AUSTRALIAN PRODUCT INFORMATION – RAMIPRIL VIATRIS (RAMIPRIL) TABLETS

1 NAME OF THE MEDICINE

Ramipril.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.25 mg, 2.5 mg, 5 mg and 10 mg of ramipril as the active ingredient.

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

3 PHARMACEUTICAL FORM

RAMIPRIL VIATRIS 1.25 mg tablets are white to off-white, oval-shaped tablet marked “RP 1” on one side.

RAMIPRIL VIATRIS 2.5 mg tablets are white to off-white, oval-shaped tablet marked “RP 2” on one side and scoreline on other side.

RAMIPRIL VIATRIS 5 mg tablets are white to off-white, oval-shaped tablet marked “RP 5” on one side and scoreline on other side.

RAMIPRIL VIATRIS 10 mg tablets are white to off-white, oval-shaped tablet marked “RP 10” on one side and scoreline on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension. Data are 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.

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.

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 or HDL cholesterol <0.9 mmol/L; current smoker; known microalbuminuria; any evidence of previous vascular disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

RAMIPRIL VIATRIS tablets should be swallowed with a generous amount of fluid, with or without food.

Hypertension

The recommended initial dosage for patients not receiving a diuretic is RAMIPRIL VIATRIS 2.5 mg once a day. Depending upon the patient's response, the dosage may then be increased at intervals of two to three weeks, first to 5 mg and then to a maximum of 10 mg once daily. If blood pressure is not controlled with RAMIPRIL VIATRIS alone, a diuretic can be added (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, 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 VIATRIS. If possible, therefore, treatment with the diuretic should be discontinued two to three days before starting treatment with RAMIPRIL VIATRIS. If this is not possible, initial treatment with RAMIPRIL VIATRIS 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 in whom fluid or salt depletion has not been completely corrected or in patients for whom a hypotensive reaction would constitute a particular risk (e.g. with relevant stenosis of coronary vessels or of those supplying the brain).

Post-myocardial infarction heart failure

The recommended initial dose is RAMIPRIL VIATRIS 5 mg 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 one to three days. The maximum permitted daily dose is ramipril 10 mg to be given in divided doses. Treatment should be started in hospital when the patient is haemodynamically stable, preferably between two and ten 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 1 g/day

The recommended initial dose is RAMIPRIL VIATRIS 1.25 mg once daily. This should be doubled at intervals of two to three 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 two to three days or longer (depending on the duration of action) or at least consideration should be given to reducing the dose before initiating RAMIPRIL VIATRIS.

Patients at increased cardiovascular risk

The recommended initial dose is RAMIPRIL VIATRIS 2.5 mg 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 VIATRIS 10 mg daily.

Impaired renal function

In hypertensive patients with creatinine clearance levels of 50 mL/minute and above (serum creatinine <1.5 mg/dL), a dosage adjustment is not required. Also, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, **Progressive renal failure** above.

For patients with creatinine clearance levels between 20 and 50 mL/minute (serum creatinine between 1.5 and 3 mg/dL), the recommended initial dose is RAMIPRIL VIATRIS 1.25 mg once daily. This should be doubled at intervals of two to three 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-myocardial infarction, as such patients may be susceptible to hypotension. Patients with impaired renal function treated for heart failure post-myocardial infarction have not been studied systematically.

Impaired hepatic function

In patients with impaired hepatic 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.

Use in the elderly

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

4.3 CONTRAINDICATIONS

Hypersensitivity to ramipril, or to any other ACE inhibitor, 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 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 aphaeresis with dextran sulphate 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 <60mL/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 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 adrenaline solution 1:1,000 (0.3 to 0.5 mL), should be promptly administered (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 the use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals.

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 (see Section 4.3 CONTRAINDICATIONS and Section 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/volume depleted persons, e.g. patients with renovascular hypertension, those treated vigorously with diuretics, after severe diarrhoea or patients undergoing dialysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Section 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 azotaemia, 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, after the first dose of an additional diuretic and after 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, 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 (eg 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 of 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 eg, diarrhea, vomiting of excessive sweating in cases where salt and fluid replacement is inadequate).

Generally, it is recommended that dehydration, hypovolemia 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, hypokalemia 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 AIIRA is contraindicated in patients with diabetes 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 (eg patients with haemodynamically relevant stenosis of the coronary arteries or of the blood vessels supplying the brain), the initial phase of treatment requires special medical supervision.

Neutropenia/agranulocytosis.

Agranulocytosis and bone marrow depression (including leucopenia or 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 white blood cell counts be monitored 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 greater than or equal to 180 micromol/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% and 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 two-thirds 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 it is 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 antihypertensive regimen may be required in severe cases. NSAIDs (e.g. sulindac) have been reported to be effective in relieving coughing induced by ACE inhibitors. In patients with mild hypertension or patients likely to be treated with other antihypertensive agents, it is unlikely that risks of prescribing an NSAID 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) is 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. Diabetic patients, and particularly elderly diabetic patients, 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 have 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 are 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 one to three 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.

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. 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 three 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 inhibition of 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 ACE inhibitors, including ramipril, may be associated with oliguria and/or progressive azotaemia 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 inhibitor 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 are 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/minute/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 deterioration in renal function has occurred after treatment with one ACE inhibitor, 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 years 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. Since ramipril leads to a decrease in aldosterone secretion, elevation of serum potassium may occur. Therefore, potassium-sparing diuretics or potassium supplements should 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Neutropenia/agranulocytosis). 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 Section 4.3 CONTRAINDICATIONS).

Extracorporeal treatments.

Extracorporeal treatments leading to contact of blood with negative charged surfaces must be avoided, such as dialysis or haemofiltration with high-flux dialyser membranes.

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 Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Angiotensin II receptor antagonists (AIIRS).

The use of ramipril in combination with an AIIR 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. Close monitoring of blood pressure is particularly 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) or 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.

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.

Non-steroidal anti-inflammatory drugs.

As with other ACE inhibitors, a decrease in the antihypertensive effects of ramipril in patients taking NSAIDs (e.g. aspirin, phenylbutazone, indomethacin) or COX-2 inhibitors (e.g. celecoxib, meloxicam) 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.

The use of an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug [non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitor] and a thiazide diuretic at the same time increases the risk of renal impairment.

This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category D

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

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced with 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. However, data 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 1st 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 with 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 ramipril 10 mg as a single dose 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 breastfeeding mothers. If treatment with ramipril is necessary during lactation, the patient should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The antihypertensive effect in individual cases may be symptomatic. Some adverse effects (eg 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 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 information available from the HOPE study in 9,200 patients does not reveal any increased risk of treatment with ramipril 10 mg 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 reactions

Cardiovascular. Symptomatic hypotension characterised by dizziness, weakness, nausea, headache, palpitations, tiredness, light-headedness, 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.

Dermatological. Apparent hypersensitivity reactions (manifested by dermatitis, pruritus or rash, with or without fever) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Musculoskeletal and connective tissue disorder. Muscle spasms (muscle cramps), myalgia.

Metabolism and nutrition disorders. Blood potassium increased.

General disorders and administration site conditions. Chest pain, fatigue.

Less common reactions

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 blood urea nitrogen 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.

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

Hepatobilliary disorder. Hepatic enzymes and/or bilirubin conjugated increased.

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

Neurological 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 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 Reactions

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 while 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 ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired (impaired reactions), burning sensation, parosmia (smell disturbances).

Ear and labyrinth disorders. Hearing impairment.

Gastrointestinal disorders. Glossitis, aphtous 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 examthema 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 venoma is increased under ACE inhibition), antinuclear antibody increased.

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

Reproductive system and breast disorders. Gynaecomastia.

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

Symptoms

In cases of overdose, the following may occur: excessive peripheral vasodilation, severe hypotension, shock, bradycardia, electrolyte disturbances, and renal failure. Immediately telephone your doctor, or the Poisons Information Centre (telephone 13 11 26), or go to Accident and Emergency at the nearest hospital.

Treatment

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 sulphate LDL aphaeresis (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 2.5 to 20 mg produce approximately 60 to 80% inhibition of ACE activity four hours after dosing with approximately 40 to 60% inhibition after 24 hours. Multiple oral doses of ramipril 2.0 mg or more cause plasma ACE activity to fall by more than 90% four 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 of 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, it 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 anti-proteinuria 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 ramipril 5 to 20 mg lowered blood pressure within one to two hours, with peak reductions achieved three to six hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (four to twelve 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 versus 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 two 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 study). 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 or 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 > 90 mmHg) and patients with controlled mild to moderate hypertension. For those with uncontrolled hypertension, the target blood pressure was pre-defined (diastolic blood pressure < 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 (greater than or equal to 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/minute/1.73 m^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 versus placebo) in the REIN study

Patient proteinuria baseline (n)	Endpoint	Ramipril + conventional therapy	Placebo + conventional therapy	P value
Proteinuria 1-3 g/24 hr (n = 186)	Secondary endpoint: end stage renal failure			
	overall	9 (9.1%)	18 (20.7%)	0.01
	baseline GFR > 45 mL/min/1.73m^2	2 (3.3%)	1 (2.4%)	Not reported
	baseline GFR ≤ 45 mL/min/1.73m^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	0.26 mL/min/1.73m^2	0.29 mL/min/1.73m^2	0.59 (comparison)
Proteinuria >3 g/24 hr (n = 166)	Primary endpoint: change in monthly GFR			
	overall	-0.54 mL/min/1.73m^2	-0.88 mL/min/1.73m^2	0.038
	baseline proteinuria 3 to < 4.5 g/24 hr	-0.53 mL/min/1.73m^2	-0.70 mL/min/1.73m^2	Not reported
	baseline proteinuria 4.5 to < 7 g/24 hr	-0.47 mL/min/1.73m^2	-0.99 mL/min/1.73m^2	Not reported
	baseline proteinuria > 7 g/24 hr	-0.64 mL/min/1.73m^2	-1.44 mL/min/1.73m^2	Not reported
	Secondary endpoint: 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 angiotensin-converting enzyme II (ACE 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 hr 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 or stroke within four 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
Myocardial infarction	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
Cardiovascular death	112 (6.2)	172 (9.7)	0.63 (0.49-0.79)	< 0.0001
Myocardial infarction	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 (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	743 (16.0)	854 (18.4)	0.85 (0.77-0.94)	0.0014
revascularisation*	580 (12.5)	688 (14.8)	0.83 (0.74-0.92)	0.0008
PTCA/CABG	191 (4.1)	213 (4.6)	0.89 (0.73-1.08)	NS
Non-coronary	141 (3.3)	161 (3.5)	0.87 (0.69-1.09)	NS
revascularisation				
Hospitalisation for heart				
failure				

* includes CABG, PTCA, carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation
NS = not significant

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)
Diabetic patients	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	
HbA1c (% of ULN, mean±SD)	124 ± 29.5	124 ± 29.1	No test reported	

* includes CABG, PTCA, carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation
NS = not significant
# expressed as percentage of non-albuminurics at baseline

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50 to 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 oral ramipril 5 mg 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, 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 two to four 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 to 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 two to four 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 six 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/minute/1.73 m2 had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations (see Section 4.2 DOSE AD 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 threefold. 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 1,000 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 humans is therefore unclear.

Fibromuscular pad formation.

In several repeated dose studies in rats, especially male animals treated with ramipril (3.2 to 500 mg/kg bodyweight/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 also partly increased formation of smooth muscle (lamina muscularis mucosae) due to a predominantly round cell inflammatory reaction. In all studies (1 to 24 month, carcinogenicity) the changes were always of the same type and no tendency of proliferation was 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

RAMIPRIL VIATRIS tablets contain sodium bicarbonate, calcium sulfate dihydrate, pregelatinised maize starch and sodium stearyl fumarate.

The tablets are gluten free.

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. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

1.25 mg tablets

Blister pack (Al/Al foil) of 30 tablets (AUST R 385153)

2.5 mg tablets

Blister pack (Al/Al) of 30 tablets (AUST R 385154)

5 mg tablets

Blister pack (Al/Al foil) of 30 tablets (AUST R 385155)

10 mg tablets

Blister pack (Al/Al foil) of 30 tablets (AUST R 385152)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

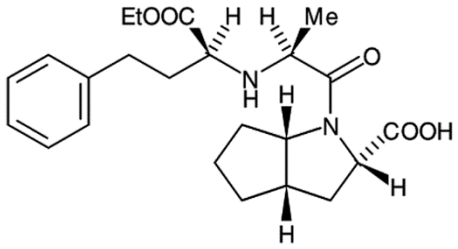
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy. [optional – use one of these statements only]

6.7 PHYSICOCHEMICAL PROPERTIES

Ramipril is a white to almost white, crystalline powder soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105^0C and 112^0C.

Chemical structure

The chemical name for ramipril is (2S,3aS,6aS)-1-[(S)-N-[(S)-1-carboxy)-3-phenylpropyl]alanyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid, 1-ethyl ester. Its structural formula is:



Its empiric formula is$C_{23}H_{32}N_2O_5$, and its molecular weight is 416.5.

Ramipril is a 2-aza-bicyclo[3.3.0]-octane-3-carboxylic acid derivative. It has five chiral centres with an S-configuration in all five asymmetric carbon atoms.

CAS number

87333-19-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine (Schedule 4)

8 SPONSOR

Helix Pharmaceuticals Pty Ltd
C/E-EGA Corporate Advisers Pty Ltd
Level 12, 468 St Kilda Rd
Melbourne VIC 3004

Contact: info@helixpharmaceuticals.com.au

9 DATE OF FIRST APPROVAL

16 August 2022

10 DATE OF REVISION

13 January 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Change in tradename
8	Change in sponsor's details