xxxxxxxx-8883

For the Use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

TOPRIL

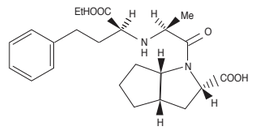
(Ramipril Capsules, 1.25 mg/2.5 mg/5 mg)

COMPOSITION

Topril-1.25 : Each hard gelatin capsule contains Ramipril B.P. 1.25mg.
Topril-2.5: Each hard gelatin capsule contains Ramipril B.P. 2.5mg.
Topril-5: Each hard gelatin capsule contains Ramipril B.P. 5mg.

PROPERTIES

Ramipril is a white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol. It is (2S, 3aS, 6aS)-1-[(S)-2-[[(S) 1-(ethoxycarbonyl)-3- phenylpropyl] amino] propanoyl] octahydrocyclopenta [b] pyrrole-2-carboxylic acid. Its empirical formula is $C_{23}H_{32}N_2O_5$ and the molecular weight is 416.5. The structure of Ramipril is:



PHARMACOLOGICAL PROPERTIES

Pharmacokinetics

Ramiprilat is an active metabolite of Ramipril. Ramipril and Ramiprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the angiotensin I to the 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 decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. 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 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.

Distribution

The serum protein binding of Ramipril is about 73% and that of Ramiprilat about 56%; in vitro, these percentages are independent of concentration over the range of 0.01 to 10 mcg/ml.

Metabolism

Ramipril is almost completely metabolized in liver to Ramiprilat, 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.

Elimination

After oral administration of Ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine and about 40% are found in the feces. Drug recovered in the feces may represent biliary excretion of both metabolites and/or unabsorbed drug, however the proportion of a dose eliminated by the bile has not been determined. Less than 2% of the administered dose is recovered in urine as unchanged Ramipril.

Plasma concentrations of Ramipril 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 dissociation from the enzyme, Ramipril 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 Ramipril/ACE complex. It does not contribute to the accumulation of the drug.

INDICATIONS

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

CONTRAINDICATIONS

Ramipril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme 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.

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. When 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.

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.

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.

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.

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.

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/l) occurred in approximately 1% of hypertensive patients receiving Ramipril. None of these patients was discontinued from the trials because of hyperkalemia.

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.

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.

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.

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.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No evidence of a tumorigenic effect was found when Ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Nursing Mothers: 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

Most Common: Nausea, dizziness, headache, dry cough.

CVS: Hypotension with associated dizziness and even syncope. In patients with congestive heart failure with/without renal insufficiency excessive hypotension has been associated with oliguria and azotemia.

Renal: Treatment may impair renal function. Increase in blood urea and serum creatinine. In patients with renal insufficiency there is a risk of hyperkalemia.

Liver: Careful monitoring in the event of hepatic impairment is essential since Ramipril is metabolized to its active metabolite in the liver.

GIT: Nausea, diarrhoea, gastric pain is often transient. Taste disturbances may occur.

Allergy: Angioneurotic edema has been noted. Pruritus, rash, fever may occur.

DRUG INTERACTIONS

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.

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 effects of the latter drug.

DOSAGE AND ADMINISTRATION

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 towards 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.

OVERDOSAGE

Laboratory determinations of serum levels of Ramipril and its metabolites are not widely available and such determinations have, in any event, no established role in the management of Ramipril overdose.

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

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 30°C

PRESENTATION AND AVAILABILITY

Topril-1.25 : Orange/white hard gelatin capsule containing white to off white powder.
Topril-2.5 : Blue/white hard gelatin capsule containing white to off white powder.
Topril-5 : Green/white hard gelatin capsule containing white to off white powder.
Topril-1.25/2.5/5 is available in blister strip of 10 capsules.

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Manufactured by :
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