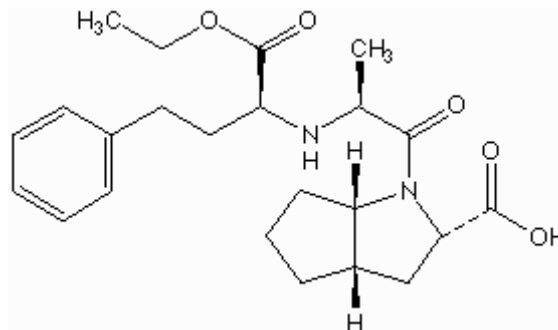


APO-RAMIPRIL CAPSULES**NAME OF THE MEDICINE**

Non-proprietary name: Ramipril

Chemical Name: (2S,3aS,6aS)-1-[(2S)-2-[[[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid

Structural Formula:



Ramipril has 5 chiral centres, with S-configuration in all 5 asymmetric carbon atoms.

Molecular Formula: $C_{23}H_{32}N_2O_5$

Molecular Weight: 416.51

CAS Registry Number: 87333-19-5

DESCRIPTION

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. It is a white, crystalline substance sparingly soluble in water and soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105°C and 112°C.

PHARMACOLOGY**Mechanism of Action**

Ramipril is a pro-drug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active moiety, ramiprilat. Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE) which is identical to kininase II. This converting enzyme (ACE) is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex, thus inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase in serum potassium.

Kininase II is one of the enzymes responsible for the degradation of bradykinin, a potent vasodepressor peptide. The inhibition of kininase II activity by ramipril prevents the degradation of bradykinin thus leading to increased levels of this potent vasodepressor substance. While the mechanism through which ramipril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ramipril has an antihypertensive effect even in patients with low renin hypertension. Although ramipril was antihypertensive in all races studied, black hypertensive patients (usually a low renin hypertensive population) had a smaller average response to monotherapy than non-black patients.

The nephroprotective effects of ramipril are in addition to its antihypertensive action. These effects are a result of its beneficial effects on glomerular permeability which reduces protein filtration (an intrinsically toxic biological process) and thus contributes to its antiproteinuria effects.

Pharmacokinetics

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 and to the diketopiperazine ester. 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.

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 and kininase II, has a half-life of 2 - 4 hours.

Because of its potent binding to 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 - 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.

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/1.73 m² had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations (see **DOSAGE and ADMINISTRATION**).

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. 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 on plasma ACE activity does not vary with hepatic function.

Pharmacodynamics

Single doses of ramipril of 2.5 - 20 mg produce approximately 60 - 80% inhibition of ACE activity 4 hours after dosing with approximately 40 - 60% inhibition after 24 hours. Multiple oral doses of ramipril of 2 mg or more cause plasma ACE activity to fall by more than 90% 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small multiple doses presumably reflects saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

CLINICAL TRIALS

Hypertension

Administration of ramipril to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt and/or volume depleted (see **PRECAUTIONS, Warnings**). Use of ramipril in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone.

In single-dose studies, doses of 5 - 20 mg of ramipril lowered blood pressure within 1 - 2 hours, with peak reductions achieved 3 - 6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (4 - 12 weeks) controlled studies, once-daily doses of 2.5 - 10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mm Hg more than placebo. In comparisons of peak *versus* trough effect, the trough effect represented about 50-60% of the peak response.

In most trials, the antihypertensive effect of ramipril increased during the first several weeks of repeated measurements. The antihypertensive effect of ramipril has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of ramipril has not resulted in a rapid increase in blood pressure.

Interaction studies of ramipril and thiazides have been carried out. Limited experience in controlled and uncontrolled trials combining ramipril with a calcium channel blocker, a loop diuretic or triple therapy (beta-blocker, vasodilator and a diuretic) indicate no unusual drug-drug interactions. Other ACE inhibitors have had less than additive effects with beta adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

Myocardial infarction

The efficacy of ramipril has been established in a study of 2000 patients with myocardial infarction who showed clinical signs of heart failure (ACUTE INFARCT RAMIPRIL EFFICACY). Treatment with ramipril resulted in a significant improvement in survival and clinical outcomes. Over an average follow-up period of 15 months, ramipril reduced all cause mortality by 6% compared to placebo (risk reduction 27%, $p = 0.002$) and reduced the risk of secondary outcomes including progression to severe/resistant heart failure, reinfarction, stroke or death (in the absence of any prior validated event) by 19% ($p = 0.008$). These results are based on intention-to-treat analysis and are therefore likely to be conservative in terms of potential benefit of ramipril. A subsidiary analysis showed that the benefit of ramipril in terms of survival was evident as early as one month into treatment. The difference in mortality in the two groups at 30 days represented a risk reduction for the ramipril group over placebo of 29% ($p = 0.053$).

Non-diabetic or diabetic nephropathy

Non-diabetic nephropathy

In **overt**, mostly non-diabetic (13% diabetic subjects included) nephropathy, the pivotal REIN Study (Ramipril Efficacy In Nephropathy) ($n = 166$) demonstrated statistically significant decreases in the rate of progression of renal insufficiency and the development of end-stage renal failure. The populations studied in this placebo-controlled trial included normotensive patients, patients with uncontrolled mild-to-moderate hypertension ($\text{DBP} > 90 \text{ mm Hg}$) and patients with controlled mild-to-moderate hypertension. For those with uncontrolled hypertension, the target blood pressure was pre-defined ($\text{DBP} < 90 \text{ mm Hg}$) and if this was not achieved with study medication (ramipril or placebo) alone, additional antihypertensives were added. The improvements observed are more dramatic with poorer (elevated) baseline proteinuria ($\geq 3 \text{ g/24 hr}$) but are also observed at lower baseline proteinuria (> 1 and $< 3 \text{ g/24 hr}$). At this level of proteinuria, subgroup analysis in the REIN study indicated that only patients with worse (lower) GFR ($< 45 \text{ mL/min/1.73 m}^2$) received statistically significant benefits in end-stage renal failure. The results of the REIN study are summarized below.

The improvement in these key endpoints was observed to increase with time, to be maintained long term and to apply to both hypertensive and non-hypertensive patients. A delay of approximately three months was seen prior to detection of the beneficial effects of ramipril, suggesting the value of early treatment.

Patient Proteinuria Baseline (n)	End Point		Ramipril + Conventional Therapy	Placebo + Conventional Therapy	p-Value
Proteinuria 1 - 3 g/24 hr (n = 186)	Secondary end point: ESRF (end-stage renal failure) overall and by baseline GFR	Overall	9 (9.1%)	18 (20.7%)	0.01
		$> 45 \text{ mL/min/1.73m}^2$	2 (3.3%)	1 (2.4%)	not reported
		$\leq 45 \text{ mL/min/1.73m}^2$	7 (17.9%)	17 (37%)	0.037
	Secondary end point: Progression to proteinuria $\geq 3 \text{ g/day}$		15 (15.2%)	27 (31%)	0.005
	Primary end point: Monthly reduction in GFR (mL/min/1.73m^2)		0.26	0.29	0.59 (comparison)

Proteinuria ≥ 3 g/24 hr (n = 166)	Primary end point: Change in monthly GFR (mL/min/1.73m ²) overall and by baseline proteinuria	Overall	-0.54	-0.88	0.038
		3 to < 4.5 g/24 hr	-0.53	-0.70	not reported
		4.5 to < 7 g/24 hr	-0.47	-0.99	not reported
		> 7 g/24 hr	-0.64	-1.44	not reported
	Secondary end point: ESRF or DOC (end-stage renal failure or doubling of creatinine)		18 (23.1%)	40 (45.5%)	0.02 (difference)

Diabetic nephropathy

Studies in **overt** diabetic nephropathy, particularly the ACE II (angiotensin-converting enzyme II) study, have demonstrated that both low and high-dose ramipril therapy can retard proteinuria and maintain renal health (maintain GFR, creatinine levels and creatinine clearance). The ACE II study, which was an open label follow-up to the ACE I study with captopril, investigated the effect of intensive (target MAP ≤ 92 mm Hg; n = 63) *versus* moderate (target MAP ≥ 100 to ≤ 107 mm Hg; n = 66) blood pressure control with ramipril on renal function. While the study observed no significant differences between these moderate and intensive BP control groups, there was no observed deterioration of renal function in this high-risk population throughout the two-year study (no statistically significant change in serum creatinine or creatinine and a significant improvement in proteinuria). The trial therefore demonstrated the benefit of ramipril in maintaining the renal health of diabetic patients. These results are presented below.

Characteristic (n = 129)	Change from Baseline	p-Value
Primary end point: 24 hr creatinine clearance (mL/min)	0.14	0.09
Secondary end point: Serum creatinine (mg/dL)	0.06	0.43
Secondary end point: Proteinuria	-0.19	0.02

Patients with an increased cardiovascular risk

The placebo-controlled HOPE study with once-daily ramipril was conducted in patients with an increased cardiovascular risk attributable to either vascular diseases (such as manifest coronary heart disease, a history of stroke or a history of peripheral vascular disease) or to diabetes mellitus plus at least one additional risk factor (such as microalbuminuria, hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels or smoking). Importantly, patient exclusion criteria included MI/stroke within 4 weeks of the start of the study, heart failure or low ejection fraction (< 0.40). Ramipril was administered adjunctive to standard therapy (e.g. in addition to aspirin, cholesterol lowering agents, other antihypertensives or oral antidiabetic agents) and on a preventative basis to over 9,200 such patients. Patients were initiated on ramipril 2.5 mg for one week which was then titrated firstly to ramipril 5 mg for three weeks and then to ramipril 10 mg. The results of the HOPE study in terms of the primary composite endpoint and its components (CV death, MI or stroke) for the whole population (ITT - Intention to Treat) and for those patients with diabetes are presented below.

Outcome	Ramipril 10 mg n (%)	Placebo n (%)	Relative Risk (95% CI)	p-Value (log-rank)
All Patients	n = 4645	n = 4652		
Primary composite end point	651 (14.0)	826 (17.8)	0.78 (0.70–0.86)	< 0.001
CV death	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	< 0.001
MI	459 (9.9)	570 (12.3)	0.80 (0.70–0.90)	< 0.001

Stroke	156 (3.4)	226 (4.9)	0.68 (0.56–0.84)	< 0.001
Patients with Diabetes	n = 1808	n = 1769		
Primary composite end point	277 (15.3)	351 (19.8)	0.75 (0.64–0.88)	0.0004
CV death	112 (6.2)	172 (9.7)	0.63 (0.49–0.79)	< 0.0001
MI	185 (10.2)	229 (13.0)	0.78 (0.64–0.94)	0.01
Stroke	76 (4.2)	108 (6.1)	0.67 (0.50–0.90)	0.0074

The results of the HOPE study in terms of the pre-specified secondary endpoints for **the whole population** (ITT - Intention to Treat) are presented below.

Pre-Specified End Point	Ramipril 10 mg n (%)	Placebo n (%)	Relative Risk (95% CI)	p-Value (log-rank)
All Patients	n = 4645	n = 4652		
All-cause mortality	482 (10.4)	569 (12.2)	0.84 (0.75–0.95)	0.005
CV death	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	< 0.001
CV revascularisation*	743 (16.0)	854 (18.4)	0.85 (0.77–0.94)	0.0014
PTCA/CABG	580 (12.5)	688 (14.8)	0.83 (0.74–0.92)	0.0008
Non-coronary revascularisation	191 (4.1)	213 (4.6)	0.89 (0.73–1.08)	n.s.
Hospitalisation for heart failure	141 (3.3)	161 (3.5)	0.87 (0.69–1.09)	n.s.

n.s. = not significant

* includes CABG, PTCA, carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation

The results of the HOPE study in terms of the pre-specified secondary endpoints for those **patients with diabetes** are presented below.

Pre-Specified End Point	Ramipril 10 mg n (%)	Placebo n (%)	Relative Risk (95% CI)	p-Value (log-rank)
Patients with Diabetes	n = 1808	n = 1769		
All-cause mortality	196 (10.8)	248 (14.0)	0.76 (0.63–0.92)	0.004
CV death	112 (6.2)	172 (9.7)	0.63 (0.49–0.79)	< 0.0001
CV revascularisation*	255 (14.1)	292 (16.5)	0.83 (0.70–0.98)	0.031
Hospitalisation for heart failure	81 (4.5)	79 (4.5)	0.99 (0.72–1.34)	n.s.
Development of overt nephropathy or dialysis	117 (6.5)	150 (8.5)	0.76 (0.59–0.96)	0.023
New microalbuminuria	424 (33.8)#	448 (37.9)#	0.92 (0.81–1.05)	n.s.
Serum creatinine (μmol/L, mean ± sd)	95.8 ± 27.4	93.7 ± 25.3	no test reported	
HbA1c (% of ULN, mean ± sd)	124 ± 29.5	124 ± 29.1	no test reported	

n.s. = not significant

* includes CABG, PTCA, carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation

expressed as percentage of non-albuminurics at baseline

INDICATIONS

- Treatment of hypertension. (Data are currently not available to support the use of ramipril in renovascular hypertension).
- Post MI heart failure.
- Prevention of progressive renal failure in patients with persistent proteinuria in excess of 1 g/day.
- For reducing the risk of myocardial infarction, stroke, cardiovascular death or the need for revascularisation procedures in patients 55 years of age or more who have clinical evidence of coronary artery disease, stroke or peripheral vascular disease.
- For reducing the risk of myocardial infarction, stroke, cardiovascular death or revascularisation procedures in diabetic patients 55 years or more with one or more of the following risk factors: systolic blood pressure > 160 mm Hg or diastolic blood pressure > 90 mm Hg (or on antihypertensive treatment); total cholesterol > 5.2 mmol/L; HDL cholesterol < 0.9 mmol/L; current smoker; known microalbuminuria; any evidence of previous vascular disease.

CONTRAINDICATIONS

- Hypersensitivity to ramipril or to any of the excipients.
- History of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor.
- Haemodynamically relevant renal artery stenosis either bilateral or unilateral in the single kidney.
- As with all vasodilators, ACE inhibitors should not be used in patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of aortic or mitral valve).
- Hypotensive or haemodynamically unstable patients.
- Pregnancy.
- Lactation.
- Renal failure (see **PRECAUTIONS**).
- High-flux dialyser membranes: Life threatening anaphylactoid hypersensitivity reactions, sometimes progressing to shock, have been described in the course of dialysis with certain high-flux membranes (e.g. polyacrylonitrile membranes such as AN69) during ACE inhibitor therapy. This combination thus needs to be avoided, either by using other medical products to control high blood pressure or cardiac insufficiency or by using other membranes during dialysis.

Similar reactions have been seen in patients undergoing low density lipoprotein apheresis with dextran sulfate during ACE inhibitor therapy.

PRECAUTIONS

Warnings

Angioedema – Head, Neck or Extremities

Ramipril is contraindicated in patients with a history of angioedema. Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. If angioedema occurs, the product should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition should resolve without treatment, although antihistamines may be useful in relieving symptoms. Laryngeal oedema, however, can be fatal, thus where there is angioedema involving swelling of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g. subcutaneous adrenalin solution 1:1000 (0.3 mL - 0.5 mL) should be promptly administered (see **ADVERSE REACTIONS**).

Angioedema may occur with or without urticaria. The onset of angioedema associated with use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free periods.

Medical therapy of progressive angioedema should be aggressive. Failing a rapid response, mechanical methods to secure an airway should be undertaken before massive oedema complicates oral or nasal intubation or surgical procedures (e.g. cricothyrotomy or tracheostomy). Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

Angioedema - Intestinal

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 facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.

Hypotension

Hypotension may occur in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in uncomplicated hypertensive patients but is a possible consequence of use in severely salt/volume depleted persons such as patients with renovascular hypertension, those treated vigorously with diuretics, after severe diarrhoea or patients undergoing dialysis (see **PRECAUTIONS**, **Drug Interactions** and **ADVERSE REACTIONS**). It is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed with ACE inhibitors. This may be associated with syncope, neurological deficit, oliguria and/or progressive azotemia, but rarely with acute renal failure and/or death. If ramipril is to be used in such patients for treatment of hypertension, therapy should be started under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage with or without a diuretic is increased. In patients with heart failure, correcting dehydration, hypovolaemia or salt depletion must be carefully weighed against the risk of volume overload.

For this reason also, in patients treated with ramipril after a myocardial infarction, treatment should not be initiated until the patient is haemodynamically stable (see **DOSAGE AND ADMINISTRATION**).

Similar consideration may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. In all high risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

In order to assess the extent of an acute fall in blood pressure and where necessary to take corrective action, blood pressure should be measured repeatedly after the first dose of ramipril, after a dosage increase of ramipril and after the first dose of an additional diuretic plus any dosage increase of the diuretic. This should be done until blood pressure has satisfactorily stabilized.

If hypotension occurs the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Impaired Renal Function

Ramipril can prevent progressive renal failure in patients with persistent proteinuria in excess of 1 g/day. The nephroprotective effect of ramipril was observed to be more evident at doses greater than 1.25 mg in a small *post hoc* analysis which examined changes in serum creatinine and GFR (rather than changes in the rate of decline of GFR) after 3 months treatment with ramipril. This effect could depend upon the selective availability at the renal tissue site and on the patient's sodium status. These studies also indicate that, in renally impaired patients, higher doses of ramipril did not represent a higher risk than did lower doses of ramipril.

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 patients after renal transplantation, there is a risk of renal impairment.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of ACE treatment and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea nitrogen and serum creatinine.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine which is usually minor and transient, especially when ramipril has been given concomitantly with a diuretic in patients with pre-existing renal impairment. Dosage reduction of ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, serum potassium should be monitored more frequently as there is a risk of hyperkalaemia.

There is insufficient experience in the use of ramipril in patients with severe renal impairment (*i.e.* creatinine clearance less than 20 mL/min/1.73 m² body surface area).

Ramipril is not suitable for the treatment of patients requiring haemodialysis for end-stage renal failure since only negligible amounts are dialysable.

Evaluation of the hypertensive patient or patient with heart failure should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**). If a deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients, other classes of antihypertensive agent should be preferred.

Impaired Liver Function

As ramipril is a pro-drug metabolized in the liver to its active moiety, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound and, therefore, the formation of the bioactive metabolite ramiprilat may be diminished, resulting in markedly elevated plasma levels of the parent compound due to the reduced activity of the esterases in the liver (see **DOSAGE AND ADMINISTRATION**).

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression (including leucopenia/neutropenia) have been reported with ACE inhibitors. These have mostly occurred in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy or a combination of these complicating factors. Most episodes of leucopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered to permit detection of a possible leucopenia, particularly in the initial phase of treatment. More frequent monitoring is advised in the initial phase of treatment and in patients with collagen vascular disease, renal disease (serum creatinine \geq 180 μ mol/L) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Cough

A persistent dry (non-productive) irritating cough has been reported with most ACE inhibitors in use. The frequency of reports has been increasing since cough was first recognized as a side-effect of ACE inhibition. In various studies, the incidence of cough varies between 2–15% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night. The cough is more common in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared to those who do not cough. The observed higher frequency of this complication in non-smokers may be due to higher level of tolerance to cough by smokers.

The mechanism of this adverse reaction is not clear but most likely to be secondary to the effects of converting-enzyme inhibitor on kinins (bradykinin and/or prostaglandin) resulting in stimulation of pulmonary cough reflex.

Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor. The reaction may recur on re-challenge with another ACE inhibitor but this is not invariably the case. A change in anti-hypertensive regime may be required in severe cases. Non-steroidal anti-inflammatory drugs (e.g. sulindac) have been reported to be effective in relieving coughing induced by ACE inhibitors. In mild hypertensive patients or patients likely to be treated with other antihypertensive agents, it is unlikely that risks of prescribing a non-steroidal anti-inflammatory drug will outweigh the benefit of relieving cough.

Hyperkalaemia

Because the ACE inhibitors decrease the formation of angiotensin II, which results in decreased production of aldosterone, increase in serum potassium levels (> 5.5 mEq/L) are not unexpected with this class of drugs. Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium-sparing diuretics or potassium supplements and/or consuming potassium-containing salt substitutes. Diabetics, and particularly elderly diabetics, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may co-exist with hyperkalaemia. It is recommended that patients undergoing ACE inhibitor treatment should have measurement of serum electrolytes (including potassium, sodium and urea) regularly. This is more important in patients taking diuretics.

Dermatological Reactions

Dermatological reactions characterized by maculo-papular pruritic rashes and sometimes photosensitivity has been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome etc.) have been reported. A causal relationship is difficult to assess.

Patients who developed a cutaneous adverse event with one ACE inhibitor may be free of reaction when switched to another drug of the same class, but there are also reports of cross-reactivity.

Taste Disturbances (Dysgeusia)

Taste disturbances were reported to be high (up to 12.5%) with high doses of another ACE inhibitor. The actual incidence of taste disturbance is probably low (< 0.5%) but data in this respect is scarce and difficult to interpret.

Taste disturbances with ACE inhibitors are described as suppression of taste or a metallic sensation in the mouth or sometimes there may be taste reduction or even complete loss of taste. The dysgeusia occurs usually in the first weeks of treatment and usually disappears within 1 - 3 months of treatment.

Surgery/Anaesthesia

In patients undergoing major surgery or anaesthesia who are being treated with agents that produce hypotension, ACE inhibitors may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Effects on the Ability to Drive and Operate Machinery

The antihypertensive effect in individual cases may be symptomatic. Treatment with any blood pressure lowering agent 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.

Laboratory Test Findings

The serum sodium level may decrease. Elevation of serum potassium may occur since ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics or potassium supplements should therefore be avoided. Increases in serum bilirubin and/or liver enzymes have been observed. Mild-to-severe decreases in haemoglobin (also due to haemolytic anaemia), red blood cells platelets and white blood cells have been observed with ACE inhibitors (see **PRECAUTIONS, Warnings**). Eosinophilia has also been seen. Raised titres of antinuclear antibodies have been observed with other ACE inhibitors.

Use in Pregnancy***Category D.***

As with all ACE inhibitors, ramipril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with ramipril and avoided during the treatment.

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

There are no adequate and well-controlled studies of ramipril in pregnant women. Data, however, show that ramipril crosses the human placenta. Post marketing experience with all ACE inhibitors suggests that exposure *in utero* may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death *in utero*.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during the first trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% CI, 1.89 - 7.3) and 4.4 times (95% CI, 1.37 - 14.02) respectively, compared to no exposure.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of neonatal hypotension, renal failure, skull hypoplasia and death.

Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial malformations, hypoplastic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease.

Use in Lactation

Ingestion of a single 10 mg dose of ramipril resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, there is evidence that ramiprilat is excreted in rat milk, hence ramipril should not be given to nursing mothers. If treatment with ramipril is necessary during lactation, the patient should not breast feed.

Use in Children

The safety and effectiveness of ramipril have not been established in children.

Use in the Elderly

In clinical trials, no overall difference in effectiveness or safety has been observed between patients over 65 and younger patients. However, since both liver and kidney function may decline with age, the starting dose of ramipril should be reduced to 1.25 mg daily.

Carcinogenicity

No evidence of a carcinogenic effect was found when ramipril was given to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1000 mg/kg/day for 18 months).

An increased incidence of oxyphilic cells in the renal tubules and oxyphilic microadenomas was also observed in rats treated for 24 months with ramipril (3.2 - 500 mg/kg/day). Data from historical control animals showed that the spontaneous occurrence of oxyphilic cells in rat kidney is age-related, is higher in males and reaches a level similar to that seen in the ramipril treated group. There is no evidence in humans that the occurrence of oxyphilic cells is age-related. Moreover, progression of oxyphilic cells to neoplasia (oncocyoma) is rare and, when it occurs, is considered to be benign. Whether this finding in rats represents any potential risk to man is therefore unclear.

Fibromuscular Pad Formation

In several repeated dose studies in rats, especially male animals treated with ramipril (3.2 - 500 mg/kg b.w./day) showed an increased incidence of so-called fibromuscular pad formation in the basal region of the gastric mucosa. The findings suggest an increased connective tissue formation and partly also increased formation of smooth muscle (lamina muscularis mucosae) due to a predominantly round cell inflammatory reaction. In all studies (1 - 24 months, carcinogenicity) the changes are always of the same type and no tendency of proliferation is obvious. Thus, it seems to be rather a reactive process with circumscribed scar tissue formation. The changes in the rat stomach mucosa could not be reproduced in other species (*i.e.* mouse, dog, rabbit, monkey).

This lesion was also observed when rats were treated with a relatively high dose (90 mg/kg/day for 3 - 6 months) of another ACE inhibitor. In the light of the available data, fibromuscular pad formation in the rat would not appear to present a serious risk in humans.

INTERACTIONS WITH OTHER MEDICINESAntihypertensive drugs

Possible potentiation of the antihypertensive effect must be anticipated when ramipril is administered concurrently with other antihypertensive agents and other substances with antihypertensive potential (e.g. nitrates, tricyclic antidepressants, anaesthetics).

Vasopressor sympathomimetics

The antihypertensive effect of ramipril may be reduced by concurrent administration of vasopressor sympathomimetics. Particularly close blood pressure monitoring is recommended.

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 (see **DOSAGE AND ADMINISTRATION**). Regular monitoring of serum sodium is necessary in patients undergoing concurrent diuretic therapy.

Potassium supplements, potassium sparing diuretics

Ramipril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene and others) and potassium supplements can increase the risk of hyperkalaemia. 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.

Lithium

Increased serum lithium levels and symptoms of lithium toxicity (e.g. cardiotoxic and neurotoxic effects) have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be co-administered 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.

NSAIDs

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

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including COX-2 inhibitor) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy and periodically thereafter.

Anaesthetics

General anaesthetics or anaesthetics with an antihypertensive action may cause the blood pressure to drop further in patients taking ramipril. Appropriate counter-measures, such as increasing the blood volume or, if necessary, administering angiotensin II, should be taken before or during surgery.

Antidiabetic agents

The possibility of an increased blood sugar reduction must be considered in patients treated concurrently with ramipril and antidiabetic agents, such as insulin and sulphonylurea derivatives.

Heparin

A rise in serum potassium concentration is possible when ramipril and heparin are administered concurrently.

Other

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatic agents and other substances that may change the blood picture. The likelihood of blood picture changes is increased when ramipril is administered with these substances.

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

ADVERSE EFFECTS

Ramipril has been evaluated for safety in over 4000 patients with hypertension. The frequency of adverse reactions associated with ramipril was low in clinical trials. Generally, adverse reactions are mild and transient and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache. Cough has been reported in clinical trials with an incidence of between less than 2% and up to 5.5%.

In placebo-controlled trials, however, there was an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough.

When used to treat nephropathy, the risks of ramipril therapy are no greater than when it is used to treat hypertension.

Similarly, the available information available from the HOPE study in 9200 patients does not reveal any increased risk of treatment with 10 mg ramipril in high risk cardiovascular patients or in diabetics.

The following lists adverse events reported in clinical trials with an incidence of greater than 2% (more common) and those with an incidence of equal to or less than 2% (less common).

More Common

Cardiovascular

Symptomatic hypotension characterized by dizziness, weakness, nausea, headache, palpitations, tiredness, lightheadedness, impaired reactions or tinnitus may occur particularly at initiation of treatment or after increasing the dose of ramipril (see **PRECAUTIONS, Warnings**).

Gastrointestinal

Nausea, vomiting, abdominal pain and diarrhoea may occur, but these reactions are often transient.

Dermatological

Apparent hypersensitivity reactions manifested by dermatitis, pruritus or rash, with or without fever (see **PRECAUTIONS**).

Cough

A persistent, dry (non-productive) cough has been reported with ramipril as with other ACE Inhibitors.

Less Common

Cardiovascular

Peripheral oedema, flushing and disturbed orthostatic regulation may be observed. Isolated cases of syncope, angina pectoris, arrhythmias, chest pain, palpitations, tachycardia, myocardial ischaemia and myocardial infarction have been observed. Exacerbation of perfusion disturbances due to vascular stenosis. Cerebral ischaemia leading to transient ischaemic attacks or stroke. Vasculitis.

Renal

Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in BUN and serum creatinine when taking ramipril, particularly when ramipril was given concomitantly with a diuretic (see **PRECAUTIONS, Warnings**). Impairment of renal function (isolated cases progressing to acute renal failure) may develop. Deterioration of pre-existing proteinuria (although ACE inhibitors usually reduce proteinuria) or an increase in urinary output may occur.

Angioedema

In very rare cases angioedema has occurred during therapy with ACE inhibitors, including ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with ramipril must be discontinued and appropriate therapy started immediately (see **PRECAUTIONS, Warnings**).

Gastrointestinal

Abdominal or gastric pain (sometimes with enzyme changes suggesting pancreatitis), pancreatitis, anorexia, constipation, diarrhoea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste or smell disturbances and vomiting.

Dermatological, mucosal and cutaneous

Reactions such as conjunctivitis, urticaria, alopecia, onycholysis, precipitation and/or intensification of Raynaud's phenomenon and sweating have been observed (also see **PRECAUTIONS**).

Neurological and Psychiatric

Amnesia, anxiety, confusion, convulsions, depression, disorders of balance, hearing loss, headache (not causally related to reduction in blood pressure), insomnia, fatigue, loss of appetite, nervousness, neuralgia, neuropathy, paraesthesia, restlessness, somnolence, tinnitus, tremor, vertigo and vision disturbances.

Other

Rarely, nasal congestion, sinusitis, bronchitis, bronchospasm, dyspnoea, muscular cramps, myalgia, arthralgia, cholestatic jaundice, liver damage (including acute liver failure), impotence and reduced libido (as generally possible in unusually low blood pressure and as possible consequence of other adverse effects) have been reported. Also photosensitivity reactions and purpura have occurred. The likelihood and the severity of anaphylactic and anaphylactoid reactions may be increased whilst taking ACE inhibitors. This must be considered when desensitisation is performed. Isolated cases of agranulocytosis, pancytopenia or bone marrow depression may occur.

DOSAGE AND ADMINISTRATION

Capsules should be swallowed whole before, during or after meals with a generous amount of fluid.

Hypertension

The recommended initial dosage for patients not receiving a diuretic is 2.5 mg ramipril once a day. Depending upon the patient's response, the dosage may then be increased at intervals of 2 - 3 weeks, first to 5 mg and then to a maximum of 10 mg once daily. If blood pressure is not controlled with ramipril alone, a diuretic can be added (see **PRECAUTIONS, Warnings** re administration with potassium-sparing diuretics and potassium supplements).

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

An initial dose of 1.25 mg should also be considered in patients where fluid or salt depletion have not been completely corrected or in patients whom a hypotensive reaction would constitute a particular risk (e.g. with relevant stenosis of coronary vessels of those supplying the brain).

Post-MI heart failure

The recommended initial dose is 5 mg ramipril daily, divided into two doses of 2.5 mg each, one in the morning and one in the evening. If the patient does not tolerate this initial dosage, it is recommended that 1.25 mg be given twice daily for two days. In either event, depending on the patient's response, the dose may then be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 - 3 days. The maximum permitted daily dose is 10 mg ramipril to be given in divided doses. Treatment should be started in hospital when the patient is haemodynamically stable, preferably between 2 and 10 days after acute myocardial infarction.

Treatment should be reviewed after 15 months with the consideration of withdrawing ACE inhibitor treatment from patients who are haemodynamically stable with no symptoms or signs of heart failure.

Sufficient experience is still lacking in the treatment of patients with severe heart failure (NYHA class IV) immediately after myocardial infarction.

Progressive renal failure in patients with persistent proteinuria in excess of 1g/day

The recommended initial dose is 1.25 mg ramipril once daily. This should be doubled at intervals of 2 - 3 weeks, depending on how the drug is tolerated. There are no efficacy data regarding doses above 5 mg/day in patients with nephropathy.

In hypertensive patients, a target diastolic blood pressure of < 90 mm Hg should be pursued.

In patients pre-treated with a diuretic, consideration must be given to discontinuing the diuretic for at least 2-3 days or longer (depending on duration of action) or at least consideration should be given to reducing the dose, before initiating ramipril.

Dosage in patients at increased cardiovascular risk

The recommended initial dose is 2.5 mg ramipril once daily. Depending on the tolerability, the dose should be doubled after one week of treatment and after three weeks should be increased to 10 mg.

The usual maintenance dose is ramipril 10 mg daily.

Dosage in patients with impaired renal function

Also see dosage in the section above ("Progressive renal failure in patients with persistent proteinuria in excess of 1g/day"). In hypertensive patients with creatinine clearance levels of 50 mL/min and above (serum creatinine < 1.5 mg/dL) a dosage adjustment is not required.

For patients with creatinine clearance levels 20-50 mL/min (serum creatinine 1.5 - 3 mg/dL), the recommended initial dose is 1.25 mg ramipril once daily. This should be doubled at intervals of 2 - 3 weeks, depending on how the drug is tolerated.

Particular care should be exercised in patients with impaired renal function who are to be treated for heart failure post MI as such patients may be susceptible to hypotension. Patients with impaired renal function treated for heart failure post MI have not been studied systematically.

Dosage in patients with impaired liver function

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

Dosage in the elderly

The recommended starting dose is 1.25 mg once daily, which can then be increased according to the individual patient's BP response.

OVERDOSAGE

In cases of overdose, the following may occur: severe hypotension, shock, bradycardia, electrolyte disturbances, renal failure.

The treatment given depends on how and when the drug was taken and on the type and severity of symptoms. Steps must be taken to eliminate ramipril which has not yet been absorbed (e.g. administration of adsorbants during the first 30 minutes if possible). Vital and organ functions must be monitored under intensive care conditions and safeguarded if necessary. In case of hypotension, administration of α 1-adrenergic agonists should be considered in addition to volume and salt substitution.

No experience is available concerning the efficacy of forced diuresis, altering urine pH, haemofiltration or dialysis in speeding up the elimination of ramipril or ramiprilat. If dialysis or haemofiltration is considered, consideration must be given to the fact that ramipril is contraindicated with certain high flux filtration membranes and with dextran sulfate LDL apheresis (see **CONTRAINDICATIONS**).

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

APO-Ramipril is intended for oral administration. Each capsule contains 1.25 mg, 2.5 mg, 5 mg or 10 mg ramipril as the active ingredient.

Each capsule fill also contains the following inactive ingredients: lactose and magnesium stearate. The capsule shell contains the following inactive ingredients: gelatin (all strengths), titanium dioxide (all strengths), yellow iron oxide (1.25 mg & 2.5 mg capsules), erythrosine (2.5 mg, 5 mg & 10 mg capsules), indigo carmine (5 mg & 10 mg capsules), black iron oxide (10 mg capsules) and black proprietary printing ink (all strengths).

The 1.25 mg capsules have a yellow cap and white body; they are imprinted with "APO 1.25" in black ink. They are packaged in blisters and supplied in cartons containing 30 capsules. AUST R 179033. They are packaged in bottles of 30 capsules. AUST R 179010.

The 2.5 mg capsules have an orange cap and white body; they are imprinted with "APO 2.5" in black ink. They are packaged in blisters and supplied in cartons containing 30 capsules. AUST R 179026. They are also packaged in bottles of 30 capsules. AUST R 179015.

The 5 mg capsules have a red cap and white body; they are imprinted with "APO 5" in black ink. They are packaged in blisters and supplied in cartons containing 30 capsules. AUST R 179028. They are also packaged in bottles of 30 capsules. AUST R 179012.

The 10 mg capsules have a blue cap and white body; they are imprinted with "APO 10" in black ink. They are packaged in blisters and supplied in cartons containing 7, 10, 14, 28 or 30 capsules. AUST R 179034. They are also packaged in bottles of 7, 10, 14, 28 or 30 capsules. AUST R 179011.

Not all strengths, pack types and/or pack sizes may be available.

Storage

Store below 25°C.

POISONS SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

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