AUSTRALIAN PRODUCT INFORMATION – TRIASYN® (RAMIPRIL/ FELODIPINE)

1 NAME OF THE MEDICINE

Triasyn 2.5/2.5 (ramipril/felodipine) 2.5 mg/2.5 mg modified release tablets

Triasyn 5.0/5.0 (ramipril/felodipine) 5.0 mg/5.0 mg modified release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Triasyn 2.5/2.5 contains 2.5 mg of ramipril and 2.5 mg of felodipine.

Triasyn 5.0/5.0 contains 5.0 mg of ramipril and 5.0 mg of felodipine.

Excipient of known effect: lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Modified release tablet.

Triasyn tablets are circular, biconvex, film-coated, two-layered tablets, with felodipine in an extended-release gel matrix formulation in one layer and rapidly dissolving ramipril in the other layer.

Triasyn 2.5/2.5: Apricot, circular, biconvex, film-coated tablets 9 mm diameter, engraved H/OD on one side and 2.5 on the other.

Triasyn 5.0/5.0: Reddish-brown, circular, biconvex, film-coated tablets 9 mm diameter, engraved H/OE on one side and 5 on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of mild to moderate hypertension. This combination should not be used to commence therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults, including the elderly:

One tablet per day of Triasyn 2.5/2.5 mg or Triasyn 5.0/5.0 mg. Patients treated with Triasyn 2.5/2.5 mg may be titrated to Triasyn 5.0/5.0 mg after 2 to 4 weeks if necessary. There is limited experience with higher doses.

Tablets must be swallowed whole. They must not be divided, crushed or chewed. They should be swallowed with a generous amount of liquid and may be administered before, after or during meals.

Elderly (over 65 years of age):

Because liver and renal function decline with age, patients over 65 whose previous therapy did not include an ACE inhibitor should be initiated on ramipril 1.25 mg. These patients may then be switched to Triasyn 2.5/2.5 mg. For elderly patients not previously taking felodipine, an initial dose of 2.5 mg may be considered appropriate and thus Triasyn 2.5/2.5 mg is the starting dose (see Section 4.5 Interactions with other medicines and other forms of interactions).

Dosage recommendations for special patient groups if the existing treatment does not include an ACE inhibitor:

Patients on diuretics

Consideration should be given to temporarily discontinuing the diuretic or at least reducing the dose 2 to 3 days before initiation of treatment with Triasyn 2.5/2.5 mg. If this is not possible, start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Triasyn 2.5/2.5 mg.

Patients with incompletely corrected fluid or salt depletion

Start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Triasyn 2.5/2.5 mg.

Patients with severe hypertension or those in whom a hypotensive reaction would constitute a particular risk

Start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Triasyn 2.5/2.5 mg.

Patients with impaired renal function (20 to 50 mL/min)

Start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Triasyn 2.5/2.5 mg daily. A maximum dose of 5 mg ramipril daily must not be exceeded.

Patients with impaired hepatic function

Treatment with ramipril should not exceed 2.5 mg daily and therefore Triasyn 2.5/2.5 is the maximum dose in this patient group. Triasyn 5.0/5.0 should not be used (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.3 CONTRAINDICATIONS

- Triasyn contraindications are in line with those expected of any ACE inhibitor-calcium channel blocker combination. These include pregnancy or lactation and hypersensitivity to felodipine, ramipril or any of the tablet excipients or any ACE inhibitor.
- As with all ACE inhibitors, Triasyn is contraindicated in renal failure or haemodynamically relevant bilateral or, in the single kidney, unilateral renal artery stenosis; in patients with a history of hereditary and/ or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor; haemodynamically relevant left ventricular inflow or outflow impediment eg. stenosis of the aortic or mitral valve; hypotensive or haemodynamically unstable patients.
- Triasyn is contraindicated in patients undergoing extracorporeal treatment leading to contact of blood with negatively charged surfaces as this may lead to severe anaphylactoid reactions. For example, dialysis with certain high-flux membranes (eg. polyacrylonitrile) or low density lipoprotein apheresis with dextrose sulfate.
- Triasyn is also contraindicated in unstable haemodynamic conditions: cardiovascular shock, untreated heart failure, acute myocardial infarction, unstable angina pectoris, stroke.
- Triasyn must not be used with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment (creatinine clearance <60 mL/min).
- Triasyn is contraindicated in patients with haemodynamically significant cardiac valvular obstruction or with dynamic cardiac outflow obstruction.
- Triasyn must not be used with angiotensin II receptor antagonists (AIIRAs) in patients with diabetic nephropathy.
- Triasyn 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 Triasyn until sacubitril/valsartan is eliminated from the body. In case of switch from Triasyn to sacubitril/valsartan, do not start sacubitril/valsartan until Triasyn is eliminated from the body.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with a Significantly Activated Renin-Angiotensin System

These 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, a fixed dose combination product containing an ACE inhibitor or a concomitant diuretic is given for the first time or for the first time at an increased dose. They therefore need close blood pressure monitoring until no further acute reduction in blood pressure is expected. Significant

activation of the renin angiotensin system is to be expected in patients with severe hypertension, patients with concomitant moderate heart failure, patients with haemodynamically relevant left-ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve) in which the initial phase of treatment requires special medical supervision, patients with haemodynamically relevant renal artery stenosis, patients on concomitant diuretic therapy or patients in whom fluid and salt depletion is present, including those who have suffered severe diarrhoea and patients undergoing dialysis.

It is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment with an ACE inhibitor.

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

Patients at Particular Risk from Pronounced Reduction in Blood Pressure

Patients with haemodynamically relevant stenosis of the coronary arteries or of the cerebral blood vessels will require careful monitoring in, preferably, a hospital or a similar setting during commencement of antihypertensive therapy, as an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

Rarely, too great a reduction in blood pressure with an initial reflexogenic increase in heart rate may lead to increased frequency, duration and/or severity of angina, particularly in patients with severe coronary artery disease. Therefore, the possibility of precipitation of myocardial ischaemia exists. This may occur in the initial stages of felodipine treatment or following a dosage increase.

Angioneurotic Oedema

Due to its ACE inhibitor component, Triasyn 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, eg. 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)) and accompanied with monitoring of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

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 (eg. cricothyrotomy or tracheostomy). Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

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).

ACE inhibitors cause an increased likelihood and greater severity of anaphylactic and anaphylactoid reactions to other substances or to, for example, insect bites.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Dual blockade of the renin-angiotensin-aldosterone system by combining Triasyn 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 Triasyn 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 Triasyn in combination with an AIIRA is contraindicated in patients with diabetic nephropathy.

Combination with Beta-Blockers in Patients with Congestive Heart Failure

Beta-blockers are contraindicated in patients with uncompensated heart failure. While felodipine may appear safe in these patients, the combination of Triasyn and beta-blockers is not recommended.

Potassium Monitoring

Because the ACE inhibitors decrease the formation of angiotensin II, which results in decreased production of aldosterone, increases 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 (eg 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. It is recommended that serum potassium be monitored regularly and more frequent monitoring of serum potassium is necessary in patients with impaired renal function.

Sodium Monitoring

Treatment with Triasyn requires regular monitoring of serum sodium.

Cough

Clinical trials have shown that patients treated with Triasyn experience significantly less cough than patients treated with ramipril monotherapy.

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 it is most likely secondary to the effects of converting-enzyme inhibition 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 (eg. 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.

Dermatological Reactions

Dermatological reactions, characterised by maculo-papular pruritic rashes and sometimes photosensitivity, have been reported. 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 1 - 3 months of treatment.

Gingival Enlargement

Mild gingival enlargement has been reported in patients taking felodipine with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful dental hygiene.

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.

Peripheral Oedema

Mild to moderate peripheral oedema resulting from precapillary vasodilation may occur in about 20% of patients treated with felodipine. This oedema appears to be dose related. The effect of a diuretic on this oedema has not been investigated.

Haematological Monitoring

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

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

Use in hepatic impairment

There is no experience with the use of Triasyn in patients with severe impairment of liver function. In 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 with ramipril. 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 hepatic esterases, 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. Therefore, Triasyn 5.0/5.0 should not be used in this patient group (see Section 4.2 Dose and method of administration).

Use in renal impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. It is recommended that renal function is monitored, particularly in the initial weeks of treatment with an ACE inhibitor. Careful monitoring is required in patients with concomitant heart failure, renovascular disease, impairment of renal function or patients who have undergone a kidney transplant.

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 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. In patients with haemodynamically relevant unilateral renal artery stenosis even a small increase in serum creatinine may be indicative of unilateral loss of renal function.

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

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine which is usually minor and transient, especially when ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ramipril and/or discontinuation of the diuretic may be required. 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 endstage renal failure, since only negligible amounts are dialysable. Therefore Triasyn should not be prescribed for such patients.

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. Therefore,

Triasyn should not be used to initiate ACE inhibitor therapy in the elderly (see Section 4.2 Dose and method of administration).

Felodipine plasma levels are higher on average in elderly patients than in young and middle-aged patients due to reduced first-pass effect, reduced clearance capacity or both. An initial dose of 2.5 mg should be considered.

Paediatric use

Clinical data on the use of Triasyn in children are not currently available, therefore use in this age group is not recommended.

Effects on laboratory tests

Ramipril

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.

Felodipine

Slight increases in thrombocyte count and rare, usually transient, elevations of enzymes such as alkaline phosphatase, ASAT and ALAT have occasionally been noted during felodipine treatment. These laboratory abnormalities have not been associated with clinical symptoms and their relationship to felodipine is uncertain.

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).

Cytochrome P450 inducers and inhibitors

Concomitant administration of substances which interfere with the cytochrome P450 system may affect plasma concentrations of felodipine. Enzyme inducers (eg. phenytoin, carbamazepine, rifampicin, barbiturates and hypericum perforatum (Saint John’s wort)) cause a decrease in plasma levels of felodipine. Enzyme inhibitors (eg. cimetidine, erythromycin, itraconazole, ketaconazole and certain flavonoids found e.g. in grapefruit juice) have been shown to cause an increase in felodipine plasma levels.

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.

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.

Grapefruit juice

An increase in the bioavailability of dihydropyridines has been shown when they have been taken with grapefruit juice. The interaction is thought to be due to a bioflavonoid present in grapefruit juice which is not found in other citrus fruits. The interaction is more pronounced with immediate release formulations.

Potassium supplements and potassium-sparing diuretics

Since ACE inhibitors may cause a rise in serum potassium, concurrent use of Triasyn and potassium-sparing diuretics (eg. spironolactone, amiloride, triamterene), potassium supplements, potassium salts or other medicinal products (eg 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 closely monitored.

High-flux dialyser membranes

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux (eg. polyacrylonitrile) membranes and low density lipoprotein apheresis with dextrose sulfate have been reported to increase the risk of severe anaphylactoid reactions. This combination should therefore be avoided.

Aliskiren-containing medicines

The combination of Triasyn 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 (AIIRAs)

The use of Triasyn 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 Triasyn is administered concurrently with other antihypertensives and other substances with antihypertensive potential (eg. nitrates, tricyclic antidepressants, narcotics, anaesthetics).

Vasopressor sympathomimetics

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

Lithium

Excretion of lithium may be reduced by ACE inhibitors. Increased serum lithium levels and symptoms of lithium toxicity (eg. cardiotoxic and neurotoxic effects) have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

NSAIDs

As with other ACE inhibitors, the antihypertensive effects of ramipril may be decreased in patients taking NSAIDs. Furthermore, concomitant administration of ACE inhibitors and NSAIDs may exacerbate declining renal function and lead to 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.

Antidiabetic agents

The possibility of a greater reduction in blood sugar must be considered in patients treated concurrently with ramipril and antidiabetic agents such as insulin metformin and sulphonylurea derivatives. This effect is most pronounced at the beginning of treatment.

Vildagliptin

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

Food and Alcohol

The absorption of Triasyn is not influenced by food intake, however, concomitant administration with alcohol may lead to increased vasodilatation. A high intake of dietary salt may decrease the antihypertensive effects of Triasyn.

Desensitisation therapy

ACE inhibitors may lead to an increased likelihood and greater severity of anaphylactoid and anaphylactic reactions. This must be considered when desensitisation is performed.

Tacrolimus

Felodipine may increase the concentration of tacrolimus. When used together, the tacrolimus serum concentration should be followed and the tacrolimus dose may need to be adjusted.

Heparin

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

Other

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

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Category D.

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

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment. Otherwise there is a risk of harm to the foetus.

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

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

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during the first trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% 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 foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial malformations, hypoplastic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. Infants exposed to ACE inhibitors *in utero* must be closely monitored for hypotension, oliguria and hyperkalaemia. If oliguria is present or developing, support of blood pressure and renal perfusion may be necessary.

Following administration of felodipine to pregnant dams during the period of organogenesis, morphological abnormalities of the phalanges were observed in the rabbit foetus.

In rats, oral doses of felodipine 3.8 mg/kg or higher, caused prolongation of labour.

Use in lactation

Both felodipine and ramipril are excreted in breast milk. It is therefore recommended that Triasyn is not given to nursing mothers. An alternative treatment with better established safety profile during breastfeeding is preferable, especially while nursing a newborn or preterm infant (see Section 4.3 Contraindications).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The antihypertensive effect in individual cases may be symptomatic. Some undesirable effects (e.g. some symptoms of reduction in blood pressure such as dizziness) may be accompanied by an impairment of the 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 with alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Generally, Triasyn is well tolerated. Most adverse reactions reported in clinical trials were mild and were typical of reactions that can be expected from experience with the individual components, felodipine and ramipril. Experience in clinical trials indicates that Triasyn may result in a lower incidence of flushing than felodipine alone as well as a lower incidence of cough than ramipril alone.

The following list of adverse reactions and their frequencies are based upon experience with the monotherapies in their usual dosage range.

Table 1 - Very Common (>10%)

Cardiovascular:	Peripheral oedema

Table 2 - Common (> 1%)

Cardiovascular:	Flushing (feeling of warmth), palpitations, hypotension, orthostatic blood pressure decreased (disturbed orthostatic regulation), syncope
Respiratory:	Non-productive tickling and/or dry cough with ACE inhibitors, bronchitis, sinusitis, dyspnoea
CNS:	Headache, tinnitus and other hearing disruptions, dizziness (light-headedness) and balance disorders (vertigo)
Gastrointestinal:	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, nausea, vomiting, abdominal pain (including gastritis) and diarrhoea may occur but are often transient
Dermatological:	Apparent hypersensitivity reactions (dermatitis, pruritus, rash with or without fever)
Musculoskeletal and connective tissue disorder:	Muscle spasms (muscle cramps), myalgia
Metabolism and nutrition disorders:	Blood potassium increased
General:	Chest pain, fatigue, weakness, decreased physical fitness, gum hyperplasia (typically attributable to felodipine, can be avoided by careful dental hygiene), rash in particular maculo-papular.

Table 3 - Uncommon (≤ 1%)

Cardiovascular:	Mild symptoms and reactions attributable to blood pressure reduction such as balance disorders, tachycardia. Myocardial ischaemia including angina pectoris, myocardial infarction, arrhythmia, peripheral oedema. Exacerbations of perfusion disturbances due to vascular stenosis (See Section 4.4 Special warnings and precautions for use). Cerebral ischemia leading to transient ischemic attacks or stroke.
Blood and lymphatic system disorders:	Eosinophilia
Respiratory, thoracic and mediastinal disorders:	Bronchospasm including asthma aggravated, nasal congestion
Gastrointestinal disorders:	Fatal pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, constipation, dry mouth
Metabolism and nutrition disorders:	Anorexia, decreased appetite
Kidney/Electrolyte:	With ACE inhibitors, renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, increases in blood urea nitrogen (BUN), serum urea and creatinine (especially when administered with a diuretic) (see Section 4.4 Special warnings and precautions for use)
Skin and subcutaneous tissue disorders:	Angioedema with fatal outcome; hyperhidrosis (sweating)
Musculoskeletal and connective tissue disorders:	Arthralgia
Reproductive system and breast Disorders:	Impotence, libido decreased
Psychiatric disorders:	Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence (drowsiness)
General disorders and administration site conditions:	Pyrexia (fever)
Anaphylactic:	Mild angioneurotic oedema due to ACE inhibitor-induced inhibition of kinin breakdown. Severe angioneurotic oedema is rare (see below).
CNS:	Paraesthesia, amnesia, convulsions, neuralgia, somnolence
Hepatic:	Increases in hepatic enzymes and/or serum bilirubin as well as cholestatic jaundice.
Other:	With ACE inhibitors, burning eyes, visual disturbance including blurred vision, increased salivation, taste disturbances (dysgeusia) or loss (ageusia) (see Section 4.4 Special warnings and precautions for use), conjunctivitis.

Table 4 - Rare (≤ 0.1%)

CNS:	Mild symptoms and reactions attributable to blood pressure reduction such as nervousness, depressed mood, tremor, restlessness, visual and sleep disturbances (insomnia), confusion and feelings of anxiety.
Psychiatric disorders:	Confusional state
Cardiovascular:	Syncope
Vascular disorders:	Vascular stenosis, hypoperfusion (exacerbation of perfusion disturbances), vasculitis
Kidney / Electrolyte:	With ACE inhibitors, increases in serum potassium

Anaphylactic:	Severe angioneurotic oedema due to ACE inhibitor induced inhibition of kinin breakdown. Angioneurotic oedema or other anaphylactic or anaphylactoid reactions due to felodipine, ramipril or any of the other ingredients in Triasyn. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment must be discontinued and appropriate therapy started immediately (see Section 4.4 Special warnings and precautions for use).
Gastrointestinal:	Dryness of the mouth, glossitis, digestive disturbances (dysphasia), diarrhoea Inflammatory reactions of the oral cavity and gastrointestinal tract (gastroenteritis), gastric pain. With ACE inhibitors, increased levels of pancreatic enzymes very rarely suggesting pancreatitis (see below).
Hepatobiliary disorders:	Jaundice, cholestatic, hepatocellular damage
Ear and labyrinth disorders:	Hearing impaired
Skin and subcutaneous tissue disorders:	Exfoliative dermatitis, urticaria, onycholysis
Haematological:	These reactions are more likely to occur in patients with impaired renal function, concomitant collagen disease (e.g. systemic lupus erythematosus or scleroderma) or in patients treated with drugs which alter the blood picture. Mild and, very rarely, severe reduction in the blood platelet and white cell count (including neutropaenia). Very rarely agranulocytosis, bone marrow depression or pancytopaenia. With ACE inhibitors mild and, very rarely, severe reduction in red cell count and haemoglobin content (very rarely due to haemolytic anaemia).
General disorders and administration site conditions:	Asthenia (weakness)
Reproductive system and breast disorders:	Sexual dysfunction

Table 5 - Very Rare (≤ 0.01%)

Cardiovascular :	With ACE inhibitors, intensification or precipitation of Raynaud's Phenomenon
Kidney/Electrolyte:	Increases in urinary outflow due to improved cardiac performance, decreases in serum sodium, impairment of renal function progressing to acute renal failure. ACE inhibitors may cause a deterioration of pre-existing proteinuria, though they usually improve this condition.
Skin/Mucous:	With ACE inhibitors, maculopapular rash, lichenoid, psoriasiform, exanthema membranes and enanthema, erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis, alopecia, photosensitivity. With felodipine, photosensitivity reactions, leucocytoclastic vascultis
Immune system disorders	With felodipine, hypersensitivity reactions e.g. angioedema, fever
Gastrointestinal:	With ACE inhibitors, pancreatitis and ileus With felodipine, gingival hyperplasia, gingivitis
Renal and urinary disorders	With felodipine, pollakisuria
Hepatic:	With ACE inhibitors, liver damage. Liver damage is potentially fatal. With felodipine, increased liver enzymes
Other:	With ACE inhibitors raised antinuclear antibody titres.

Other adverse effects have been reported:

Bone marrow failure, pancytopaenia, haemolytic anaemia, psychomotor skills impaired (impaired reactions), burning sensation, parosmia (smell disturbances), aphtous stomatitis (inflammatory reactions of the oral cavity), pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, Syndrome of inappropriate antidiuretic hormone secretion (SIADH), blood sodium decreased, anaphylactic or anaphylactoid reactions (severe anaphylactic and anaphylactoid reactions to insect venoma is increased under ACE inhibition), antinuclear antibody increased, acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional), gynaecomastia and disturbance in attention.

Reporting suspected adverse reactions

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

Overdosage may cause excessive peripheral vasodilatation with marked hypotension and sometimes bradycardia, shock, electrolyte disturbances and renal failure.

Management

Primary detoxification by, for example, gastric lavage, administration of adsorbents and/or sodium sulfate if possible should be initiated during the first 30 minutes.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. In cases of accompanying bradycardia, atropine 0.5 - 1.0 mg should be administered intravenously. If this is not sufficient, plasma volume should be increased by electrolyte infusion (eg. glucose, saline or dextran). Sympathomimetic drugs with predominant effect on the alpha adrenoreceptors or angiotensin II should be considered if the above-mentioned measures are insufficient.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antihypertensive drugs. ATC code: C09B B05.

Mechanism of action

The calcium antagonist felodipine and the angiotensin converting enzyme (ACE) inhibitor ramipril both reduce blood pressure by vasodilatation. However, they have complementary mechanisms of action. Calcium antagonists dilate the arterial beds while ACE inhibitors dilate both arterial and venous beds. This vasodilatation and reduction of blood pressure may lead to activation of the sympathetic nervous system. ACE inhibitors reduce this sympathetic nervous system activation and block the renin-angiotensin system. These complementary mechanisms of action underlie the additive antihypertensive response and the improved side-effect profile observed with combinations of calcium antagonists and ACE inhibitors.

The onset of the antihypertensive effect of a single dose of Triasyn is 1-2 hours. The maximum antihypertensive effect occurs within 2-4 weeks and is maintained on long-term therapy. The blood pressure reduction is even and effective throughout the 24-hour dosage interval.

Felodipine:

Felodipine is a calcium antagonist which lowers arterial blood pressure by decreasing vascular resistance. It exhibits a high degree of selectivity for smooth muscle in the arterioles and in therapeutic doses has no direct effect on cardiac contractility or conduction. Felodipine inhibits the electrical and contractile activity of vascular smooth muscles via an action at the cell membrane. Because of its lack of effect on venous smooth muscle and its adrenergic vasomotor control, felodipine does not cause orthostatic hypotension.

The renal vascular resistance is decreased by felodipine. Normal glomerular filtration rate is unchanged. In patients with impaired renal function glomerular filtration rate may be increased. Felodipine possesses a mild natriuretic/diuretic effect and therefore does not produce any general fluid retention.

Ramipril:

Ramiprilat, the active metabolite of the prodrug ramipril, is a potent and long acting ACE inhibitor. In plasma and tissue, ACE catalyses the conversion of angiotensin I to the vasoconstrictor angiotensin II and also the breakdown of the vasodilator bradykinin. The vasodilatation induced by ramiprilat causes a reduction in blood pressure pre-load and after-load.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in the secretion of aldosterone. The latter decrease may result in a small increase in serum potassium. In hypertensive patients, ramipril leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

Whilst the mechanism by which ramiprilat lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ramiprilat has an antihypertensive effect even in patients with low renin hypertension.

Clinical trials

2194 patients have participated in short-term studies and 278 patients have participated in long-term studies investigating the efficacy and safety of the combination of ramipril and

felodipine. These studies have shown that the combination significantly reduced blood pressure both at the beginning and at the end of the dosage period.

The efficacy of felodipine in combination with ramipril was studied in four pivotal clinical studies. The findings of these studies are summarised in the following tables.

Table 6 - Additive Effects of Felodipine:

Combination	Comparator	Additive antihypertensive effect*	P-value
Ramipril 5mg + felodipine 5 mg	Ramipril 5 mg	-5.8	<0.001
Ramipril 5mg + felodipine 5 mg	Ramipril 5 mg	-3.9	<0.001
Ramipril 5mg + felodipine 5 mg	Ramipril 5 mg	-3.2	0.057
Ramipril 2.5mg + felodipine 2.5 mg	Ramipril 2.5 mg	-1.6	0.07

*reduction in supine diastolic blood pressure (mmHg)

Table 7 - Additive Effects of Ramipril:

Combination	Comparator	Additive antihypertensive effect*	P-value
Ramipril 5mg + felodipine 5 mg	Felodipine 5 mg	-2.7	0.114
Ramipril 5mg + felodipine 5 mg	Felodipine 5 mg	-1.9	0.015
Ramipril 2.5mg + felodipine 2.5 mg	Felodipine 2.5 mg	-2.4	0.009

*reduction in supine diastolic blood pressure (mmHg)

In patients not responding to ramipril monotherapy, the addition of felodipine resulted in a further decrease in blood pressure. No data have been evaluated on the efficacy of the addition of ramipril to patients not responding to felodipine monotherapy.

Long-term studies using the approved dosages demonstrated that the combination maintains antihypertensive efficacy over a 12 month period.

5.2 PHARMACOKINETIC PROPERTIES

In Triasyn, the pharmacokinetics of felodipine, ramipril and ramiprilat are essentially unaltered from those of the monocomponents. Felodipine does not influence the ACE inhibition caused by ramipril. The fixed combination tablets are thus regarded as bioequivalent to the free combination.

Felodipine:

Absorption

Felodipine is completely absorbed from the gastrointestinal tract after administration, regardless of food intake. Peak plasma concentrations following administration are usually reached within 3-5 hours.

The systemic availability of felodipine is independent of dose in the therapeutic dose range. Due to pre-systemic metabolism of felodipine, the bioavailability of extended release

felodipine is approximately 20%. Extended release felodipine produces a relatively flat plasma concentration versus time curve, minimising the post-absorption peak seen with conventional tablets and maintaining therapeutic levels over the 24 hours following dosing. This permits single daily dosing of felodipine.

In some patients administered a single dose of 5 mg felodipine, there was no detectable blood level of felodipine, indicating a significant inter-individual variation in pharmacokinetic response.

Distribution

The plasma protein binding of felodipine in man is approximately 99%. It is bound predominantly to the albumin fraction. In man, felodipine has a volume of distribution at steady state of approximately 10 L/kg.

Metabolism

Felodipine is extensively metabolised by the liver. All identified metabolites are inactive.

Excretion

Approximately 70% of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0.5% of a dose is recovered unchanged in urine.

The elimination of felodipine from plasma follows a biphasic pattern, with the mean half-life of the α-phase approximately 4 hours and that of the β-phase approximately 24 hours. There is no significant accumulation during long-term treatment.

Use in the elderly

Average peak plasma concentrations of felodipine tend to be higher in elderly patients than in young healthy individuals. This can be attributed to reduced systemic clearance of felodipine and a corresponding increase in plasma half-life.

The systemic availability, time to peak plasma concentration and volume of distribution do not appear to be significantly affected by age.

Ramipril:

Absorption

Following oral administration, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced. Peak plasma concentrations of ramiprilat are reached within 2 to 4 hours and the absolute bioavailability of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg oral ramipril was compared with the same dose of IV ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose proportional. The 24-hour AUC for ramiprilat, however, is proportional to dose over the 2.5-20 mg dose range.

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 larger peripheral compartment and subsequent binding to both plasma and tissue ACE and KININASE II, has a half-life of 2-4 hours. The effective half-life, which is relevant for dosage, is 13 to 17 hours under multiple dose conditions and the terminal phase with very low ramiprilat plasma concentrations has a prolonged half life of >50 hours. This terminal phase is probably due to the slow dissociation of ramiprilat from ACE. After once daily doses, steady-state plasma concentrations are obtained by the fourth dose. There is no relevant accumulation of ramipril and ramiprilat after oral administration.

The protein binding of ramipril and ramiprilat is approximately 73% and 56%, respectively.

Metabolism

The prodrug ramipril undergoes extensive hepatic first-pass metabolism (hydrolysis) which is essential for the formation of ramiprilat, the sole active metabolite. In addition to this activation into ramiprilat, ramipril is glucuronized to form ramipril diketopiperazine (ester).

Excretion

After oral administration of ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine and about 40% in the faeces. Less than 2% of the administered dose is recovered in the urine as unchanged ramipril.

Use in hepatic impairment

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.

Use in renal impairment

Renal excretion of ramiprilat is reduced in patients with impaired renal function and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in patients with normal renal 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.

An increased incidence of benign interstitial cell testicular tumours (Leydig cell tumours) has been observed in rats but not in mice following dosing with felodipine. The relevance of this finding in man is not known, although clinical studies have demonstrated that felodipine has no influence on testosterone formation or on luteinising hormone secretion.

Fibromuscular Pad Formation

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

The excipients contained in Triasyn tablets are aluminium sodium silicate, microcrystalline cellulose, hyprolose, hypromellose, iron oxide red CI 77491, iron oxide yellow CI 77492, lactose, macrogol 6000, hard paraffin, PEG-40 hydrogenated castor oil, propyl gallate, sodium stearylfumarate, pregelatinised maize starch and titanium dioxide.

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

Triasyn is packaged in PVC/PVDC/Aluminium foil blister packs.

Pack sizes: 30 tablets.

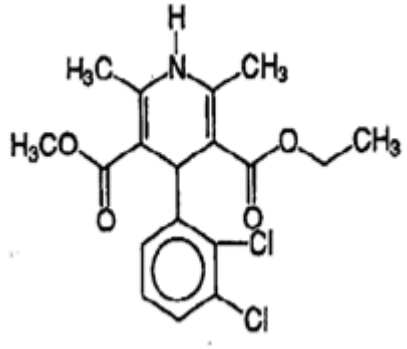
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

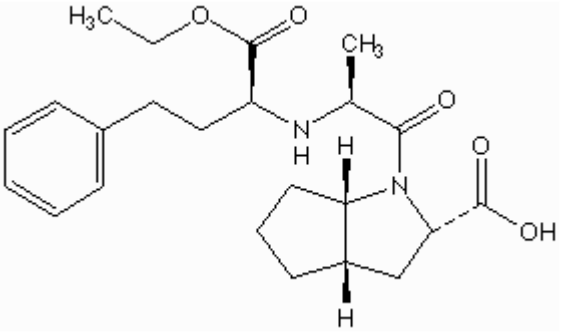
Felodipine structural formula:



Felodipine is a racemic mixture of ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro 2,6-dimethyl-3,5 pyridine dicarboxylate. It is a slightly yellowish crystalline powder with a melting point between 142 and 145°C. Felodipine is freely soluble in ethanol, acetone and

dichloromethane, but practically insoluble in water at 37°C. It is moderately light sensitive and has a molecular weight of 384.26. The empirical formula is $C_{18}H_{19}Cl_2NO_4$.

Ramipril structural formula:



Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. It is a white to almost white crystalline powder with a melting point between 105°C and 112°C. Ramipril is freely soluble in polar organic solvents and buffered aqueous solutions. It is slightly soluble in water. Ramipril has a molecular weight of 416.52 and an empirical formula of $C_{23}H_{32}N_2O_5$. Its chemical name is (2S,3aS,6aS)-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid,1-ethyl ester.

CAS number

Felodipine: CAS No. 72509 76 3

Ramipril: CAS No. 87333 19 5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Australia
Toll Free Number (medical information): 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

18 December 1998

10 DATE OF REVISION

24 November 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Deletion of 5, 7, 10, 28 pack sizes
6.7	Correction of empirical formula