# Triltec®

**Ramipril Capsules**

## USE IN PREGNANCY

**When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus.**When pregnancy is detected, TRILTEC® should be discontinued as soon as possible.

## QUALITATIVE AND QUANTITATIVE DESCRIPTION

Ramiprilat, the diacid metabolite of Ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to Ramiprilat by hepatic cleavage of the ester group.

TRILTEC®(Ramipril) is supplied as hard shell capsules for oral administration containing 1.25 mg, 2.5 mg, 5 mg, and 10 mg of Ramipril. The inactive ingredients present are pregelatinized starch NF, sodium stearyl fumarate, gelatin and titanium dioxide. The 1.25 mg capsule shell contains yellow iron oxide, the 2.5 mg capsule shell contains yellow iron oxide and FD&C red #3, the 5 mg capsule shell contains azorubine and the 10 mg capsule shell contains FD&C blue #2 and FD&C red #3.

## INDICATIONS AND USAGE

***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 because of 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), to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. Ramipril can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

***Hypertension***: Ramipril is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using Ramipril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that Ramipril does not have a similar risk.

In considering use of Ramipril, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients.

***Heart Failure Post Myocardial Infarction***: Ramipril is indicated in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining 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.

## CONTRAINDICATIONS

Ramipril is contraindicated in patients who are hypersensitive to this product or any other angiotensin converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

## WARNINGS

***Anaphylactoid and Possibly Related Reactions***: Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Ramipril) may be subject to a variety of adverse reactions, some of them may be serious.

***Head and Neck Angioedema***: Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Ramipril should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered.**

***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); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. 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 ACE inhibitors presenting with abdominal pain.

***Anaphylactoid reactions during desensitization*:** Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

***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.

***Hypotension***: Ramipril can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, Ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with Ramipril. In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, Ramipril therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of Ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. Ramipril treatment usually can be continued following restoration of blood pressure and volume.

***Hepatic Failure***: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

***Neutropenia/Agranulocytosis***: As with other ACE inhibitors, rarely, a mild - in isolated cases severe - reduction in the red blood cell count and hemoglobin content, white blood cell or platelet count may develop. 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. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

***Fetal/Neonatal Morbidity and Mortality***: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible. The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure. These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of Ramipril as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is observed, Ramipril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as 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. No teratogenic effects of Ramipril were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

## PRECAUTIONS

***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 Ramipril, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/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 angiotensin converting enzyme inhibitor suggests that these increases are usually 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.

**Evaluation of the hypertensive patient should always include assessment of renal function.**

***Hyperkalemia***: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving Ramipril. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Ramipril.

***Cough***: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

***Impaired Liver Function***: Since Ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of Ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function. However, since the renin-angiotensin system may be activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients.

***Surgery/Anesthesia***: 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. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

## INFORMATION FOR PATIENTS

***Pregnancy***: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

***Angioedema***: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

***Symptomatic Hypotension***: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, Ramipril should be discontinued until the physician has been consulted. All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

***Hyperkalemia***: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

***Neutropenia***: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

## DRUG INTERACTIONS

***With nonsteroidal anti-inflammatory agents***: Rarely, concomitant treatment with ACE inhibitors and nonsteroidal anti-inflammatory agents have been associated with worsening of renal failure and an increase in serum potassium.

***With diuretics***: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Ramipril. The possibility of hypotensive effects with Ramipril can be minimized by either 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.

***With potassium supplements and potassium-sparing diuretics***: Ramipril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

***With lithium***: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

***With Oral Hypoglycemic Agents or Insulin***: Rarely, hypoglycemia has been reported during concomitant therapy. Upon initiation of Ramipril or with an increase in dose, such patients should be closely monitored for symptoms of hypoglycemic reactions with dosage adjustment of concomitant oral hypoglycemic agents or insulin therapy as necessary.

***Other***: Neither Ramipril nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of Ramipril and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate). The co-administration of Ramipril and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, co-administration of Ramipril with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation.

***Nursing Mothers***

Ingestion of single 10 mg oral dose of Ramipril resulted in undetectable amounts of Ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving Ramipril should not breast feed.

***Geriatric Use***

No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

***Pediatric Use***

Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

Headache, dizziness, fatigue, hypotension, increased cough, angina pectoris, nausea, syncope, vomiting, vertigo.

## CLINICAL LABORATORY TEST FINDINGS:

***Creatinine and Blood Urea Nitrogen***: Increases in creatinine levels occurred in 1.2% of patients receiving Ramipril alone, and in 1.5% of patients receiving Ramipril and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving Ramipril alone and in 3% of patients receiving Ramipril with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. Since Ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently.

***Hemoglobin and Hematocrit***: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving Ramipril alone and in 1.5% of patients receiving Ramipril plus a diuretic.

***Other (causal relationships unknown)***: Clinically important changes in standard laboratory tests were rarely associated with Ramipril administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

## OVERDOSAGE

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of Ramipril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of Ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat Ramipril overdose by infusion of normal saline solution.

## DOSAGE AND ADMINISTRATION

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, the initial starting dose should be 1.25 mg once daily.

***Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes***: Ramipril should be given at an initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg, once a day. If the patient is hypertensive or recently suffered post myocardial infarction, it can also be given as a divided dose.

***Hypertension***: The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 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, a diuretic can be added.

***Heart Failure Post Myocardial Infarction***: For the treatment of post-infarction patients who have shown signs of congestive 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, and after one week at the starting dose, patients should then be titrated (if tolerated) toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart. 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 which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of Ramipril does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The Ramipril Capsule is usually swallowed whole. The Ramipril Capsule can also be opened and the contents sprinkled on a small amount (about 4 oz.) of apple sauce or mixed in 4 oz. (120 ml) of water or apple juice. To be sure that Ramipril is not lost when such a mixture is used, the mixture should be consumed in its entirety. The described mixtures can be pre-prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration. Concomitant administration of Ramipril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Ramipril. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with Ramipril. Then, if blood pressure is not controlled with Ramipril alone, diuretic therapy should be resumed. If the diuretic cannot be discontinued, an initial dose of 1.25 mg Ramipril should be used to avoid excess hypotension.

**Dosage Adjustment in Renal Impairment:**

In patients with creatinine clearance <40 ml/min/1.73m$^2$ (serum creatinine approximately >2.5 mg/dl) doses of only 25% of those normally used should be expected to induce full therapeutic levels of ramiprilat.

***Hypertension***: For patients with hypertension and renal impairment, the recommended initial dose is 1.25 mg Ramipril 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 renal impairment, the recommended initial dose is 1.25 mg Ramipril once daily. The dose may be increased to 1.25 mg b.i.d. and up to a maximum dose of 2.5 mg b.i.d. depending upon clinical response and tolerability.

## STORAGE CONDITIONS

Store in the original package.
Do not store above 25°C.

## PRESENTATION

TRILTEC® 1.25 mg, 2.5 mg, 5 mg, and 10 mg are available each in packs of 30 capsules.

**Keep medicament out of the reach and sight of children.**

**Do not use after expiry date.**

**This is a medicament**

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor´s prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

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