etc.) or a history of hereditary or idiopathic angioedema.
• Patients undergoing extracorporeal treatments (leading to contact of blood with negatively charged surfaces) must not be treated concomitantly with Ramipril, because there is the risk of serious analphylactoid reactions.
• Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
• Second and third trimesters of pregnancy.
• Hypotensive or hemodynamically unstable patients.
• The concomitant use of Ramipirl with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min).

WARNINGS AND PRECAUTIONS

- Pregnancy and fetal toxicity
Ramipril is not recommended during the first trimester of pregnancy and contraindicated during the second and third trimesters of pregnancy.
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, Ramipril must be discontinued as soon as possible and alternative anti-hypertensive therapy should be considered.

- Patients at particular risk of developing hypotensive states

Patients with strongly activated renin-angiotensin-aldosterone system
Patients with strongly activated renin-angiotensin-aldosterone system (RAAS) 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 at first dose increase.
Significant activation of RAAS is to be anticipated in the following conditions:
- Patients with severe hypertension.
- Patients with decompensated congestive heart failure.
- Patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve).
- Patients with unilateral renal artery stenosis with a second functional kidney.
- Patients in whom fluid or salt depletion exists or may develop (including patients using diuretics or with dietary salt reduction, diarrhea or vomiting).
- Patients with liver cirrhosis and/or ascites.
- Patients undergoing major surgery or during anesthesia with agents that produce hypotension.

Transient or persistent heart failure post myocardial infarction
In patients with heart failure post-myocardial infarction who are being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Ramipril. If the initial dose of 2.5 mg Ramipril cannot be tolerated, an initial dose of 1.25 mg Ramipril should be used to avoid excessive hypotension. Reduction in the dose of concomitant diuretic to decrease the incidence of hypotension can also be considered.

Surgery and Anesthesia
It is recommended that treatment with angiotensin converting enzyme inhibitors such as Ramipril should be discontinued where possible one day before surgery. In patients undergoing surgery or during anesthesia with agents that produce hypotension, Ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Resultant hypotension can be corrected by volume expansion.

- Renal Impairment and/or renal artery stenosis
Changes in renal function may be anticipated in susceptible individuals using Ramipril. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including Ramipril, may be associated with oliguria or progressive azotemia and rarely with acute renal failure or death.
In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another ACE inhibitor suggests that these increases would be reversible upon discontinuation of Ramipril 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 Ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of Ramipril and/or discontinuation of the diuretic may be required.

- Anaphylactoid and possibly related reactions
Drugs acting directly on the renin-angiotensin-aldosterone system (e.g., ACE inhibitors) affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, so patients receiving Ramipril may be subject to a variety of serious anaphylactoid reactions.
Angioedema has been reported in patients treated with ACE inhibitors including Ramipril. Patients with a history of angioedema unrelated to ACE inhibitor therapy may also be at increased risk of angioedema while receiving an ACE inhibitor. In case of angioedema, Ramipril must be discontinued. Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of symptoms.

Head and Neck Angioedema
Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, Ramipril must be discontinued and appropriate therapy should be given immediately. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy (e.g., subcutaneous epinephrine solution 1:1000 [0.3 mL to 0.5 mL]) must be given promptly.

Intestinal Angioedema
Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting). The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the

differential diagnosis of patients on Ramipril presenting with abdominal pain.

Anaphylactoid Reactions during Desensitization
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of Ramipril tablets should be considered prior to desensitization.

Anaphylactoid Reactions during Membrane Exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

- Hyperkalemia
In clinical trials with Ramipril, reversible hyperkalemia (serum potassium >5.7 mEq/L) occurred in approximately 1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, age > 70 years, dehydration, metabolic acidosis and the concomitant use of other drugs that raise serum potassium levels. If concomitant use of Ramipril with plasma potassium increasing agents is required, regular monitoring of serum potassium should be done.

- Hyponatremia
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatremia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatremia.

- Neutropenia/Agranulocytosis
In rare instances, treatment with ACE inhibitors may be associated with mild reductions in red blood cell count and hemoglobin content, blood cell or platelet counts. In isolated cases, agranulocytosis, pancytopenia, and bone marrow depression may occur. Hematological reactions to ACE inhibitors are more likely to occur in patients with collagen-vascular disease (e.g., systemic lupus erythematosus, scleroderma) and renal impairment. Consider monitoring white blood cell counts in patients with collagen-vascular disease; especially if the disease is associated with impaired renal function.

- Cough
Presumably caused by inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. The possibility of angiotensin converting enzyme inhibitor induced-cough should be considered in the differential diagnosis of cough.

- Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.
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.

- Effects on ability to drive and use machines
Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk during driving or operating a vehicle or machinery. This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

ADVERSE REACTIONS

Cardiac disorders
Uncommon: angina pectoris, myocardial infarction, tachycardia, arrhythmia, palpitations, peripheral edema
Blood and lymphatic system disorders
Uncommon: Eosinophilia
Rare: White blood cell count decreased (neutropenia, agranulocytosis), red blood cell count decreased, hemoglobin decreased, platelet count decreased
Frequency unknown: Bone marrow failure, pancytopenia, hemolytic anemia
Nervous system disorders
Common: Headache, dizziness
Uncommon: Vertigo, paraesthesia, ageusia, dysgeusia
Rare: Tremor, balance disorder
Frequency unknown: ischemic stroke, transient ischemic attack, psychomotor skills impaired, burning sensation, parosmia
Eye disorders
Uncommon: Visual disturbance including blurred vision
Rare: Conjunctivitis
Ear and labyrinth disorders
Rare: Hearing impaired, tinnitus
Respiratory, thoracic and mediastinal disorders
Common: Non-productive tickling cough, bronchitis, sinusitis, dyspnea
Uncommon: Bronchospasm, nasal congestion
Gastrointestinal disorders
Common: Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhea, nausea, vomiting
Uncommon: Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, upper abdominal pain, gastritis, constipation, dry mouth
Rare: Glossitis
Frequency unknown: Aphtous stomatitis
Renal and urinary disorders
Uncommon: Renal impairment, acute renal failure, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased.
Skin and subcutaneous tissue disorders
Common: maculo-papular rash
Uncommon: Angioedema; pruritus, hyperhidrosis
Rare: Exfoliative dermatitis, urticaria, onycholysis
Very Rare: Photosensitivity reaction
Frequency unknown: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia.
Musculoskeletal and connective tissue disorders
Common: Muscle spasms, myalgia
Uncommon: Arthralgia
Metabolism and nutrition disorders
Common: Hyperkalemia
Uncommon: Anorexia, decreased appetite
Frequency unknown: hyponatremia
Vascular disorders
Common: Hypotension, orthostatic blood pressure decreased, syncope
Uncommon: Flushing
Rare: Vascular stenosis, hypoperfusion, vasculitis
Frequency unknown: Raynaud's phenomenon
General disorders and administration site conditions
Common: Chest pain, fatigue
Uncommon: Pyrexia
Rare: Asthenia
Immune system disorders
Frequency unknown: anaphylactoid reactions, antinuclear antibody increased
Hepatobiliary disorders
Uncommon: Hepatic enzymes and/or conjugated bilirubin increased,
Rare: Cholestatic Jaundice, hepatocellular damage
Frequency unknown: Acute hepatic failure, cholestatic or cytolytic hepatitis
Reproductive system and breast disorders
Uncommon: Transient erectile dysfunction, libido decreased
Frequency not known: Gynaecomastia
Psychiatric disorders
Uncommon: Depressed mood, anxiety, nervousness, restlessness, sleep disorders, somnolence
Rare: Confusional state
Frequency unknown: Disturbance in attention

DRUG INTERACTIONS

Major drug-drug interactions

Concomitant use of Ramipril with Aliskiren or Angiotensin receptor blockers
Dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Ramipril and Aliskiren:
Ramipril together with Aliskiren is contraindicated in patients with diabetes and in patients with renal impairment (Creatinine clearance < 60 mL/min). Moreover, combination of Aliskiren and Ramipril should generally be avoided due to above safety concerns.

Ramipril and Angiotensin Receptor blockers:
Ramipril and angiotensin II receptor blockers (ARBs) should not generally be used concomitantly due to potential risk of clinically important renal dysfunction (death, doubling of serum creatinine, or dialysis)
Concomitant use of Ramipril and ARBs is also harmful in patients with diabetic nephropathy and should be avoided.

Other drug-drug interactions for Ramipril

- Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim, tacrolimus, ciclosporin):

Hyperkalemia may occur; therefore close monitoring of serum potassium is required.

- Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin):

Potentiation of the risk of hypotension is to be anticipated. The possibility of hypotensive effects with a diuretic can be minimized by either decreasing or discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Ramipril. If this is not possible, the starting dose should be reduced.

- Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of Ramipril:

Blood pressure monitoring is recommended.

- Allopurinol, immunosuppressants, corticosteroids, procainamide, cytotoxic (antineoplastic) drugs and other substances that may change the blood cell count:

Increased likelihood of deranged blood cell counts.

- Lithium salts:

Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored. Risk of lithium toxicity is increased if diuretic is also used.

- Non-steroidal anti-inflammatory drugs and selective COX II inhibitors:

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including ramipril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Renal function should be monitored.
Moreover, the antihypertensive effect of ACE inhibitors, including ramipril, may be reduced by NSAIDs.

- mTOR inhibitors and DPPIV inhibitors:
Patients taking concomitant mTOR inhibitor (e.g. temsirolimus, everolimus etc.) or DPPIV inhibitor (Vildagliptin) with Ramipril therapy may be at increased risk for angioedema

- Antidiabetic agents and insulin
Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

Other forms of interactions

Anaphylactic reactions due to Membrane exposure
There is an increased risk of severe anaphylactoid reactions in patients taking Ramipril and concomitantly undergoing 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 sulphate). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Pregnancy D. Ramipril is not recommended during the first trimester of pregnancy and contraindicated during the second and third trimesters of pregnancy.
Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Should exposure to ACE inhibitor have occurred since or during the second/third trimester of pregnancy, ultrasound check of renal function and skull of the newborn is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia.
If oliguria or hypotension occurs, blood pressure support and renal perfusion should be considered. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Ramipril, which crosses the placenta, can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

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

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Elderly
Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of adverse effects especially in very old and frail patients. A reduced initial dose of 1.25 mg Ramipril should be considered in the elderly population.

Hepatic impairment
In patients with impaired liver function, the metabolism of Ramipril to ramiprilat appears to be slowed, possibly because of diminished activity of hepatic esterases, and plasma ramipril levels in these patients are increased about 3-fold. In patients with hepatic impairment, treatment with Ramipril should be initiated only under close medical supervision and the maximum daily dose is 2.5 mg. (See DOSAGE AND ADMINISTRATION)

Renal Impairment
The baseline renal function must be established in patients starting Ramipril. No dosage adjustment is required in patients with estimated creatinine clearance > 40 mL/min. In patients with moderate or severe renal impairment (creatinine clearance < 40 ml/min and < 15 ml/min respectively), the dose of Ramipril must be adjusted. (See DOSAGE AND ADMINISTRATION)

OVER DOSAGE

Symptoms
Symptoms associated with over dosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Treatment
The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore hemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. It is reasonable to treat Ramipril overdose by infusion of normal saline solution. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by hemodialysis.

PRESENTATION
Ramipace 1.25mg, 2.5mg, 5mg &10mg tablets are available in pack of 28's.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at
reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔
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