AUSTRALIAN PRODUCT INFORMATION

TRYZAN® CAPS
TRYZAN® TABS

(ramipril) capsule and tablet

1 NAME OF THE MEDICINE

Ramipril

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TRYZAN CAPS capsule contains ramipril 1.25 mg, 2.5 mg, 5 mg or 10 mg as the active ingredient.

Each TRYZAN TABS tablet contains ramipril 1.25 mg, 2.5 mg, 5 mg or 10 mg as the active ingredient.

Excipient with known effect:

TRYZAN CAPS contain phenylalanine and sulfites.

TRYZAN TABS contain sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

TRYZAN CAPS

TRYZAN CAPS 1.25:	Hard gelatin capsule with a white opaque body and yellow opaque cap. The body has 'G' and the cap has 'RM 1.25' both printed in black. Capsules contain a white to off-white powder.
TRYZAN CAPS 2.5:	Hard gelatin capsule with a white opaque body and orange opaque cap. The body has 'G' and the cap has 'RM 2.5' both printed in black. Capsules contain a white to off-white powder.
TRYZAN CAPS 5:	Hard gelatin capsule with a white opaque body and Swedish orange opaque cap. The body has 'G' and the cap has 'RM 5' both printed in black. Capsules contain a white to off-white powder.
TRYZAN CAPS 10:	Hard gelatin capsule with a white opaque body and blue opaque cap. The body has 'G' and the cap has 'RM 10' both printed in black. Capsules contain a white to off-white powder.

TRYZAN TABS

TRYZAN TABS 1.25:	white to off-white, capsule-shaped, uncoated, flat tablets.
TRYZAN TABS 2.5:	yellow, capsule-shaped, uncoated, flat tablets, scored on one side and side walls, marked R2.
TRYZAN TABS 5:	pink, capsule-shaped, uncoated, flat tablets, scored on one side and side walls, marked R3.
TRYZAN TABS 10:	white to off-white, capsule-shaped, uncoated, flat tablets, scored on one side and side walls, marked R4.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Treatment of hypertension. Data is currently not available to support the use of ramipril in renovascular hypertension.
- Post myocardial infarction 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 mmHg or diastolic blood pressure > 90 mmHg (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.

4.2 DOSE AND METHOD OF ADMINISTRATION

TRYZAN CAPS capsules and TRYZAN TABS tablets 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hyperkalaemia 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 to 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 Myocardial Infarction 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 to 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.

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.

Progressive Renal Failure in Patients with Persistent Proteinuria in Excess of 1 g/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 mmHg 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.

Renal Impairment

Also see dosage in the above sub-section (*Progressive Renal Failure in Patients with Persistent Proteinuria in Excess of 1 g/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 between 20 and 50 mL/min (serum creatinine between 1.5 and 3 mg/dL), the recommended initial dose is 1.25 mg ramipril once daily. This should be doubled at intervals of 2 to 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.

Hepatic Impairment

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 Elderly

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to ramipril, or to any other ACE inhibitor, or to any of the excipients of TRYZAN CAPS and TRYZAN TABS.
- 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- Extracorporeal treatments leading to contact of blood with negatively charged surfaces must be avoided, such as dialysis or haemofiltration with high-flux dialyser membranes: Life threatening anaphylactoid hypersensitivity reactions, sometimes progressing to shock, have been described in the course of dialysis with high-flux membranes (e.g. polyacrylonitrile membranes such as AN69) during ACE inhibitor therapy. This combination must 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.
- Ramipril must not be used with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment (creatinine clearance < 60 mL/min).
- Ramipril must not be used with angiotensin II receptor antagonists (AIIRAs) in patients with diabetic nephropathy.
- Ramipril must not be used concomitantly with sacubitril/valsartan therapy (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Do not initiate ramipril until sacubitril/valsartan is eliminated from the body. In case of switch from ramipril to sacubitril/valsartan, do not start sacubitril/valsartan until ramipril is eliminated from the body.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Angioedema – head, neck or extremities

Ramipril is contraindicated in patients with a history of angioedema. Angioedema can occur immediately after starting treatment with an ACE inhibitor, however severe angioedema may also occur at any time during long-term treatment with an ACE inhibitor. 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 must 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 adrenaline (epinephrine) solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Healthcare professionals should review the response to treatment noting standard therapies for histamine-mediated angioedema may be ineffective for bradykinin-mediated angioedema. Hospitalisation of the patient is advisable with observation for at least 12 to 24 hours and discharge only upon complete resolution of the symptoms.

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.

An increased risk of angioedema is possible with concomitant use of other drugs which may cause angioedema, mTOR inhibitors, NEP inhibitors and vildagliptin (see Sections 4.3 CONTRAINDICATIONS and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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 or volume

depleted persons such as patients with renovascular hypertension, those treated vigorously with diuretics, after severe diarrhoea or patients undergoing dialysis (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 section 4.2 DOSE AND METHOD OF 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 stabilised.

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.

Patients with Hyper-stimulated Renin Angiotensin System

In the treatment of patients with a hyper-stimulated renin-angiotensin system, particular caution must be exercised. Such patients are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or for the first time at an increased dose. Initial doses or initial dose increases must be accompanied by close blood pressure monitoring until such time as no further acute reduction in blood pressure is to be anticipated. Significant activation of the renin angiotensin system is to be anticipated, for example:

- in patients with severe, and particularly with malignant hypertension. The initial phase of treatment requires special medical supervision.
- in patients with heart failure, particularly if severe or if treated with other substances having antihypertensive potential. If heart failure is severe, the initial phase of treatment requires special medical supervision.
- in patients with haemodynamically relevant left-ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve). The initial phase of treatment requires special medical supervision.
- in patients with haemodynamically relevant renal artery stenosis. The initial phase of treatment requires special medical supervision. Discontinuation of diuretic therapy may be required.
- in patients pre-treated with diuretics. Where discontinuing use or reducing the dose of the diuretic is not possible, the initial phase of treatment requires special medical supervision.
- in patients in whom fluid or salt depletion exist or may develop (as a result of insufficient fluid or salt intake, or as a result of, e.g. diarrhoea, vomiting or excessive sweating in cases where salt and fluid replacement is inadequate).

Generally, it is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed against the risk of volume overload). When these conditions have become clinically relevant, treatment with ramipril must

only be started or continued if appropriate steps are taken concurrently to prevent an excessive fall in blood pressure and deterioration of renal function.

Dual Blockade of the Renin-angiotensin-aldosterone System (RAAS)

Dual blockade of the renin-angiotensin-aldosterone system by combining ramipril with an angiotensin II receptor antagonist (AIIRA) or with aliskiren is not recommended since there are increased risks of hypotension, hyperkalaemia and changes in renal function. The use of ramipril in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (creatinine clearance <60 mL/min) (see section 4.3 CONTRAINDICATIONS).

The use of ramipril in combination with an AIIRA is contraindicated in patients with diabetic nephropathy.

Monitoring of Renal Function

It is recommended that renal function be monitored, particularly in the initial weeks of treatment with an ACE inhibitor. Particularly careful monitoring is required in patients with:

- heart failure.
- renovascular disease, including patients with haemodynamically relevant unilateral renal artery stenosis. In the latter patient group, even a small increase in serum creatinine may be indicative of unilateral loss of renal function.
- impairment of renal function.
- kidney transplant.

Electrolyte Monitoring

It is recommended that serum potassium and serum sodium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

Patients at Particular Risk from a Pronounced Reduction in Blood Pressure

In patients who would be at particular risk from an undesirably pronounced reduction in blood pressure (e.g. patients with haemodynamically relevant stenoses of the coronary arteries or of the blood vessels supplying the brain), the initial phase of treatment requires special medical supervision.

Neutropenia and Agranulocytosis

Agranulocytosis and bone marrow depression (including leukopenia/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 leukopenia 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 white blood cell counts be monitored to permit detection of a possible leukopenia, 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 ≥ 180 μmol/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 recognised as a side-effect of ACE inhibition. In various studies, the incidence of cough varies between 2 to 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 rechallenge 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, or in patients taking other medicines associated with increases in serum potassium (e.g. trimethoprim containing medicines). Diabetics, and particularly elderly diabetics, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may coexist 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 characterised 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 to 3 months of treatment.

Surgery and 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.

Use in Hepatic Impairment

As ramipril is a prodrug metabolised in the liver to its active moiety, particular caution and close monitoring should be applied to patients with impaired liver function, as the response to treatment may be either increased or reduced. 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients in whom severe liver cirrhosis with oedema and/or ascites is present, the renin angiotensin system may be significantly activated; therefore, particular caution must be exercised in treating these patients.

Use in Renal Impairment

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. Even a small increase in serum creatinine may be indicative of unilateral loss of renal function.

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 m^2 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 Section 4.2 DOSE AND METHOD OF 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.

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. Some elderly patients may be particularly responsive to ACE inhibitors. Evaluation of renal function at the beginning of treatment is recommended.

Paediatric Use

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

Effects on Laboratory Tests

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. Eosinophilia has also been seen. Raised titres of antinuclear antibodies have been observed with other ACE inhibitors.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Sacubitril/valsartan

The concomitant use of ACE inhibitors with sacubitril/valsartan therapy is contraindicated as this increases the risk of angioedema (see Other [below] and Section 4.3 CONTRAINDICATIONS).

Extracorporeal Treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces must be avoided, such as dialysis or haemofiltration with high-flux dialyser membranes and low-density lipoprotein apheresis with dextran sulfate due to the risk of severe anaphylactoid reactions.

Aliskiren-containing Medicines

The combination of ramipril with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or with moderate to severe renal impairment (creatinine clearance < 60 mL/min) and is not recommended in other patients (see Sections 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Angiotensin II Receptor Antagonists (AIIRAs)

The use of ramipril in combination with an AIIRA is contraindicated in patients with diabetic nephropathy and is not recommended in other patients.

Antihypertensive 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). Regular monitoring of serum sodium is recommended in patients undergoing concurrent diuretic therapy.

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 minimised 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Regular monitoring of serum sodium is necessary in patients undergoing concurrent diuretic therapy.

Potassium Supplements and Potassium Sparing Diuretics

Ramipril can attenuate potassium loss caused by thiazide diuretics. Potassium sparing diuretics (spironolactone, amiloride, triamterene and others), potassium supplements, potassium salts or other medicinal products (e.g. trimethoprim containing medicines) that may increase serum potassium levels can increase the risk of hyperkalaemia. This increase can sometimes be severe, and should be anticipated. 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

Excretion of lithium may be reduced by ACE inhibitors. 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, a decrease in the antihypertensive effects of ramipril in patients taking non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid, phenylbutazone, indometacin) is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening renal function and an increase in serum potassium.

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

ACE inhibitors may reduce insulin resistance. The possibility of an increased blood sugar reduction must be considered in patients treated concurrently with ramipril and antidiabetic agents such as insulin and sulfonylurea derivatives. Particularly close blood glucose monitoring is, therefore, recommended in the initial phase of co-administration.

Vildagliptin

An increased incidence of angioedema was found in patients taking ACE inhibitors and vildagliptin.

Heparin

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

Alcohol

Concomitant administration with alcohol may lead to increased vasodilation. Ramipril may potentiate the effect of alcohol.

Desensitisation Therapy

The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

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.

mTOR inhibitors (e.g. temsirolimus): an increased incidence of angioedema was observed in patients taking ACE inhibitors and mTOR inhibitors (mammalian target of rapamycin inhibitors).

Neprilysin (NEP) inhibitors: an increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitors (see Sacubitril/valsartan [above]).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: D

As with all ACE inhibitors, ramipril must not be taken during pregnancy. Pregnancy must be excluded before starting treatment with ramipril and avoided during treatment. Otherwise, there is a risk of harm to the fetus.

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 fetus. ACE inhibitors have also been associated with fetal 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% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 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 fetal renal function; oligohydramnios has been associated with fetal 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The antihypertensive effect in individual cases may be symptomatic. Some adverse effects (e.g. some symptoms of reduction in blood pressure such as light-headedness, dizziness) may impair the patient’s ability to concentrate and react. 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Ramipril has been evaluated for safety in over 4,000 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 recognised, 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 9,200 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 characterised by dizziness, weakness, nausea, headache, palpitations, tiredness, dizziness, lightheadedness, impaired reactions or tinnitus may occur particularly at initiation of treatment or after increasing the dose of ramipril (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Orthostatic blood pressure decreased (disturbed orthostatic regulation), syncope.

Gastrointestinal

Nausea, vomiting, abdominal pain and diarrhoea may occur, but these reactions are often transient. Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia.

Dermatologic

Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash, with or without fever) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Rash in particular maculo-papular.

Cough

A persistent, dry (non-productive) and/or tickling cough has been reported with ramipril as with other ACE inhibitors. Bronchitis, sinusitis, dyspnoea.

Musculoskeletal and connective tissue disorders

Muscle spasms (muscle cramps), myalgia.

Metabolism and nutrition disorders

Blood potassium increased.

General disorders and administration site conditions

Chest pain, fatigue.

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 ischemia and myocardial infarction have been observed. Exacerbation of perfusion disturbances due to vascular stenosis. Cerebral ischemia leading to transient ischemic 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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. Blood urea and blood creatinine may also be increased.

Angioedema

In uncommon cases angioedema, and rarely including fatal 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Gastrointestinal

Abdominal pain or gastric pain including gastritis (sometimes with enzyme changes suggesting pancreatitis), pancreatitis (cases of fatal outcome have been exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, anorexia, decreased appetite, constipation, dry mouth, dysphagia, gastroenteritis, increased salivation, taste or smell disturbances and ageusia (loss of taste), dysgeusia (taste disturbances).

Hepatobiliary disorder

Hepatic enzymes and/or bilirubin conjugated increased.

Dermatologic, mucosal and cutaneous

Reactions such as conjunctivitis, urticaria, pruritus, alopecia, onycholysis, precipitation and/or intensification of Raynaud's phenomenon and hyperhidrosis (sweating) have been observed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Neurologic and psychiatric

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

Blood and lymphatic system disorders

Eosinophilia.

Respiratory, thoracic and mediastinal disorders

Bronchospasm including aggravated asthma, nasal congestion.

Reproductive system and breast disorders

Impotence and reduced libido (as generally possible in unusually low blood pressure and as possible consequence of other adverse effects).

Musculoskeletal and connective tissue disorders

Arthralgia.

General disorders and administration site conditions

Pyrexia (fever).

Other

Rarely, cholestatic jaundice, liver damage (including acute liver failure), 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 or failure may occur.

Blood and lymphatic system disorders

Decreased white blood cell count (including neutropenia or agranulocytosis), red blood cell count, haemoglobin and platelet count, haemolytic anaemia.

Nervous system disorders

Balance disorder, cerebral ischemia including ischemic stroke and transient ischemic attack, psychomotor skills impaired (impaired reactions), burning sensation, parosmia (smell disturbances).

Ear and labyrinth disorders

Hearing impairment.

Gastrointestinal disorders

Glossitis, aphthous stomatitis (inflammatory reactions of the oral cavity).

Skin and subcutaneous tissue disorders

Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia.

Endocrine disorders

Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders

Blood sodium decreased.

Vascular disorders

Hypoperfusion (exacerbation of perfusion disturbances), Raynaud’s phenomenon.

General disorders and administration site conditions

Asthenia (weakness).

Immune system disorders

Anaphylactic or anaphylactoid reactions (severe anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition), antinuclear antibody increased.

Hepatobiliary disorders

Hepatocellular damage, acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).

Reproductive system and breast disorders

Gynecomastia.

Psychiatric disorders

Confusional state, disturbance in attention.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In cases of overdose, the following may occur: excessive peripheral vasodilation, 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 adsorbents 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 Section 4.3 CONTRAINDICATIONS).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Single doses of ramipril of 2.5 to 20 mg produce approximately 60 to 80% inhibition of ACE activity 4 hours after dosing, with approximately 40 to 60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 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.

Mechanism of Action

Ramipril is a prodrug 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 antiproteinuric effects.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 to 20 mg of ramipril lowered blood pressure within 1 to 2 hours, with peak reductions achieved 3 to 6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (4 to 12 weeks) controlled studies, once daily doses of 2.5 to 10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mmHg more than placebo. In comparisons of peak vs. trough effect, the trough effect represented about 50 to 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 2,000 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 Nephropathy

In **overt**, mostly non-diabetic (13% diabetic subjects included) nephropathy, the pivotal Ramipril Efficacy In Nephropathy (REIN) Study ($N = 166$) has 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 (diastolic blood pressure (DBP) > 90 mmHg) and patients with controlled mild to moderate hypertension. For those with uncontrolled hypertension, the target blood pressure was pre-defined (DBP < 90 mmHg) 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 (≥ 3 g/24 hours) but are also observed at lower baseline proteinuria (> 1 and < 3 g/24 hours). At this level of proteinuria, subgroup analysis in the REIN study indicated that only patients with worse (lower) GFR (< 45 mL/min/1.73m^2) received statistically significant benefits in end stage renal failure. The results of the REIN study are summarised in Table 1.

Table 1: Endpoints for non-diabetic nephropathy (ramipril vs placebo) in the REIN study

Patient proteinuria baseline (n)	Endpoint	Ramipril + conventional therapy	Placebo + conventional therapy	p-value
Proteinuria 1-3 g/24h (n = 186)	Secondary endpoint: ESRF (end-stage renal failure)			
	- overall	9 (9.1%)	18 (20.7%)	0.01
	- baseline GFR > 45 mL/min/1.73 m^2	2 (3.3%)	1 (2.4%)	Not reported
	- baseline GFR ≤ 45 mL/min/1.73 m^2	7 (17.9%)	17 (37%)	0.037
	Secondary endpoint: progression to proteinuria ≥ 3 g/day	15 (15.2%)	27 (31%)	0.005
	Primary endpoint: monthly reduction in GFR (mL/min/1.73m^2)	0.26	0.29	0.59 (comparison)
Proteinuria ≥ 3 g/24h (n = 166)	Primary endpoint: change in monthly GFR (mL/min/1.73m^2)			
	- overall	- 0.54	- 0.88	0.038
	- baseline proteinuria 3 to < 4.5 g/24 h	- 0.53	- 0.70	Not reported
	- baseline proteinuria 4.5 to < 7 g/24 h	- 0.47	- 0.99	Not reported
	- baseline proteinuria > 7 g/24 h	- 0.64	- 1.44	Not reported
	Secondary endpoint: ESRF or DOC (end-stage renal failure or doubling of creatinine)	18 (23.1%)	40 (45.5%)	0.02 (difference)

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.

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 Mean Arterial Pressure (MAP) ≤ 92 mmHg; n = 63) versus moderate (target MAP ≥ 100 to ≤ 107 mmHg; n = 66) blood pressure control with ramipril on renal function. While the study observed no significant differences between these moderate and intensive blood pressure 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 demonstrates the benefit of ramipril in maintaining the renal health of diabetic patients. These results are presented in Table 2.

Table 2: Primary and secondary endpoints for diabetic nephropathy in the ACE II study

Endpoint (n = 129)	Change from baseline	p-value
Primary endpoint: creatinine clearance		
24 h creatinine clearance (mL/min)	0.14	0.09
Secondary endpoint: serum creatinine (mg/dL)	0.06	0.43
Secondary endpoint: 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, 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 in Table 3.

Table 3: HOPE study results (primary composite endpoint and components, all patients and patients with diabetes) (intention to treat)

Outcome	Ramipril 10 mg n (%)	Placebo n (%)	Relative risk (95% CI)	P-value (log-rank)
All patients	**n = 4645**	**n = 4652**		
Primary composite endpoint	651 (14.0)	826 (17.8)	0.78 (0.70 - 0.86)	< 0.001
Cardiovascular 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
Diabetics	**n = 1808**	**n = 1769**		
Primary composite endpoint	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 in Table 4.

Table 4: HOPE study results (pre-specified secondary endpoints) (intention to treat)

Pre-specified endpoint	**Ramipril 10 mg n (%)**	**Placebo n (%)**	**Relative risk (95% CI)**	**P-value (log-rank)**
All patients	**n = 4645**	**n = 4652**		
Cardiovascular death	282 (6.1)	377 (8.1)	0.74 (0.64 - 0.87)	< 0.001
All-cause mortality	482 (10.4)	569 (12.2)	0.84 (0.75 - 0.95)	0.005
Cardiovascular 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)	NS
Hospitalisation for heart failure	141 (3.3)	161 (3.5)	0.87 (0.69 - 1.09)	NS

NS = 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 in **Table 5**.

Table 5: HOPE study results (pre-specified secondary endpoints, patients with diabetes) (intention to treat)

Pre-specified endpoint	**Ramipril 10 mg n (%)**	**Placebo n (%)**	**Relative risk (95% CI)**	**P-value (log-rank)**
Patients with diabetes	**n = 1808**	**n = 1769**		
Cardiovascular death	112 (6.2)	172 (9.7)	0.63 (0.49 - 0.79)	< 0.0001
All-cause mortality	196 (10.8)	248 (14.0)	0.76 (0.63 - 0.92)	0.004
Cardiovascular 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)	NS
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)	NS
Serum creatinine (μmol/L, mean ± SD)	95.8 ± 27.4	93.7 ± 25.3	No test reported	No test reported
HbA1c (% of ULN, mean ± SD)	124 ± 29.5	124 ± 29.1	No test reported	No test reported

NS = Not Significant
* Includes CABG, PTCA, carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation
† Expressed as percentage of non-albuminurics at baseline

5.2 PHARMACOKINETIC PROPERTIES

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 gastrointestinal tract, although the rate of absorption is reduced.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour area under the curve (AUC) for ramiprilat, however, is dose-proportional over the 2.5 to 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.

Distribution

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase and 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 to 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 to 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 to 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.

Metabolism

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 to 4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%. Ramipril is almost completely metabolised 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.

Excretion

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/1.73m^2 had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Impaired Liver Function

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

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 observed in rats treated for 24 months with ramipril (3.2 to 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 (oncocytoma) 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 body weight/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 month, 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 to 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TRYZAN CAPS

TRYZAN CAPS contain the following inactive ingredient: pregelatinised maize starch.

The hard gelatin capsules are registered as proprietary ingredients:

1.25 mg: Empty Hard Gelatin Capsule Size 4 White/Yellow #G41CSRR0495 (ID 107565)

2.5 mg: Empty Hard Gelatin Capsule Size 4 White/Orange #G41CSRR0494 (ID 107558)

5 mg: Empty Hard Gelatin Capsule Size 4 White/Swedish Orange #G41CSRR0493 (ID 107560)

10 mg: Empty Hard Gelatin Capsule Size 4 White/Blue #G41CSRR0496 (ID 107564)

Opacode Black S-1-8114/S-1-8115 (ID 2328) is used as the printing ink.

TRYZAN TABS

TRYZAN TABS contain the following inactive ingredients: sodium bicarbonate, lactose monohydrate, pregelatinised maize starch, croscarmellose sodium and sodium stearylfumarate.

The colouring agents are Pigment Blend PB-22960 Yellow (ID 12073 – 2.5 mg tablets) and Pigment Blend PB-24877 Pink (ID 12074 – 5 mg tablets).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Al/Al blister pack

Pack sizes:

Capsule: 7 (starter), 10, 21, 30

Tablet: 7, 10, 21, 30

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 127085 – TRYZAN CAPS 1.25 ramipril 1.25 mg capsules blister pack

AUST R 127088 – TRYZAN CAPS 2.5 ramipril 2.5 mg capsules blister pack

AUST R 127152 – TRYZAN CAPS 5 ramipril 5 mg capsules blister pack

AUST R 127153 – TRYZAN CAPS 10 ramipril 10 mg capsules blister pack

AUST R 129873 – TRYZAN TABS 1.25 ramipril 1.25 mg tablets blister pack

AUST R 129916 – TRYZAN TABS 2.5 ramipril 2.5 mg tablets blister pack

AUST R 129918 – TRYZAN TABS 5 ramipril 5 mg tablets blister pack

AUST R 129921 – TRYZAN TABS 10 ramipril 10 mg tablets blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

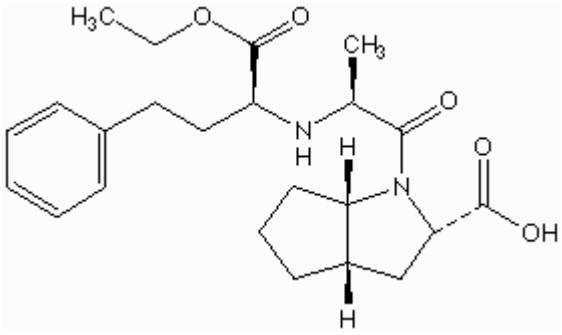
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative.

It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105°C and 112°C.

Chemical Structure



Chemical name: (2S,3aS,6aS)-1[(S)-N-[(S)-l-Carboxy-3-phenylpropyl] -alanyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid, 1-ethyl ester

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

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

Molecular weight: 416.5

CAS Number

87333-19-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

TRYZAN CAPS: 28/06/2007

TRYZAN TABS: 07/08/2007

10 DATE OF REVISION

23/06/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor Editorial Changes
4.4	Additional warning statements pertaining to angioedema of the head, neck and extremities.

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TRYZAN CAPS&TABS_pi\Jun26/00