AUSTRALIAN PRODUCT INFORMATION

GOPTEN®

(trandolapril) capsule

1 NAME OF THE MEDICINE

Trandolapril

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each GOPTEN capsule contains 0.5 mg, 1 mg, 2 mg or 4 mg of trandolapril as active ingredient.

Excipients with known effect: Contains sugars as lactose and sulfites.

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

3 PHARMACEUTICAL FORM

GOPTEN 0.5 mg	White to off white granules filled in Size 4 hard gelatin capsules with yellow opaque cap and red opaque body.
GOPTEN 1 mg	White to off white granules filled in Size 4 hard gelatin capsules with orange opaque cap and red opaque body.
GOPTEN 2 mg	White to off white granules filled in Size 4 hard gelatin capsules with red opaque cap and red opaque body.
GOPTEN 4 mg	White to off white granules filled in Size 2 hard gelatin capsules with maroon opaque cap and red opaque body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

GOPTEN is indicated for the treatment of hypertension. Data to support the usage of GOPTEN in renovascular hypertension is, at present, not available.

GOPTEN is also indicated for patients with left ventricular dysfunction post myocardial infarction [ejection fraction ≤ 35% or WMI (Wall Motion Index) ≤ 1.2].

4.2 DOSE AND METHOD OF ADMINISTRATION

GOPTEN has a duration of action of greater than 24 hours and should not be administered at intervals of less than 24 hours. Monitoring of trough BP should be done initially to ensure control lasts over the dosing period. Should daily doses of more than one capsule be required, they should be administered together as a single daily dose.

Since there is no clinically significant effect of food on the absorption of GOPTEN, the capsules may be taken before, during, or after a meal.

Hypertension

The usual starting dose is one 1 mg capsule once daily. Maximum response is usually achieved within 2 - 4 weeks.

Some patients not responding to 1 mg once daily may respond to 2 mg once daily. An alternative to increasing the dose is to add a calcium channel blocker or diuretic (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The maximum daily dose of GOPTEN should not exceed 4 mg.

Left Ventricular Dysfunction Post-Myocardial Infarction (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hypotension)

Following a myocardial infarction, therapy may be initiated as early as on the third day using an aggressive titration dose regimen. After a 0.5 mg test dose, treatment should commence with 1 mg once daily for the next three days. The dose should then be increased to 2 mg for a further four weeks. After the initial four-week treatment, the dose should be increased to a maximum daily dose of 4 mg once daily and maintained at that level subject to tolerability, such as symptomatic hypotension.

Elderly Hypertensives

In patients older than 65 years with normal renal and hepatic function, there is no need to reduce the dose of GOPTEN.

Diuretic Treated or Severely Salt Depleted Patients

As with other ACE inhibitors, in cases of prior diuretic treatment it is advisable either to discontinue the diuretic at least 3 days before starting treatment with GOPTEN or commence with GOPTEN 0.5 mg daily. If diuretic treatment is continued, plasma creatinine levels should be monitored.

Renal Impairment

If creatinine clearance is less than 10 ml/min, treatment should be initiated and maintained at 0.5 mg daily. Patients with clearance rates greater than 10 ml/min but less than or equal to 50 ml/min should be initiated on 0.5 mg. The dose may be increased according to patient response, to a maximum daily dose of 1 mg.

Impaired Liver Function

Treatment should be initiated at 0.5 mg daily and adjusted according to therapeutic response.

Cardiac Failure

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients, therapy should be started at a dose of 0.5 mg GOPTEN once daily under close medical supervision.

4.3 CONTRAINDICATIONS

GOPTEN is contraindicated in:

- patients who are hypersensitive to GOPTEN or any other ACE inhibitor, or to any of the excipients listed in Section 6.1 LIST OF EXCIPIENTS
- patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor
- pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy)
- lactation (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Lactation)
- children
- concomitant use with neprilysin (neutral endopeptidase, NEP) inhibitors such as sacubitril and racecadotril (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- haemodialysis and other extracorporeal treatments. Patients haemodialysed using high-flux polyacrylonitrile (‘AN69’) membranes or patients undergoing low-density lipoprotein apheresis with dextran sulfate are highly likely to experience anaphylactoid reactions if they are treated with ACE

inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes (eg. cuprophane or polysulphone PSF) for haemodialysis

- combination with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73m^2) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

- liver cirrhosis with ascites

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Angioedema

Since 1984, severe life-threatening angioedema has been reported with most of the 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. ACE inhibitors have been shown to cause a higher rate of angioedema in black patients than in non-black patients. In the majority of reported cases, the symptoms occurred during the first week of therapy, however severe angioedema may also develop after months or years of long-term treatment with an ACE inhibitor. 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. Usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes. Angioedema may occur with or without urticaria.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. In such cases, the product should be discontinued promptly and the patient observed carefully until the swelling disappears. In instances when 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. Angioedema involving the tongue, glottis or larynx requires immediate subcutaneous administration of 0.3 – 0.5 mL of adrenaline (epinephrine) solution (1:1000) along with other therapeutic measures as appropriate. Response to treatment should be reviewed by healthcare professionals, noting standard therapies for histamine-mediated angioedema may be ineffective for bradykinin-mediated angioedema.

There are case reports where changing the patient over to another ACE inhibitor was followed by a recurrence of angioedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class (see Section 4.3 CONTRAINDICATIONS).

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

Where 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. Failing a rapid response, oral/nasal intubation or securing an airway by surgical means (e.g. cricothyrotomy or tracheostomy) may be necessary, followed by mechanical ventilation. Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

Intestinal angioedema has also been reported in patients treated with ACE inhibitors. This should be considered in patients on trandolapril presenting with abdominal pain (with or without nausea or vomiting).

As the concomitant inhibition of ACE and neprilysin (neutral endopeptidase, NEP) may increase the risk of angioedema, co-administration of ACE inhibitors and NEP inhibitors (e.g. sacubitril and racecadotril) is contraindicated. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of

trandolapril therapy. If treatment with sacubitril/valsartan is stopped, trandolapril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients experiencing angioneurotic oedema must immediately discontinue treatment and be monitored until the oedema resolves.

Patients with Renovascular Hypertension

Treatment of renovascular hypertension is by revascularisation. However, ACE inhibitors may be useful while waiting for the revascularisation or when the procedure is not carried out. The risk of severe arterial hypotension and renal insufficiency is increased when patients with prior unilateral or bilateral renal artery stenosis are treated with an ACE inhibitor. Diuretics may further increase the risk. Loss of renal function may occur with only small changes in the serum creatinine, even in patients with unilateral renal artery stenosis. For these patients treatment should be initiated in the hospital under close medical supervision with low doses and careful dose adjustment. Diuretic treatment should be discontinued, and renal function and serum potassium monitored during the early weeks of treatment.

Anaphylactoid and Possibly Related Reactions

Desensitisation

Anaphylactoid reactions (in some cases life threatening) may develop in patients receiving ACE inhibitors therapy and concomitant desensitisation (e.g. against animal venoms).

Low Density Lipoprotein (LDL)-apheresis

Life threatening anaphylactoid reactions have been noted when patients on LDL-apheresis take ACE inhibitors at the same time.

Hypotension

Hypotension may occur in patients commencing 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 that are salt/volume depleted because of renovascular disease, diuretic therapy, vomiting or diarrhoea and in patients undergoing dialysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

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

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

Hypotension Post Myocardial Infarction

If hypotension is present, after MI, it is recommended that the patient be closely monitored for at least six hours following the initial 0.5 mg dose. Therapy should be initiated after hyponatraemia and/or hypovolemia (if present) is corrected.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies with ACE inhibitors 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 treatment. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or with bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea nitrogen and serum creatinine which is usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. 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 usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors. Some ACE inhibitors including trandolaprilat have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium sparing diuretics or high doses of other diuretics, limited cardiac-reserve, or treatment with a non-steroidal anti-inflammatory drug.

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Impaired Liver Function

As GOPTEN is a pro-drug metabolised in the liver to its active moiety, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound and, therefore, the formation of the bioactive metabolite trandolaprilat may be diminished, resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of the esterases in the liver). GOPTEN therapy should be initiated with the 0.5 mg dose in this case (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Cough

During treatment with an ACE inhibitor, a dry and non-productive cough may occur, which disappears after discontinuation.

A persistent dry (non-productive) irritating cough has been reported with most of the ACE inhibitors. The frequency of reports has been increasing since cough was first recognised as a side-effect of ACE inhibitor therapy. 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, and has been reported more frequently in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side-effect in non-smokers may be due to a higher level of tolerance of smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins that accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

Hyperkalaemia

Because the ACE inhibitors decrease the formation of Angiotensin II and the subsequent production of aldosterone, serum potassium concentrations exceeding 5.5 mEq/L may occur. Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium-sparing diuretics or potassium supplements, potassium-containing salt substitutes, the concomitant use of agents to treat hypokalaemia and in those patients taking other active substances associated with increases in serum potassium (e.g. co-trimoxazole also known as trimethoprim/sulfamethoxazole) concomitantly. Diabetics, particularly elderly diabetics, and patients with left ventricular dysfunction after myocardial infarction, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may coexist with hyperkalaemia. It is recommended that patients taking an ACE inhibitor should have serum electrolytes (including potassium, sodium & urea) measured from time to time. This is more important in patients taking diuretics.

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression (including leukopenia/neutropenia) have been reported with ACE inhibitors. The risk of neutropenia appears to be dose-and type-related and is dependent on the patient's clinical status. These have mostly occurred in patients with pre-existing impaired renal function, connective tissue diseases such as collagen vascular disease, immunosuppressant therapy or a combination of these complicating factors. Most episodes of leukopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered 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. The condition is reversible after discontinuation of the ACE inhibitor.

Dermatological Reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity have been reported rarely with ACE inhibitors. Rare and occasionally severe skin reactions (e.g. lichenoid eruptions, psoriasis, pemphigus-like rash, rosacea, Stevens-Johnson syndrome) have also been reported. A causal relationship is sometimes difficult to assess.

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.

Taste Disturbances (Dysgeusia)

The incidence of taste disturbance was reported to be high (up to 12.5%) with high doses of one ACE inhibitor, but the overall incidence for the class is probably low (< 0.5%). However, the relevant data are scarce and difficult to interpret.

The taste disturbance has been described as a suppression of taste or a metallic sensation in the mouth. The dysgeusia usually occurs in the first few weeks of treatment and may disappear within 1 - 3 months despite continued treatment.

Surgery/Anaesthesia

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. If perioperative hypotension occurs, volume expansion would be required.

Dialysis

It is not known for certain if trandolapril or trandolaprilat are removed by dialysis. However, it would be expected that dialysis could remove the active moiety, trandolaprilat, from the circulation, resulting in a possible loss of control of blood pressure. Therefore, careful monitoring of the patient's blood pressure during dialysis is required and the dosage of trandolapril adjusted if needed.

Valvular Stenosis

Trandolapril should not be used in patients with aortic stenosis or outflow obstructions. There has been some concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators, including ACE inhibitors. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain.

Excipients - Lactose

The medicine contains lactose monohydrate, therefore patients with rare hereditary forms of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption syndrome should not take this medicine.

Use in Hepatic Impairment

Following oral administration in patients with mild to moderate alcoholic cirrhosis, plasma concentrations of trandolapril and trandolaprilat were, respectively, 9-fold and 2-fold greater than in normal subjects, but inhibition of ACE activity was not affected. Lower doses should be considered in patients with hepatic insufficiency (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in Renal Impairment

Compared to normal subjects, the plasma concentrations of trandolapril and trandolaprilat are approximately 2-fold greater and renal clearance is reduced by about 85% in patients with creatinine clearance below 30 ml/min and in patients with haemodialysis. Dosage adjustment is recommended in renally impaired patients (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the Elderly

A pharmacokinetic study of GOPTEN in hypertensive patients aged more than 65 years with normal renal function for their age shows that no dosage adjustment is necessary. In subjects with impaired renal function, impaired hepatic function and in sodium-deficient subjects, the starting dose should be reduced to 0.5 mg daily.

Paediatric Use

The safety and efficacy of GOPTEN have not been established in children. Interaction studies have only been performed in adults.

Effects on Laboratory Tests

In some cases, an elevation of urea and plasma creatinine has been observed in patients treated with GOPTEN. This increase is most frequently found when GOPTEN is prescribed with diuretics or renal insufficiency, severe heart failure or renovascular hypertension are present.

Hyperkalaemia has rarely been observed in patients treated with GOPTEN. No other electrolyte disturbances nor changes in plasma lipids (total cholesterol, HDL, LDL, VLDL) or glucose tolerance have been observed in patients.

In some cases, an increase in alkaline phosphatase and transaminases has been reported.

Decreased haemoglobin, haematocrit, platelets and white cell count and individual cases of agranulocytosis or pancytopenia, have been reported with ACE inhibitor treatment; also evaluate liver enzymes and serum bilirubin. Haemolytic anaemia has been reported in some patients with a congenital deficiency concerning G-6 PDH (glucose-6-phosphate dehydrogenase) during treatment with ACE inhibitors.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

NEP inhibitors

Co-administration of ACE inhibitors and NEP inhibitors e.g. sacubitril (available as fixed-dose combination with valsartan) and racecadotril, is contraindicated as the concomitant inhibition of ACE and neprilysin (neutral endopeptidase, NEP) may increase the risk of angioedema (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Diuretics

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. 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 the ACE inhibitor should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised.

The combined use of the three classes of drugs, thiazides, an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension.

Angiotensin II receptor blockers, Aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a high frequency of adverse events such a hypotension, hyperkalaemia and decreased renal function (including acute

renal failure) compared to the use of a single RAAS-acting agent (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Agents Affecting Serum Potassium

ACE inhibitors can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. The concomitant therapy of an ACE inhibitor with a potassium-sparing diuretic (eg. spironolactone, triamterene, or amiloride), potassium supplement, or potassium-containing salt substitute can increase the risk of hyperkalaemia, therefore if coadministration is indicated they should be used with caution and the patient's serum potassium should be monitored frequently.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Combination use of ACE Inhibitors or Angiotensin Receptor Antagonists, Anti-Inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Non-Steroidal Anti-Inflammatory Drugs

Drugs with prostaglandin synthetase inhibitory properties (e.g. indometacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors and may increase the risk of hyperkalaemia. As with all antihypertensives, NSAIDs (including aspirin used in higher doses as an anti-inflammatory drug e.g. for pain relief) may reduce the antihypertensive effects of trandolapril.

NSAIDs including aspirin, unless aspirin is used in lower doses as a platelet aggregation inhibitor, should be avoided with ACE inhibitors in patients with heart failure.

Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with trandolapril.

The combined use of the three classes of drugs, thiazides, an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Agents Affecting Sympathetic Activity

Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neurone blocking agents) may be used with caution. Beta-adrenergic blocking drugs will increase the antihypertensive effect of ACE inhibitors, and therefore the patient will need to be closely supervised. The antihypertensive effects of ACE inhibitors may be reduced by sympathomimetics. Patients should be carefully monitored.

Alcohol

Alcohol increases the bioavailability of ACE inhibitors and the risk of hypotension

Antacids

As antacids decrease the bioavailability of ACE inhibitors, it is recommended that these products are taken separately.

Antidiabetic Agents

Concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia. Therefore, blood glucose should be closely monitored in diabetics treated with a hypoglycaemic agent and trandolapril, particularly when starting or increasing the dose of ACE inhibitor or in patients with impaired renal function.

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

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Mammalian Target of Rapamycin (mTOR) Inhibitors

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

Others

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide may increase the risk of leucopoenia, if used concomitantly with ACE inhibitors.

The effects of certain anaesthetics may be enhanced by ACE inhibitors.

As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

No pharmacokinetic interaction has been noted when GOPTEN was combined with digoxin, furosemide or nifedipine.

No modification of the anticoagulant properties of warfarin has been observed following simultaneous administration with GOPTEN.

No clinically significant interaction has been found between trandolaprilat (trandolapril active metabolite) and cimetidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Reproduction toxicity studies showed effects on renal development in offspring with increased incidence of renal pelvic dilation; this was seen at doses of 10 mg/kg/day and above in the rat but these changes did not affect the normal development of the offspring.

Fertility of male and female rats was unaffected following oral administration of trandolapril at doses of up to 100 mg/kg/day (600 mg/m^2/day), which is ca. 200 times the maximum clinical dose based on body surface area.

Use in Pregnancy

Pregnancy Category: D

As with all ACE inhibitors, GOPTEN should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with GOPTEN 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 mediation and further management.

The use of Trandolapril is contraindicated in pregnancy. Pregnancy should be excluded before start of treatment and avoided during treatment. There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models. Data however show that ACE inhibitors cross 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. As with all ACE inhibitors, GOPTEN must not be used in pregnancy.

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

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

Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion.

Use in Lactation

The use of GOPTEN is contraindicated in breastfeeding.

Ingestion of a single 10 mg dose of trandolapril in rats resulted in small amounts of trandolapril and its metabolites in breast milk. There is also evidence that other ACE inhibitors are excreted in rat milk, hence GOPTEN must not be given to nursing mothers. No information is available regarding the use of trandolapril during breastfeeding. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Ability to concentrate and react, and thus ability to drive or operate machinery, may be impaired due to the blood pressure lowering effects of ACE inhibitors. This may occur mainly during initiation of treatment, when changing over from other medication or during concomitant use of alcohol. Therefore after the first dose or subsequent increases in dose, it is not advisable to drive or operate machinery for several hours.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse events reported are usually mild to moderate. The type and frequency of adverse events reported for elderly patients are similar to those reported for young patients. Clinical studies did not reveal any adverse effects due specifically to GOPTEN except those believed to be a class effect due to ACE inhibition.

Patients with Hypertension

GOPTEN has been evaluated for safety in more than 1,900 patients with hypertension, including 448 treated for one year or more. 7.8% of these patients were at least 65 years old.

In long-term studies, 1,049 patients were exposed to GOPTEN, either alone or in combination with diuretics and/or calcium channel inhibitors, for a mean duration of 45 weeks. The most common adverse events (incidence > 1%) are detailed below:

	Incidence (n=1,049)	*Possibly/ probably related*	*Leading to discontinuation*
Body as a whole			
Asthenia	3.1%	2.1%	0.4%
Malaise	1.1%	0.5%	0.1%
Flu-like syndrome	2.4%	0%	0%
Digestive System			
Gastrointestinal pain	1.2%	0.1%	0.2%
Diarrhoea	1.1%	0.2%	0.1%
Nervous System			
Headache	4.9%	2.3%	0.8%
Dizziness	2.4%	1.7%	0.5%
Respiratory System			
Cough	4.8%	3.9%	1.3%
Bronchitis	3.9%	0.3%	0.3%
URTI	3.4%	0.2%	0.1%
Rhinitis	1.4%	0%	0%
Skin and Appendages			
Skin rash	1.2%	0.4%	0.2%
Urogenital System			
Urinary infection	1.5%	0%	0%

Less frequent adverse events (0.1 to 1%) possibly/probably related to treatment included:

Body as a whole:	abnormal feeling, abdominal pain
Cardiovascular System:	hypotension, palpitation, chest pain, syncope, tachycardia, arrhythmias, angina pectoris, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage, angioedema
Digestive System:	nausea, gastrointestinal disorder, vomiting, constipation, dry mouth
Metabolic and Nutritional Disorders:	gout
Musculoskeletal System:	cramps
Nervous System:	depression, insomnia, libido decreased, paraesthesia, somnolence
Respiratory System:	dyspnoea
Skin and Appendages:	non-specific skin disorder, pruritus
Urogenital System:	impotence, deterioration of renal function, acute, renal failure
Hepatic:	There have been reports of individual incidents of cholestatic jaundice, hepatitis, pancreatitis and ileus connected with the use of ACE inhibitors.
Hypersensitivity:	Allergic hypersensitivity reactions such as pruritus and rash have been reported. Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences and alopecia, which may be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA (anti-nuclear antibody) titres have been occasionally reported with ACE inhibitor treatment.

In very rare cases, angioedema has occurred (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients with Acute Myocardial Infarction (TRACE study)

Adverse reactions related to GOPTEN occurring at a rate greater than that observed in placebo-treated patients with left ventricular dysfunction are shown below in Table 1. The incidences represent the experiences from the TRACE study. Despite the use of a forced titration regimen to ensure that the highest possible dose (to a maximum of 4 mg) was used, observed reactions were those normally seen with ACE inhibitors. The follow up time was between 24 and 50 months for this study.

Table 1:

Placebo-Controlled (TRACE) Mortality Study		
Adverse Event	**Trandolapril N=876**	**Placebo N=873**
Cough	35	22

Placebo-Controlled (TRACE) Mortality Study		
Adverse Event	**Trandolapril N=876**	**Placebo N=873**
Dizziness	23	17
Hypotension	11	6.8
Elevated serum uric acid	15	13
Elevated BUN	9.0	7.6
PTCA or CABG	7.3	6.1
Dyspepsia	6.4	6.0
Syncope	5.9	3.3
Hyperkalaemia	5.3	2.8
Bradycardia	4.7	4.4
Hypocalceamia	4.7	3.9
Myalgia	4.7	3.1
Elevated creatinine	4.7	2.4
Gastritis	4.2	3.6
Cardiogenic shock	3.8	<2
Intermittent claudication	3.8	<2
Stroke	3.3	3.2
Asthenia	3.3	2.6

Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

The listed ADRs in Table 2 have been reported during the clinical phase, the post-marketing surveillance or the phase IV clinical trials.

The following convention is used for the frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). When frequency cannot be estimated from the available data, category frequency: Not known (cannot be estimated from the available data) applies

Table 2:

MedDRA System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Upper respiratory tract infection	Bronchitis Urinary tract infection Pharyngitis		
Blood and lymphatic system disorders			Anaemia Leukopaenia Platelet disorder White blood cell disorder		Agranulocytosis Pancytopenia Platelet count decreased

MedDRA System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders			Allergic hypersensitivity reactions including pruritus and rash		
Metabolism and nutrition disorders			Anorexia Increased appetite Hyperlipidaemia Hypercholesterolemia Hyperglycaemia Hyponatraemia Hyperuricaemia Gout Enzyme abnormality		Hyperkalaemia
Psychiatric disorders		Insomnia Libido decreased	Depression Hallucinations Anxiety Agitation Apathy Sleep disorder		
Nervous system disorders	Headache Dizziness	Somnolence	Cerebrovascular accident Syncope Migraine Migraine without aura Paraesthesia Dysgeusia Myoclonus		Transient Ischaemic Attack Cerebral haemorrhage Balance disorder
Eye disorders			Visual impairment Blepharitis Conjunctional oedema Eye disorder		
Ear and labyrinth disorders		Vertigo	Tinnitus		
Cardiac disorders		Palpitations	Myocardial infarction Myocardial ischaemia Tachycardia Ventricular tachycardia Bradycardia Cardiac failure Angina pectoris		Atrioventricular block Arrhythmia Cardiac arrest
Vascular disorders	Hypotension	Hot flush	Orthostatic hypotension Hypertension Angiopathy		

MedDRA System Organ Class	Common	Uncommon	Rare	Very rare	Not known
			Peripheral vascular disorder Varicose vein		
Respiratory, thoracic and mediastinal disorders	Cough	Upper respiratory tract inflammation Upper respiratory tract congestion	Dyspnoea Productive cough Pharyngeal inflammation Oropharyngeal pain Epistaxis Respiratory disorder		Bronchospasm
Gastrointestinal disorders		Nausea Diarrhoea Constipation Gastrointestinal pain Gastrointestinal disorder	Vomiting Dyspepsia Gastritis Abdominal pain Dry mouth Hematemesis Flatulence		Pancreatitis Ileus
Hepatobiliary disorders			Hepatitis	Cholestasis	Jaundice Liver function tests abnormal
Skin and subcutaneous tissue disorders		Rash Pruritis	Angioedema Hyperhidrosis Psoriasis Eczema Acne Dry skin Skin disorder	Psoriasis Dermatitis	Alopecia Sweating Stevens-Johnson syndrome Toxic epidermal necrolysis Urticaria
Musculoskeletal and connective tissue disorders		Muscle spasm Back pain Pain in extremity	Arthralgia Osteoarthritis Bone pain		Myalgia
Renal and urinary disorders			Pollakiuria Polyuria Renal failure Azotemia		
Reproductive system and breast disorders		Erectile dysfunction			
Congenital, familial and genetic disorders			Congenital arterial malformation Ichthyosis		
General disorders and administration site conditions	Asthenia	Chest pain Oedema peripheral Malaise Feeling abnormal	Oedema Fatigue		Pyrexia

MedDRA System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Investigations			Hyperbilirubinemia	Blood potassium increased Gamma-glutamyl transferase increased Lipase increased Immunoglobulin increased	Platelet count decreased Blood creatinine increased Blood urea increased Blood lactate dehydrogenase increased Blood alkaline phosphatase increased Aspartate aminotransferase increased Alanine aminotransferase increased Hepatic enzymes (including SGOT and SGPT) increased Decreased haemoglobin Decreased haematocrit Electrocardiogram abnormal
Injury, poisoning and procedural complications			Injury		

The following adverse events shown below in Table 3 have been reported with ACE inhibitors as a class:

Table 3:

Body System	Adverse Event
Infections and Infestations	Sinusitis Rhinitis Glossitis
Blood and lymphatic system Disorders	Pancytopenia Haemolytic anaemia
Skin and subcutaneous tissue disorders	Erythema multiforme Dermatitis psoriasiform
Gastrointestinal disorders	Intestinal angioedema
Psychiatric disorders	Confusional state
Eye disorders	Vision blurred

Reporting Suspected Adverse Effects

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

4.9 OVERDOSE

In clinical trials doses of up to 16 mg have been administered and were well tolerated. There is no experience with overdosage. Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance, renal failure, hyperventilation, tachycardia, palpitations, dizziness, anxiety, and cough. In the event of overdosage following recent ingestion, consideration should be given to emptying the stomach contents. Blood pressure should be monitored and if hypotension develops, volume expansion should be considered. There is no specific antidote for trandolapril overdose.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

GOPTEN is an orally active angiotensin converting enzyme (ACE) inhibitor. It is administered as a pro-drug (trandolapril) which is rapidly converted to its biologically active metabolite trandolaprilat: a compound which binds tightly to, and dissociates slowly from, ACE. There is evidence that trandolapril itself has a marked affinity for angiotensin converting enzyme, and may therefore have an antihypertensive effect.

Angiotensin converting enzyme is a peptidyl-dipeptidase which catalyses the transformation of angiotensin I to vasoconstrictive angiotensin II and the degradation of bradykinin to inactive fragments. By potently inhibiting converting enzyme at very low concentrations, GOPTEN decreases angiotensin II production and causes a reduction in aldosterone secretion and an increase in plasma renin activity by suppressing negative feedback.

GOPTEN thus modulates the renin-angiotensin-aldosterone system that plays a major part in regulating blood volume and blood pressure.

Other mechanisms of action that may be related to the vasodilator activity of converting enzyme inhibitors include inhibition of the degradation of bradykinin, prostaglandin release and a decrease in sympathetic nervous system activity.

The decrease in peripheral resistance induced by GOPTEN reduces systolic and diastolic blood pressure. There is a marked reduction of both supine and erect blood pressure. The decrease is not accompanied either by water and sodium retention or tachycardia. The antihypertensive activity of GOPTEN is independent of plasma renin levels.

GOPTEN is highly lipophilic compared with other ACE inhibitors (trandolaprilat > ramiprilat > perindoprilat > enalaprilat > captopril), allowing high tissue penetration.

Recent data show that renin and angiotensin are locally generated in many organ tissues involved in cardiovascular regulation. This implies that angiotensin II does not only act as a circulating hormone but also as a locally generated modulator of organ function at the tissue level and may play an important role in the tonic control of vascular resistance, and cardiac and renal functions.

Studies with rats show that GOPTEN inhibits plasma and tissue (particularly vascular, renal, cardiac and adrenal) ACE.

Inhibition of ACE activity in tissues with subsequent local reduction of angiotensin II generation may significantly contribute to the antihypertensive effect of ACE inhibitors and is important for effective treatment of hypertension and its consequences. GOPTEN's affinity for the tissue isoenzyme may be the basis of the regression of cardiac and vascular hypertrophy and improvement in vascular compliance observed in rats.

Hypertension is associated with significant changes in arterial wall functions due to the increase in thickness of the tunica media caused by hypertrophy and hyperplasia of the smooth muscle cell and in collagen network density. A number of animal studies have shown that GOPTEN treatment significantly regressed vascular hypertrophy of the aorta, the femoral artery and the mesenteric artery. Marked regression in left ventricular hypertrophy has also been noted.

Other animal studies have demonstrated a total inhibition of induction by angiotensin I of several cardiac and vascular growth signals (the c-fos and c-myc oncogenes and the stress protein HSP 68) and rectification of the V3/V1 myosin ratio.

Animal studies on renal function have shown an increase in urine flow and sodium and chloride excretion. GOPTEN was shown to cause a regression of renal hypertrophy.

In man, GOPTEN's antihypertensive activity appears one hour after administration and persists for greater than 24 hours without modifying the circadian rhythm of blood pressure. The antihypertensive activity continues without the appearance of acquired tolerance in long-term treatment. There is no rebound effect on discontinuation of treatment.

GOPTEN has a sustained effect on blood pressure. Comparing the fall in blood pressure at the steady state trough level of trandolaprilat (ie. at 24 hours, immediately before the next dose) with that at the steady state peak level, the trough/peak ratio is almost 100% for a 24 hour period and approximately 70 - 80% for a 48 hour period after a dose. Thus, at steady state, the antihypertensive effect of GOPTEN is maintained for up to 48 hours after a dose. GOPTEN is, however, administered as a single daily dose to achieve and maintain effective steady state levels.

Combinations with hydrochlorothiazide or nifedipine produced further falls in blood pressure without increasing adverse events.

In a long-term clinical study involving hypertensive patients with abnormal fasting glucose levels and/or diabetes mellitus, and hypertensive patients without signs of glucose intolerance, GOPTEN produced a similar efficacy level and incidence of side effects in both groups. No cases of hypoglycaemia were reported.

The study also included hypertensive patients who were overweight (> 130% of ideal weight at baseline). In comparison with patients of normal weight, no significant differences in efficacy or the incidence of side effects were observed during GOPTEN therapy.

The same study also included hypertensive patients with elevated serum creatinine and patients with normal creatinine levels. Efficacy and the incidence of side effects produced by GOPTEN were similar in both groups.

In studies in spontaneously hypertensive (SH) rats or in other rat studies of cardiac failure secondary to myocardial infarction (eg ligation of left coronary artery, doxorubicin hydrochloride induced impairment of cardiac function, pacing induced cardiac failure), trandolapril showed a beneficial effect on cardiac failure.

The beneficial effects included reduction of cardiac hypertrophy and myocardial fibrosis, normalisation of cardiac reserve, improved left ventricular end diastolic pressure (LVEDP) etc. The ultimate demonstration of efficacy in cardiac failure, however, would depend upon clinical data.

Clinical Trials

TRACE study (TRAndolapril Cardiac Evaluation study)

In a multicentre, double blind, placebo controlled, parallel group study conducted in 27 centres in Denmark, 1,749 patients (GOPTEN = 876 patients; placebo = 873 patients) with left ventricular dysfunction (LVD) following myocardial infarction (MI) were studied. Subjects with residual ischaemia or overt heart failure were included. The LVD was measured by standard echocardiographic examination and patients with a wall motion index (WMI) of ≤ 1.2 (corresponding to a LV ejection fraction of approximately 35%) were eligible for entry into the study.

GOPTEN or placebo was started between days 3 and 7 after MI. After administration of a test dose of 0.5 mg, the medication (GOPTEN 1 mg or placebo) was started. Patients were given the highest tolerated dose of GOPTEN (up to a maximum of 4.0 mg daily). The duration of follow-up was 24 to 50 months. Results of the TRACE study are presented below in Table 4:

Table 4:

Endpoints	GOPTEN	Placebo	Statistical significance
Primary			
Total mortality	304/876 (34.7%)	369/873 (42.3%)	P=0.001 R.R*=0.78 (95% CI 0.67-0.91)
Secondary			
Cardiovascular mortality	226/876 (25.8%)	288/873 (33%)	P=0.001 R.R*=0.74 (95% CI 0.63-0.89)
Sudden death	105/876 (12%)	133/873 (15.2%)	P=0.03 R.R*=0.7 (95% CI 0.58-0.97)
Re-infarction (fatal and non-fatal)	99/876 (11.3%)	113/873 (12.9%)	P=0.29 (N.S) R.R*=0.86 (95%CI 0.66-1.13)
Progression to severe congestive heart failure	125/875 (14.3%)	171/872 (19.6%)	P=0.003 R.R*=0.7 (95% CI 0.56-0.89)

*R.R= relative risk

The long-term use of GOPTEN was associated with a reduction in all-cause mortality (22%), largely cardiovascular mortality. GOPTEN was also associated with a 29% reduction in risk to progression of heart failure.

The beneficial effect of GOPTEN on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction was not affected by concomitant administration of thrombolytics, aspirin, heparin, beta-blockers, calcium-channel blockers, nitrates, diuretics or digoxin.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Trandolapril is very rapidly absorbed after oral administration and achieves its peak plasma level at 30 minutes after administration. Trandolapril disappears rapidly from plasma with a half-life of less than one hour, being non-specifically hydrolysed to its potent, long-acting, active metabolite, trandolaprilat. The peak plasma concentration of trandolaprilat is achieved after 4 to 6 hours.

The absolute bioavailability of trandolaprilat is 40 - 60% after administration of GOPTEN capsules.

While food intake delays T_{max} from 0.5 to 2 hours for trandolapril and from 6 to 8 hours for trandolaprilat, there is no significant clinical alteration in the other aspects of their pharmacokinetics and pharmacodynamics. Since there is no clinically significant effect of food on the absorption of GOPTEN, the capsules may be taken before, during, or after a meal.

Distribution

Protein binding of trandolapril and trandolaprilat are 80% and 94% respectively. Trandolaprilat binds with a high affinity to converting enzyme. The major proportion of circulating trandolaprilat is also non-saturably bound to albumin.

After repeated administration of GOPTEN in single daily doses, steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. At a dose regimen of 2 mg once daily, minimum plasma concentrations, as measured just prior to the next dose, were 1.9 ng/ml.

Excretion

The effective elimination half-life of trandolaprilat is 22 hours.

Trandolaprilat eliminated in the urine in unchanged form accounts for 15% of the dose of trandolapril administered. After oral administration of radio-labelled product to man, 33% of the radioactivity was found in urine and 66% in faeces.

Heart Failure

There are no noteworthy differences in the pharmacokinetics of trandolapril and trandolaprilat as compared to other patient groups. The rate of absorption and clearance remains unchanged with T_{max} = 30 minutes and half-life less than one hour. Steady state is reached on the fourth day without further accumulation, and inhibition of the angiotensin converting enzyme is maintained at the same level under continuous treatment.

Effect of Race

Ethnic differences: In black patients, ACE inhibitors are less effective in lowering blood pressure than in white patients.

Effect of Gender and Advanced Age

Trandolapril pharmacokinetics have been investigated in the elderly (>65 years) and in both genders. The plasma concentration of trandolapril is increased in elderly hypertensive patients. The pharmacokinetics of trandolapril and trandolaprilat and inhibition of ACE activity are similar in male and female elderly hypertensive patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Trandolapril had no mutagenic or clastogenic activity in a standard battery of tests.

Carcinogenicity

At least one ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in man is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign. No carcinogenic effect has been noted with long term rat (24 months up to 8 mg/kg/day) or mice (18 months up to 25 mg/kg/day) studies with trandolapril.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each capsule also contains the following inactive ingredients: lactose monohydrate, maize starch, povidone and sodium stearylfumarate in a gelatin capsule (which contains gelatin, titanium dioxide, sodium lauryl sulfate, iron oxide yellow and erythrosine. The 4 mg capsule also contains iron oxide black).

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

GOPTEN 0.5 mg, 1 mg and 2 mg capsules are available in PVC/PVDC/Al blister packs of 7, 10, 14, 15, 28 and 30 capsules. GOPTEN 4 mg capsules are available in PVC/PVDC/Al blister packs of 7 and 28 capsules.

Australian Register of Therapeutic Goods (ARTG)

AUST R 45456 – GOPTEN trandolapril 0.5mg capsule blister pack

AUST R 45455 – GOPTEN trandolapril 1 mg capsule blister pack

AUST R 45457 – GOPTEN trandolapril 2 mg capsule blister pack

AUST R 96969 – GOPTEN trandolapril 4 mg capsule blister pack

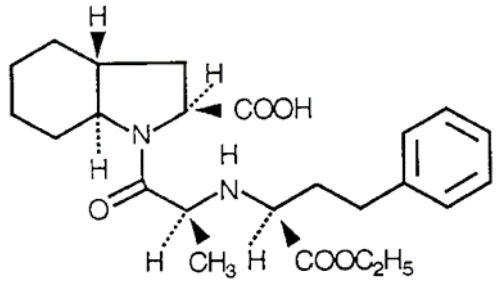
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

GOPTEN is trandolapril, a long acting, highly lipophilic, non-peptide, angiotensin converting enzyme (ACE) inhibitor with a carboxyl group but without a sulphydryl group. Trandolapril is a colourless, crystalline substance that is soluble in chloroform, dichloromethane and methanol. It is slightly soluble in water and sparingly soluble in hydrochloric acid.

Chemical Structure



Chemical Name

The chemical name is [2S-(1(R*(R*));2a, 3aa, 7ab)]-1-[2-[(1-(ethoxy-carbonyl)-3-phenylpropyl) amino]-1-oxopropyl] octahydro-1H-indole-2-carboxylic acid.

Chemical Formula

$C_{24}H_{34}N_2O_5$

CAS Number

87679-37-6

Molecular Weight

430.54

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

10/06/2004

10 DATE OF REVISION

21/09/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes

4.4	Added warning for delayed onset angioedema

GOPTEN® is a Viatris company trade mark

GOPTEN_pi\Sep26/00 (CCDS 23-Mar-2026)