AUSTRALIAN PRODUCT INFORMATION

ZEDACE®

(Captopril) tablet

1 NAME OF THE MEDICINE

Captopril

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Captopril is a highly specific competitive inhibitor of angiotensin I converting enzyme, the enzyme responsible for the conversion of angiotensin I to angiotensin II.

Each ZEDACE tablet 25 mg contains 25 mg of captopril as the active ingredient.

Each ZEDACE tablet 50 mg contains 50 mg of captopril as the active ingredient.

Excipients with known effect: sugars as lactose and traces of phenylalanine.

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

3 PHARMACEUTICAL FORM

ZEDACE tablet 25 mg: white, octagonal, biconvex tablet, approx. 6.5 mm in diameter, quadrisected on one side with one character "C", "T", "2" and "5" in each quadrant and "G" on the reverse.

ZEDACE tablet 50 mg: white oval, biconvex tablet, approx. 11.3 mm x 5.8 mm, with "CT/50" on one side and "G" on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension.

In using ZEDACE, consideration should be given to the risk of neutropenia/agranulocytosis (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

ZEDACE is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics. The hypotensive effects of captopril and thiazides are approximately additive.

Myocardial infarction

ZEDACE may be used to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction, manifested as an ejection fraction ≤ 40%, and to decrease the incidence of overt heart failure and subsequent hospitalisations for congestive heart failure in these patients. The efficacy data for the use of captopril following myocardial infarction are strongest for commencement of therapy beyond three days post infarction.

Heart Failure

Treatment of heart failure. It is recommended that ZEDACE be administered together with a diuretic in symptomatic patients.

Diabetic nephropathy

ZEDACE is also indicated in the treatment of diabetic nephropathy in patients with Type 1 insulin-dependent diabetes mellitus.

4.2 DOSE AND METHOD OF ADMINISTRATION

A first dose hypotensive effect, severe in some patients, may occur. To minimise this effect, the dosage should be individualised and titrated from a low starting dose to the maintenance dose.

ZEDACE should be taken one hour before meals.

Hypertension

Consideration of recent antihypertensive drug treatment, salt restriction, the extent of blood pressure elevation, and other clinical circumstances, should be given before initiating treatment with captopril. If possible, the patient's previous antihypertensive drug regimen should be discontinued one week before starting ZEDACE.

In most patients, a starting dose of 12.5 mg may be used. The dose may then be increased to 25 mg twice a day. If a satisfactory lowering of blood pressure has not been achieved after two to four weeks, the dose of ZEDACE may be increased to 50 mg twice a day. Concomitant sodium restriction may be beneficial when ZEDACE is used alone.

In patients in whom a satisfactory decrease in blood pressure is not achieved after a further two weeks at this dosage, it is likely that the hypertension may have a substantial volume dependent component. In these patients it may be appropriate to add a thiazide diuretic. The diuretic dose may be increased at one to two week intervals until its highest usual antihypertensive dose is reached. The usual effective dose of ZEDACE in mild to moderate hypertension does not exceed 50 mg twice a day.

In patients with severe refractory hypertension, or on high doses of diuretics, dialysis or low salt diet, a lower initial dose (6.25 to 12.5 mg) may be used, with titration to daily doses of 25 or 50 mg twice a day.

If ZEDACE is being added to the existing drug regimen of a patient who is already being treated with a diuretic, ZEDACE therapy should be initiated under close medical supervision (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERCATIONS**).

In severe hypertension where further blood pressure reduction is needed, larger or more frequent dosing may be necessary. A daily dose of ZEDACE 75 mg twice a day should not normally be exceeded.

For patients with accelerated or malignant hypertension, particularly those unresponsive to conventional therapy, it may be necessary to implement the schedule given above at intervals of 24 hours, under continuous medical supervision, until a satisfactory blood pressure response is achieved or the maximum dose of ZEDACE is reached.

Myocardial infarction

Therapy may be commenced as early as three days following a myocardial infarction. After an initial dose of 6.25 mg, ZEDACE therapy should be increased as tolerated to 25 mg three times a day during the next several days and to a final target dose of 50 mg three times a day over the next several weeks.

If symptomatic hypotension occurs, the dosage may need to be lowered. Subsequent attempts at achieving the target dose of 150 mg should be based on the patient's tolerance to ZEDACE.

ZEDACE may be used in patients already receiving other post-myocardial infarction therapies, e.g. thrombolytics, aspirin and beta-blockers.

Heart Failure

Treatment with ZEDACE must be initiated under close medical supervision. It should be added to conventional treatment with a diuretic (and digitalis where indicated).

Heart failure patients may demonstrate sensitivity to the effects of captopril in the early stages of therapy.

In patients in whom greater sensitivity may be suspected (e.g. sodium depletion and/or high doses of diuretics), the hypotensive effects of the first dose may be minimised by the use of a 2.5 mg starting dose. This product is not suitable in initiating therapy in such patients, as the smallest achievable dose with ZEDACE tablets is 6.25 mg. In other patients, an initial dose of 6.25 mg three times a day may be used, although a transient hypotensive effect may occur at this dosage.

The maintenance dose of ZEDACE is usually in the range of 25 to 75 mg twice a day. Where possible, a period of at least two weeks should be allowed before dose increase within this range. A maximum daily dose of 150 mg should normally not be exceeded.

Patients treated for severe congestive heart failure should be warned to increase their physical activity gradually.

Diabetic Nephropathy

In patients with diabetic nephropathy, the recommended dose of captopril is 75 to 100 mg daily, in divided doses. Clinical trials in normotensive type 1 diabetic patients with microalbuminuria (albumin excretion rate between 30 and 300 mg/day) showed that captopril at a dose of 50 mg twice daily attenuated the progression of the disease.

Clinical trials in normotensive and controlled hypertensive type 1 diabetic patients with overt proteinuria (total protein excretion >500 mg/day) demonstrated that captopril at a dose of 25 mg three times daily had significant beneficial effects by reducing the need for dialysis and transplantation or the occurrence of death.

The effects of captopril were independent of, and additional to, its antihypertensive activity. If further blood pressure reduction is needed, other antihypertensive agents such as diuretics, centrally acting agents, beta-adrenoceptor blockers or vasodilators may be administered concomitantly with captopril.

Impaired renal function

The excretion of captopril is decreased in the presence of impaired renal function. Accordingly, for patients with significant renal impairment, initial daily dosage of ZEDACE should be reduced, and smaller increments utilised for titration, which should be quite slow (one to two week intervals). After the desired therapeutic effect has been obtained, the total daily dose should be lowered or the dose intervals increased.

Captopril is removed by haemodialysis.

When concomitant diuretic therapy is required, a loop diuretic (e.g. furosemide (frusemide)) rather than a thiazide diuretic, is preferred in patients with impaired renal function.

4.3 CONTRAINDICATIONS

History of previous hypersensitivity to captopril or any of the excipients (see **Section 6.1 LIST OF EXCIPIENTS)**.

Pregnancy (See **Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy**).

ZEDACE is also contraindicated in patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous ACE inhibitor therapy.

Concomitant use with sacubitril/valsartan therapy. Captopril must not be initiated earlier than 36 hours after last dose of sacubitril/valsartan (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)**.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anaphylactoid and possibly related reactions

Presumably because angiotensin-converting enzyme (ACE) is essential for degradation of endogenous bradykinin, patients receiving ACE inhibitors are subject to a variety of adverse reactions producing effects ranging from relatively mild, such as cough (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**), to serious, such as the following:

Head and neck angioedema

Severe life-threatening angioedema has been reported rarely with ACE inhibitors. The overall incidence is approximately 0.1% to 0.2%. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. In the majority of reported cases, the symptoms occurred during the first week of therapy. However, the onset of angioedema may be delayed for weeks to months. Patients may have multiple episodes of angioedema with long symptom free intervals. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Angioedema may occur with or without urticaria but usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes.

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. In such cases, the product should be discontinued promptly and appropriate monitoring instituted to ensure complete resolution of symptoms. In instances where swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with antihistamines. Angioedema associated with laryngeal oedema is potentially life-threatening. When involvement of the tongue glottis, or larynx is likely to cause airway obstruction, appropriate therapy including adrenaline (epinephrine) and oxygen administration, should be carried out promptly or the patient hospitalised. Patients who respond to medical treatment should be observed carefully for any possible re-emergence of symptoms of angioedema.

There are reports where changing the patient over to another ACE inhibitor was followed by re-emergence of oedema and others where it was not. Because of the potential severity of this rare event, patients with a history of angioedema to an ACE inhibitor, should not be given another drug of the same class (see **Section 4.3 CONTRAINDICATIONS**).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of captopril. Treatment with captopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see **Section 4.3 CONTRAINDICATIONS** and **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)**.

Intestinal angioedema

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including CT scans or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) or vildagliptin may be at increased risk for angioedema.

Anaphylactoid reactions during desensitisation

Two patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor, enalapril, sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent

rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialysis/lipoprotein apheresis membrane exposure

Patients haemodialysed using high-flux polyacrylonitrile ("AN69") membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. Anaphylactoid reactions have also been reported in patients undergoing low density lipoprotein apheresis with dextran sulfate absorption. These combinations should therefore be avoided, either by use of a different class of medication or alternative membranes (e.g. cuprophane or polysulfone [PSF] for haemodialysis).

Proteinuria

In about 0.7% of patients receiving captopril, total urinary proteins were greater than 1 g/day. The majority of these patients were receiving relatively high doses (>150 mg/day), or had prior renal disease, or both. In mild to moderate hypertensive patients the incidence fell to 0.06%. Changes in renal function (as assessed by serum creatinine and blood urea nitrogen) were infrequent and did not occur in patients who had no prior renal disease.

Nephrotic syndrome (hypoalbuminaemia, oedema and proteinuria >3 g/day) occurred in about one-fifth of the proteinuric patients. In most cases, the proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as blood urea nitrogen (BUN) and creatinine, were seldom altered in the patients with proteinuria.

Although membranous glomerulopathy was found in biopsies taken from proteinuric patients, a causal relationship to captopril has not been established since pre-treatment biopsies were not taken and membranous glomerulopathy has been shown to occur in hypertensive patients not receiving captopril.

In a multicentre, double blind, placebo controlled trial in 207 patients with diabetic nephropathy and proteinuria (≥500 mg/day) administered 75 mg of captopril per day for a median of three years, there was a consistent reduction in proteinuria. It is unknown whether long-term therapy in patients with other types of renal disease would have similar effects.

Patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimations (dipstick on first morning urine) prior to treatment, and periodically thereafter.

Neutropenia/Agranulocytosis

Neutropenia has occurred in some patients taking captopril, but this has been limited chiefly to those who had pre-existing impaired renal function, immunosuppressant therapy, collagen vascular disease, or a combination of these complicating factors.

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia.

In patients with collagen vascular disease (e.g. systemic lupus erythematosus, scleroderma), particularly those with co-existing renal impairment, ZEDACE should be prescribed only after an assessment of benefit and risk since neutropenia has occurred in 8 of the 124 such patients in clinical trials.

Neutropenia was noted 2 to 13 weeks after captopril treatment had been started and it developed relatively slowly, the white cell count dropping to its nadir over 10 to 30 days. Neutropenia was usually not associated with significant alterations in red blood cell or platelet counts.

Evaluation of white cell counts in the total patient population suggests a possible general, but milder, effect on neutrophils. In most studies, there was a 5 to 10% decrease in leucocyte count over the first eight weeks of treatment. This reduction was not seen in patients on hydrochlorothiazide, propranolol or placebo, although it was seen on standard triple therapy. The alteration in white cell count was not progressive and the effect was no longer apparent after 12 weeks in most patients. The significance of these alterations is uncertain.

For patients with significantly impaired renal function, collagen vascular disease, or who are being treated with immunosuppressant drugs and for patients with pre-existing neutropenia, white blood cell and differential counts should be done before commencement of captopril treatment and at regular intervals thereafter.

All patients taking ZEDACE should be instructed to report any signs of infection (e.g. fever, sore throat). When such signs are reported, a complete white blood cell count should be performed immediately.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of neutropenia cases have resulted in death, but almost all fatalities involved patients with serious illness i.e. renal failure, collagen vascular disease, immunosuppressant therapy, heart failure or a combination of these complicating factors.

Assessment of renal function should always be included in the evaluation of patients with hypertension or heart failure.

If ZEDACE is to be prescribed to patients with impaired renal function, white blood cell and differential counts should be performed prior to commencement of therapy and at approximately two week intervals for about three months, then periodically thereafter.

Since discontinuation of captopril and other drugs has generally led to speedy return of the white cell count to normal, upon confirmation of neutropenia (neutrophil count <1,000/mm3), ZEDACE should be withdrawn and the patient's progress followed closely by the doctor.

Anaemia

Anaemia with reduced haemoglobin level was reported in renal transplant or haemodialysis patient. The reaction was greater in patients with higher baseline levels. Anaemia does not appear to be dose-dependent, however it is linked to ACE inhibitors mechanism of action. It is reversible upon captopril discontinuation.

Hypotension

Hypotension may occur occasionally in patients starting treatment with ACE inhibitors. Excessive hypotension is rarely seen in patients with uncomplicated hypertension but can develop in patients with impaired renal function, in those who are salt/volume depleted because of renovascular disease, vomiting or diarrhoea, diuretic treatment and in dialysis patients (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS** and **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

In heart failure, where the blood pressure was either low or normal, transient reductions in mean blood pressure > 20% are recorded in about half of the patients. This transient hypotension may occur after any of the initial several doses and is usually well tolerated, producing either no symptoms or brief mild light headedness, although in rare instances it has been linked with conduction defects or arrhythmia. Hypotension was the reason for discontinuation of drug in 3.6% of heart failure patients.

Only a few patients with refractory heart failure secondary to a mechanical lesion of the heart have been studied with captopril. The potentially harmful consequences of reduced coronary perfusion secondary to hypotension are possible concerns in patients with aortic and mitral valve stenosis. Patients treated for severe congestive heart failure should be warned to increase their physical activity slowly.

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been seen. This may be associated with neurological deficits, syncope, oliguria and/or progressive azotaemia and, rarely, with acute renal failure and/or death. In these patients, therapy should be

initiated at low doses (6.25 or 12.5 mg twice or three times daily) under very close supervision because of the potential fall in blood pressure. Such patients should be monitored closely for the initial two weeks of therapy and whenever the dosage is increased, or diuretic treatment is started or increased.

Similar considerations may apply to patients with cerebrovascular or ischemic heart disease in whom an excessive drop in blood pressure could lead to cerebrovascular accidents or myocardial infarction, respectively. In all high risk patients, it is advisable to commence therapy at lower dosages than those normally recommended for patients with uncomplicated disease states.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, be administered an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be administered without difficulty once the blood pressure has increased. The magnitude of the blood pressure fall, is greatest early in the course of therapy; this effect stabilises within a week or two, and generally returns to pre-treatment levels, without a reduction in therapeutic efficacy, within two months.

Use in Hepatic Impairment

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes death. The mechanism of this syndrome is not understood. Patients on ACE inhibitor therapy who develop jaundice or marked elevations of hepatic enzymes should stop taking their ACE inhibitor and receive appropriate medical attention.

Hyperkalaemia

Because ACE inhibitors reduce the production of angiotensin II and the subsequent formation of aldosterone, serum potassium concentrations greater than 5.5 mEq/L may occur, although frank hyperkalaemia is uncommon. Hyperkalaemia is more likely in patients with some degree of renal impairment, those receiving potassium supplements or potassium sparing diuretics, and in those taking potassium containing salt substitutes or other drugs associated with elevations in serum potassium (e.g. ciclosporin, heparin, trimethoprim containing medicines). Diabetic patients, and in particular, elderly diabetic patients, may have a higher risk of hyperkalaemia. It is recommended that patients treated with ACE inhibitors should have their serum electrolytes (including potassium, urea and sodium) measured from time to time. This is more important in patients receiving diuretics.

Cough

A persistent, dry (non-productive) cough has been reported with all of the ACE inhibitors and appears to be a class effect. In studies with various ACE inhibitors, the incidence of cough varies between 2 and 15% depending upon the drug, dosage and duration of use. The cough appears to be more common in women (approximately 2:1) and is often worse when the patient is lying down. It may resolve or diminish with continued use or with dose reduction, but usually recurs on rechallenge. The cough may be caused by increased bronchial reactivity attributed to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins which accumulate because of the inhibition of angiotensin-converting enzyme. Once a patient has developed intolerable cough, an attempt may be made to change the patient to another ACE inhibitor; the reaction may recur but this is not always the case. A change to another drug class may be necessary in severe cases. No residual effects have been reported. ACE inhibitor-induced cough should be considered part of the differential diagnosis of cough.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, captopril will inhibit angiotensin II formation secondary to compensatory renin release. This may result in hypotension, which can be corrected by volume expansion.

Use in diabetic nephropathy

In managing a patient with microalbuminuria, the physician should be mindful of the importance of reducing other risk factors for progression to proteinuria, for example, the need to maintain adequate control of blood glucose and blood pressure.

The physician should also alert normotensive patients with diabetic nephropathy to the possibility of the rare occurrence of hypotension during treatment with captopril.

Use in Renal Impairment

Hypertension

Some renal disease patients, in particular those with renal artery stenosis, have developed elevations in serum concentrations of BUN and serum creatinine after reduction of blood pressure with captopril, usually in conjunction with a diuretic. ZEDACE dosage reduction and/or discontinuation of diuretic may be necessary. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion; therefore, it may be necessary to titrate to acceptable levels of blood pressure.

In patients with low renal perfusion pressure (bilateral renal artery stenosis, renal artery stenosis to a solitary kidney) the renin-angiotensin system may be an important regulator of glomerular filtration rate. Caution should be exercised if captopril is to be administered in such patients.

Assessment of renal function should always be included in the evaluation of the patient with hypertension (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). If deterioration in renal function has developed after therapy with one ACE inhibitor, then it is likely to be precipitated by another. Therefore, in these patients, it would be preferable to use another class of antihypertensive agent. 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.

Heart failure

About 20% of patients sustain stable increases of BUN and serum creatinine >20% above normal or baseline upon long-term captopril therapy. Less than 5% of patients, generally those with severe pre-existing renal disease, needed cessation of treatment due to progressively increasing creatinine. Subsequent improvement probably depends upon the severity of the underlying renal disease.

Use in the Elderly

No data available.

Paediatric Use

Safety and effectiveness in children have not been established, although there is limited experience in children with secondary hypertension, apnoea, seizures and varying degrees of renal failure. On a weight basis, dosage in children was comparable to adult dosages. ZEDACE should only be given if the potential benefit justifies the risk.

Oliguria is a risk in premature patients treated with captopril.

Leukopenia has been reported in children with renal impairment treated with captopril.

Effects on Laboratory Tests

Captopril may cause a false positive urine test for acetone.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Hypotension in patients on diuretic therapy

When a diuretic is added to the drug regimen of a patient treated with captopril, the antihypertensive effect is usually additive. Patients treated with diuretics, particularly those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive lowering of blood pressure usually within the first hour after initiation of therapy with captopril. The possibility of hypotensive effects may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, the starting dose of ZEDACE should be lowered and the patient observed closely for several hours following the initial dose and until blood pressure has stabilised.

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.

Dual blockade of the Renin-Angiotensin System (RAS) with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalaemia and changes in renal function compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients using captopril in combination with other captopril agents that block RAS.

Lithium

Raised serum lithium levels and symptoms of lithium toxicity have been reported in patients treated with lithium together with drugs that cause sodium elimination, including ACE inhibitors. Caution should be exercised if these drugs are to be administered together, and frequent monitoring of the patient's serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be higher.

Agents affecting sympathetic activity

The sympathetic nervous system may be particularly important in supporting blood pressure in patients treated with captopril alone or with diuretics. Therefore, drugs affecting sympathetic activity (e.g. adrenergic neuron blocking agents or ganglionic blocking agents) should be administered with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Close supervision will be required in these patients. Concomitant use of alpha blocking agents may increase the antihypertensive effects of captopril and increase the risk of orthostatic hypotension.

Agents increasing serum potassium

Since captopril reduces the production of aldosterone, elevation of serum potassium may occur. Potassium sparing diuretics (e.g. triamterene, spironolactone or amiloride) or potassium supplements should be administered only for documented hypokalaemia, and then with caution, since they may lead to a significant rise in serum potassium. Salt substitutes containing potassium or other medicines associated with increases in serum potassium (e.g. trimethoprim containing medicines, ciclosporin, heparin) should also be used with caution.

Non-steroidal anti-inflammatory drugs (NSAIDs)

There is some evidence to suggest that concomitant administration of NSAIDs such as indometacin may decrease the response to ACE inhibitors, but further data are required to clarify whether such an effect is of clinical significance. The concomitant administration of the two drug classes may also increase the risk of hyperkalaemia.

Agents having vasodilator activity

Data on the effect of concomitant administration of other vasodilators in patients treated with captopril for heart failure are not available. Therefore, glyceryl trinitrate or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be ceased before starting ZEDACE. If resumed during ZEDACE therapy, such drugs should be given cautiously and perhaps at lower dosage.

Haemodialysis membranes

Hypersensitivity-like (anaphylactoid) reactions have been reported with high-flux dialysis membranes (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Mammalian Target of Rapamycin (mTOR) Inhibitors

Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

Combination of ACE inhibitors and Vildagliptin

Patients taking concomitant vildagliptin therapy may be at increased risk for angioedema.

Combination of ACE inhibitors and Sacubitril/Valsartan

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.

Allopurinol, Procainamide, cytostatic, or immuno-suppressive agents:

Concomitant administration with ACE inhibitors may lead to increased risk for leukopenia especially when the latter are used at higher than currently recommended doses.

Tricyclic anti-depressants, neuroleptics, amifostine, baclofen:

Co-administration of these drugs with captopril may potentially increase antihypertensive effects and risk of postural hypotension.

Antidiabetics:

Pharmacological studies have shown that ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in diabetics. Should this very rare interaction occur, it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with ACE inhibitors.

Gold

In rare cases, nitritoid reactions with symptoms such as flushing, dizziness, nausea, vomiting and drop in blood pressure up to circulatory collapse have been observed in patients treated with ACE inhibitors and injectable gold preparations (sodium aurothiomalate) at the same time.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: D

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

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

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

When used in pregnancy, ACE inhibitors can cause injury or even death to the developing foetus.

The use of ACE inhibitors during the second or third trimesters of pregnancy has been associated with foetal and neonatal injury including hypotension, neonatal skull hypoplasia anuria, reversible and irreversible renal failure and death.

Oligohydramnios has also been reported, presumably resulting from reduced foetal renal function. Oligohydramnios has been associated with foetal limb contractures, hypoplastic lung development, craniofacial deformities and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have also been reported.

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 to no exposure.

Use in Lactation

Following oral administration, captopril concentrations in breast milk are ≤1% of the maternal blood concentrations. The effect of this low level of captopril on the breastfed infant has not been determined. Caution should be used when captopril is given to a nursing woman and, in general, breastfeeding should be interrupted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of captopril include dizziness and disturbed vision, which could affect the ability to drive or use machines. See **Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS)**.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reported incidences are based on clinical trials involving approximately 7,000 patients treated with captopril.

More common adverse effects

Cardiovascular

Hypotension occurs in about 2% of patients (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Dermatological

Rash occurred in 13.1% of patients with evidence of prior renal function impairment and 3.8% of patients with normal renal function. The rash is usually maculopapular and pruritic, but rarely urticarial, and generally occurs during the first four weeks of therapy. It is usually self-limited and reversible and may respond to antihistamine therapy. In the majority of patients, the condition resolves with the continuation of treatment.

Fever and arthralgia sometimes accompanied the rash and, in 7 to 10% of patients, eosinophilia and/or positive antinuclear antibody (ANA) titres were also present.

Pruritus with or without a rash, alopecia.

Cough

Cough has been reported in 0.5 to 2% of patients in clinical trials of captopril (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Taste disturbances (dysgeusia)

1.6% of patients treated with ≤150 mg of captopril per day developed a diminution of, or loss of, taste perception. At doses greater than 150 mg/day, 7.3% of patients sustained this effect. Taste impairment is reversible and usually self-limited to two to three months, even with continued drug therapy. Weight loss may be associated with the loss of taste.

Psychiatric disorders

Sleep disorders are common adverse reactions (1-10% of patients).

Less common adverse effects

Cardiovascular

Chest pain, tachycardia and palpitations have been observed in about 1% of patients.

Angina pectoris, Raynaud's phenomenon, myocardial infarction and congestive heart failure have occurred in 0.2 to 0.3% of patients. Cardiac arrest, cerebrovascular accident/insufficiency including stroke, rhythm disturbances/orthostatic hypotension, syncope, cardiogenic shock.

Gastrointestinal

Abdominal pain, gastric irritation and pancreatitis have been reported. Nausea, diarrhoea, vomiting, anorexia, intestinal angioedema and constipation may occur. Stomatitis resembling aphthous ulcers, tongue ulceration, glossitis, peptic ulcer and a scalded sensation of the oral mucosa have been reported. Cases of hepatitis have been reported in association with captopril treatment. The predominant form of captopril associated hepatic injury is cholestasis, although mixed or pure hepatocellular injury has also been reported.

Genitourinary

Proteinuria (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Renal insufficiency, acute renal failure, oliguria, polyuria and increased urinary frequency have been reported in 0.1 to 0.2% of patients. Cases of glomerulopathy and nephrotic syndrome have also been reported.

Haematological and reticuloendothelial

Neutropenia/agranulocytosis (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Reversible lymphadenopathy, eosinophilia, anaemia, pancytopenia, auto-immune disease and thrombocytopenia have been reported.

Dermatological

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been observed in about 1 in 1,000 patients (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Flushing or pallor has been reported in 0.2 to 0.5% of patients. Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis, photosensitivity.

Other

Paraesthesias of the hands, headache, serum sickness-like syndrome, myalgia, fatigue, malaise and drowsiness, dizziness have been reported. Dry mouth, dyspnoea, bronchospasm, disturbed vision, itching and/or dry eyes, impotence, loss of libido, and insomnia have occurred rarely, often in patients on multiple drug therapy. Asthenia and gynaecomastia.

Severe or life-threatening adverse effects

Angioedema/hypotension (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Neutropenia/agranulocytosis (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Altered laboratory findings

Elevations of hepatic transaminases, serum bilirubin and alkaline phosphatase have occurred but no causal relationship to captopril use has been established.

A transient increase of BUN and serum creatinine may occur, particularly in patients who have renovascular hypertension or who are volume depleted. In instances of rapid decrease in longstanding or severely elevated blood pressure, the glomerular filtration rate may drop transiently, also resulting in transient rises in serum creatinine and BUN.

Small increases in the serum potassium concentration (hyperkalaemia) frequently occur, particularly in renal impairment patients (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Hyponatraemia may occur, especially in patients taking diuretics concomitantly or in patients with low sodium diets. Hypoglycaemia may occur.

Alterations in blood cell counts and anaemia have occurred during captopril therapy (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - LESS COMMON REACTIONS**, **Haematological and reticuloendothelial**).

Paediatric Population:

The major adverse events seen in the paediatric population were persistent dry cough, hyperkalaemia, angioedema, decreased GFR, hypotension, neutropenia, impaired hepatic function and renal disorders.

The reactions most frequently observed during captopril therapy were headache, tachycardia, vomiting, postural symptoms, anaemia, rash and anorexia

Adverse effects such as apnoea, seizures, renal failure, and severe unpredictable hypotension are very common in the first month of life and it is therefore recommended that ACE inhibitors are used with caution, particularly in preterm neonates (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Oliguria is a risk in premature patients treated with captopril (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Post-Introduction Safety Experience

Other clinical adverse effects reported since the medicine was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Foetal/Neonatal Morbidity and Mortality

The use of ACE inhibitors during pregnancy has been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported. More recently, prematurity, patent ductus arteriosus and other structural cardiac

malformations, as well as neurologic malformations, have been reported following exposure limited to the first trimester of pregnancy (see **Section 4.6 FERTILITY, PRENANCY AND LACTATION – Use in Pregnancy**).

Musculoskeletal

Myasthenia.

Skin and Subcutaneous Tissue Disorders

Frequency unknown: psoriasis/psoriasis aggravation.

Nervous/Psychiatric

Ataxia, confusion, depression, nervousness, somnolence.

Respiratory

Eosinophilic pneumonitis, rhinitis.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated erythrocyte sedimentation rate (ESR).

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

Treatment

In the event of an overdosage, treatment should be symptomatic.

The primary concern would be to correct the hypotension. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by haemodialysis, there are inadequate data concerning the effectiveness of haemodialysis for removing it from the circulation of children or neonates. Peritoneal dialysis is not effective for removing captopril. There is no information concerning exchange transfusion for removing captopril from the general circulation.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacodynamics

Captopril administration results in a decrease in peripheral arterial resistance in hypertensive patients with either no change or an increase in cardiac output.

Clinically significant reductions in blood pressure are often observed 60 to 90 minutes after oral administration of captopril. However, the reduction in blood pressure is usually progressive and to achieve maximal therapeutic effects of a given dosage regimen, several weeks of administration may be required. The duration of effect appears to be dose related.

Blood pressure is lowered in both standing and supine positions. Orthostatic effects and tachycardia are infrequent, occurring most commonly in volume-depleted patients. No sudden increase in blood pressure after withdrawal of the drug has been observed.

Studies have shown an increase in renal blood flow after captopril administration. Glomerular filtration rate is usually unchanged. In instances of rapid reduction of long-standing or severely elevated blood pressure, the glomerular filtration rate may be temporarily reduced resulting in transient rises in serum creatinine and urea nitrogen. In humans, the renin-angiotensin system plays a role in regulating the glomerular filtration rate when renal perfusion pressure is low. Administration of captopril may result in acute deterioration of glomerular filtration in such patients.

Mechanism of Action

The mechanism of action of captopril has not yet been fully elucidated, however its beneficial effects in hypertension and heart failure appear to result mainly through suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between plasma renin levels and response to captopril. Renin, an enzyme synthesised by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted enzymatically by angiotensin-converting enzyme (ACE) to the octapeptide angiotensin II, one of the most potent endogenous vasoconstrictor substances. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention and potassium loss.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxyhydrolase. This is reflected by a decrease in the pressor substance, angiotensin II, and an increase in plasma renin activity (PRA). The latter is due to the relative lack of negative feedback on renin release caused by the reduction in angiotensin II levels. Decreased concentrations of aldosterone are found in blood and urine and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

ACE is identical to “bradykininase” and captopril may also interfere with the degradation of bradykinin. Increased concentrations of bradykinin or prostaglandin E2 may also have a role in the therapeutic effect of ZEDACE.

Clinical Trials

Among the 2,231 patients with myocardial infarction who took part in the Survival and Ventricular Enlargement (SAVE) trial, captopril was observed to improve long-term survival and clinical outcome when compared to placebo. The study was a randomised, double blind, placebo controlled, multicentre trial. The inclusion criteria for the study was that the patients (age 21 to 79 years) had to demonstrate left ventricular dysfunction (ejection fraction < 40%) without overt heart failure. Specifically, captopril, when given 3 to 16 days (mean 11 days) after myocardial infarction, reduced the following: all cause mortality (risk reduction 19%, p=0.022); cardiovascular death (risk reduction 21%, p=0.017); manifestations of heart failure requiring initiation or augmentation of digitalis and diuretics (risk reduction 19%, p=0.008) or requiring the use of ACE inhibitor therapy (risk reduction 35%, p<0.001); hospitalisation for heart failure (risk reduction 20%, p=0.034); clinical recurrent myocardial infarction (risk reduction 25%, p=0.011); and coronary revascularisation procedures [coronary artery bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA)] (risk reduction 24%, p=0.014).

Potential mechanisms by which captopril improves survival and clinical outcome in patients following myocardial infarction include inhibition of neurohumoral activation, and attenuation of the progressive left ventricular dilatation and deterioration in left ventricular function.

Heart failure patients treated with captopril demonstrate increases in ability to perform at higher workloads, exercise time, and improvement in functional capabilities by New York Heart Association criteria. Captopril therapy in heart failure patients has resulted in consistent increases in cardiac index, cardiac output and stroke volume index. The effects were accompanied by decreases in systemic vascular resistance, total vascular resistance, pulmonary vascular resistance, pulmonary arterial pressure, right atrial pressure and pulmonary capillary wedge pressure. A consistent drop in mean arterial pressure was generally seen but it rarely became

symptomatic. After short term treatment, a slight decrease in heart rate occurred which generally returned to pre-captopril levels with long term therapy. Occasionally a more pronounced decrease in heart rate may occur.

In studies involving a small number of heart failure patients, a decrease in coronary blood flow which correlated with a drop in myocardial oxygen demand has been observed, with simultaneous increases in cardiac index and reduction in systemic vascular resistance.

In a multicentre, double blind, placebo-controlled trial among 409 patients aged 18 to 49 of either gender, with or without hypertension, with type 1 (juvenile type, onset before age 30) insulin-dependent diabetes mellitus, retinopathy, proteinuria ≥ 500 mg per day and serum creatinine ≤ 2.5 mg/dL, patients were randomized to placebo or captopril (25 mg three times a day) and followed for up to 4.8 years (median 3 years). To achieve blood pressure control, additional antihypertensive agents (diuretics, beta-blockers, centrally active agents or vasodilators) were added as needed for patients in both groups.

The captopril group had a 51% risk reduction in doubling of serum creatinine ($p \leq 0.01$), and a 51% risk reduction for the combined morbidity/mortality endpoint of end-stage renal disease (dialysis or renal transplantation) or death ($p \leq 0.01$). Captopril treatment resulted in a 30% reduction in urine protein excretion within the first 3 months ($p < 0.05$), which was maintained throughout the trial. The captopril group had somewhat better blood pressure control than the placebo group, but the effects of treatment with captopril on the preservation of renal function are in addition to any benefit that may have been derived from the reduction in blood pressure. Captopril was well tolerated in this patient population.

In two multicentre, double-bind, placebo controlled studies, a total of 235 normotensive patients with insulin-dependent diabetes mellitus (of 4 to 30 years duration with onset before the age of 39 years), retinopathy, serum creatinine within the normal range and microalbuminuria (albumin excretion rate 20 to 200 mcg/min) were randomised to placebo or captopril (50 mg twice a day) and followed for up to 2 years. Catopril delayed the progression to overt nephropathy (albumin excretion rate > 200 mcg/min i.e. proteinuria ≥ 500 mg/day) in both studies (risk reduction 67% to 76%, $p < 0.05$). However, the long-term clinical benefit of reducing the progression from microalbuminuria to proteinuria has not been established

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following a 100 mg oral dose of captopril, rapid absorption occurs with peak blood levels of approximately 1 μg/mL being found in half to one hour. The average minimal absorption is approximately 75%. Absorption of captopril is decreased by 25 to 40% if food is present in the gastrointestinal tract. The apparent oral bioavailability is increased in patients on chronic captopril therapy compared with acute use. It may be possible to reduce the dosage during chronic therapy and still maintain adequate blood pressure control.

Distribution

Captopril appears to be distributed between three compartments in humans. The terminal phase volume of distribution (2 L/kg) suggests that captopril is distributed into deep tissues.

Approximately 30% of the drug is bound to plasma proteins.

Metabolism

Captopril is extensively metabolised. The major metabolite is the captopril dimer (SQ 14,551). *In vitro* studies have demonstrated that SQ 14,551 is significantly less active than captopril as an inhibitor of angiotensin-converting enzyme.

Excretion

Captopril and its metabolites (captopril dimer and conjugates with endogenous thiol compounds, e.g. captopril-cysteine) are excreted principally in the urine. *In vitro* studies suggest that the metabolites are labile and that interconversions may occur *in vivo.* Approximately 40% of an administered dose is excreted

unchanged in the urine in 24 hours and 35% as metabolites. Total body clearance is approximately 0.8 L/kg/hour.

The elimination half-life of captopril is 1 to 2 hours and of total radioactivity is approximately 4 hours. The elimination half-life of captopril increases with decreasing renal function; the elimination rate correlates with creatinine clearance. The half-life for non-renal elimination is 156 hours. Dosage adjustment is required in patients with renal impairment (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

Two year studies with doses of 50 to 1350 mg/kg/day in rats and mice failed to show any evidence of carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablet contains microcrystalline cellulose, maize starch, lactose, stearic acid and sodium starch glycollate.

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 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/PE blister packs

Pack sizes: 90 tablets

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

Australian Register of Therapeutic Goods (ARTG)

AUST R 57370 - ZEDACE Captopril 25mg tablet blister pack

AUST R 57371 - ZEDACE Captopril 50mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

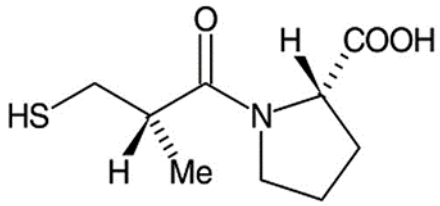
6.7 PHYSICOCHEMICAL PROPERTIES

Captopril is a white to almost white, crystalline powder.

Chemical name

1-[(2S)-3-mercapato-2-methyl-propionyl]-L-proline

Chemical Structure



Molecular formula

$C_9H_{15}NO_3S$

Molecular weight

217.3

CAS Number

62571-86-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

10/10/1996

10 DATE OF REVISION

20/10/2025

Summary Table of Changes

Section Changed	Summary of New Information
4.8	Addition of psoriasis/psoriasis aggravation

ZEDACE® is a Viatris company trade mark

ZEDACE_pi/Oct25/00