AUSTRALIAN PRODUCT INFORMATION

PERISYL®

perindopril erbumine tablet

1 NAME OF THE MEDICINE

Perindopril erbumine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PERISYL tablet contains 2 mg, 4 mg or 8 mg of perindopril erbumine as the active ingredient.

Excipient with known effect: Sugars as lactose

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

3 PHARMACEUTICAL FORM

PERISYL 2 mg	Green coloured mottled, round, biconvex tablets debossed with "PT" over "2" on one side of the tablet & "M" on the other side.
PERISYL 4 mg	Green coloured mottled, capsule shaped, biconvex tablets with side notch, debossed with "PT4" on one side of the tablet & "M" on the other side.
PERISYL 8 mg	Green coloured mottled, round, biconvex tablets debossed with "PT8" on one side of the tablet & "M" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PERISYL is indicated for:

- the treatment of hypertension;
- the treatment of heart failure. In such patients it is recommended that perindopril be given with a diuretic and/or digoxin under close medical supervision. (The safety and efficacy of perindopril has not been demonstrated for New York Heart Association Category IV patients); and
- patients with established coronary artery disease (see Section 5.1 PHARMACODYNAMIC PROPERTIES) who are stable on concomitant therapy and have no heart failure, to reduce the risk of non-fatal myocardial infarction or cardiac arrest.

4.2 DOSE AND METHOD OF ADMINISTRATION

Hypertension

The usual starting dose of perindopril is 4 mg once daily, taken in the morning. Optimum control of blood pressure is achieved by increasing the dose, titrating it against the blood pressure to a maximum of 8 mg once daily.

A starting dose of 2 mg per day of perindopril is recommended in the following patients who may be at risk of ACE inhibitor-induced hypotension:

Combination with a Diuretic

The administration of perindopril to patients under current diuretic therapy may induce hypotension and sometimes, but more rarely, acute renal failure, at the beginning of the treatment. It is recommended to monitor plasma creatinine during the first month of treatment.

Elderly patients with hypertension

Elderly patients with hypertension should start treatment with 2 mg daily, with titration to 4 mg if necessary. It is recommended that renal function be assessed before starting treatment.

Other patients who may be at risk of ACE inhibitor-induced hypotension

Patients with renovascular hypertension, salt and/or volume depletion, or cardiac decompensation may have a strongly activated renin-angiotensin-aldosterone system. These patients may experience an excessive drop in blood pressure following the first dose of an ACE inhibitor.

Congestive Heart Failure

Treatment of congestive heart failure with perindopril should be initiated under close medical supervision.

2 mg is the usual starting dose, which should be given with a diuretic and/or digitalis. This is increased to 4 mg daily for maintenance.

Patients with severe hepatic or renal impairment and/or severe salt/volume depletion are particularly sensitive to ACE inhibitors. Doses in these patients should be carefully titrated as no pharmacokinetic and dose titration studies have been conducted.

Reduction of risk of cardiovascular events

For stable coronary artery disease, perindopril should be introduced at a dose of 4 mg once daily for two weeks, and then increased to 8 mg once daily, depending on tolerance and renal function.

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on tolerance and renal function (see Table 1 under Patients with Renal impairment heading).

Elderly Patients

Renal insufficiency is commonly observed in elderly people. Care should therefore be taken when prescribing perindopril to elderly patients. The initial dose of perindopril should always be 2 mg daily and patients should be monitored closely during the initial stages of treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Particular care should be taken in elderly patients with congestive heart failure who have renal and/or hepatic insufficiency.

Patients with Renal Impairment

In patients with renal failure, treatment should begin with 2 mg daily. Dosage should be adjusted as indicated below (see Table 1) according to creatinine clearance. Creatinine and potassium levels should be closely monitored.

Table 1: Dose adjustment according to creatinine clearance

Creatinine Clearance (mL/min)	**Dosage**

Between 30 and 60	2 mg daily
Between 15 and 30	2 mg every 2 days
Below 15	2 mg on day of dialysis [Perindopril is dialysable (70 mL/min)]

Patients with Hepatic Impairment

The small changes in the kinetics of perindoprilat do not justify the need to change the usual dosage in most patients with hepatic failure (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Food

Food intake may reduce hepatic biotransformation of perindopril to perindoprilat. Whilst this effect has not been shown to be clinically significant, it is recommended that perindopril should be taken before meals.

4.3 CONTRAINDICATIONS

PERISYL is contraindicated:

- in patients with a history of previous hypersensitivity to the active ingredient perindopril or any of the excipient ingredients present in PERISYL
- during pregnancy and for lactating women
- in patients with bilateral or unilateral renal artery stenosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- in patients with a history of hereditary and/or idiopathic angio-oedema or angio-oedema associated with previous ACE inhibitor treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- in patients receiving extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile membranes such as "AN69") and low density lipoprotein apheresis with dextran sulfate due to increased risk of severe anaphylactoid reactions following treatment with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive medicines or alternative membranes [e.g. cuprophane or polysulfone (PSF)] (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- combined use with aliskiren-containing products in patients with diabetes or renal impairment (GFR < 60 mL/min/1.73 m²) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- combined use with sacubitril/valsartan fixed dose combinations- perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Precautions

Hyperkalaemia

Since ACE inhibitors reduce angiotensin II formation resulting in decreased production of aldosterone, an increase in serum potassium may be observed in some patients treated with ACE inhibitors including perindopril. The effect is usually not significant in patients with normal renal function. Serum electrolytes (including sodium potassium and urea) should be measured from time to time when ACE inhibitors are given and especially in combination with diuretics.

Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and combined use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, other ACE inhibitors, angiotensin receptor blocker, aspirin ≥ 3 g/day, COX-2 inhibitors and other non-selective NSAIDS, immunosuppressant agents such as ciclosporin or tacrolimus, co-trimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. Potassium-sparing diuretics and angiotensin receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. Combined use of the above-mentioned medicines should be used with caution in combination with ACE inhibitors. Frequent monitoring of serum potassium is needed (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). In some patients hyponatraemia may co-exist with hyperkalaemia.

Patients with diabetes

Glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor in patients with diabetes treated with oral medicines or insulin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Lithium

The combination of lithium and perindopril is generally not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Potassium sparing medicines, potassium supplements or potassium-containing salt substitutes

The combination of perindopril and potassium sparing medicines, potassium supplements or potassium-containing salt substitutes is generally not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Angioedema

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see Section 4.3 CONTRAINDICATIONS).

Life-threatening angioedema has been reported with most ACE inhibitors. The overall incidence is approximately 0.1-0.2%. The aetiology is thought to be non-immunogenic and may be related to accentuated

bradykinin activity. Usually the angioedema is non-pitting oedema of the skin mucous membrane and subcutaneous tissue.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors and has been reported uncommonly with perindopril [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. This may occur at any time during treatment. In such cases perindopril should be promptly discontinued and the patient carefully observed until the swelling disappears. Where such cases have been described with other ACE inhibitors and swelling has been confined to the face and lips, the condition has generally resolved without treatment although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal or near fatal. In most cases symptoms occurred during the first week of treatment and the incidence appears to be similar in both sexes or those with heart failure or hypertension.

Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate treatment (e.g. adrenaline (epinephrine) and oxygen) should be given promptly. Treatment of progressive angioedema should be aggressive and failing a rapid response to medical treatment, mechanical methods to secure an airway should be undertaken before massive oedema complicates oral or nasal intubation.

Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

The onset of angioedema associated with use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals.

Angioedema may occur with or without urticaria.

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 facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, 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.

ACE inhibitors should not be reintroduced in patients who have a history of angioedema due to rare reports of recurrence.

The combined use of perindopril with sacubitril/valsartan fixed dose combinations is contraindicated due to the increased risk of angioedema (see Section 4.3 CONTRAINDICATIONS). Sacubitril/valsartan fixed dose combinations must not be initiated until 36 hours after taking the last dose of perindopril. If treatment with sacubitril/valsartan fixed dose combinations is stopped, perindopril must not be initiated until 36 hours after the last dose of sacubitril/valsartan fixed dose combination (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The combined use of perindopril with NEP inhibitors, mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin, alogliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Caution should be used when commencing treatment with these above-mentioned medicines in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis and haemodialysis

Rarely, patients treated with ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis. Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, who are treated with an ACE inhibitor. Extracorporeal treatments leading to contact of blood with negatively charged surfaces (e.g. polyacrylonitrile membranes such as "AN69") are contraindicated. If such treatment is required, consideration should be given to using a different type of dialysis membrane (e.g. cuprophane or polysulfone (PSF)) or a different class of antihypertensive medicines (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Anaphylactic reactions during desensitisation

Patients treated with ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hypotension

Hypotension has been reported in patients commencing treatment with ACE inhibitors. Symptomatic hypotension is rarely seen in uncomplicated hypertension but is a potential consequence of perindopril use in patients with salt/volume depletion, for example, in patients vigorously treated with diuretics, in patients on dialysis, with impaired renal function, following severe diarrhoea or vomiting, in patients on dietary restrictions, or in those with severe renin-dependent hypertension [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Administration of perindopril 2 mg to patients with mild-moderate heart failure was not associated with any significant reduction in blood pressure. In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is more likely to occur in those patients with severe heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. This may be associated with syncope, neurological deficits, oliguria and/or progressive increase in blood nitrogen, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, treatment 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 dose is increased, or diuretic treatment is commenced or increased.

Patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident should be closely followed for the first two weeks of treatment and whenever the dose of perindopril and/or diuretic is increased. In all high-risk patients it is advisable to initiate treatment with perindopril 2 mg once daily.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This is anticipated and is usually not a reason to discontinue treatment. If symptomatic hypotension occurs, a reduction of dose or discontinuation of perindopril may be necessary.

If hypotension occurs the patient should be placed in a supine position and if necessary infused with normal saline. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty when blood pressure has increased following volume expansion.

Renovascular hypertension

If renovascular hypertension is also present treatment should be started under close medical supervision with low doses and careful dose titration. There is an increased risk of severe hypotension and renal insufficiency. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril treatment. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Kidney transplantation

There is no experience regarding the administration of perindopril in patients with a recent kidney transplantation.

Hepatic failure

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 treated with ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Ethnicity

ACE inhibitors cause a higher rate of angioedema in patients of indigenous African origin than in patients of other racial origin. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in people of indigenous African origin than in people of other racial origin, possibly because of a higher prevalence of low-renin states in this population. It is unknown if the same observations have been made in patients of indigenous Australian origin.

Cough

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 class-effect of ACE inhibitor treatment with the incidence of cough varying between 2-15% depending upon the medicine, dose 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 two thirds 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, which 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.

Proteinuria

Perindopril treatment has occasionally been associated with mild or transient proteinuria (<1 gram/per 24 hours). However in the majority of patients with pre-existing proteinuria treated with perindopril, proteinuria disappeared or remained stable. ACE inhibitors have a real potential to delay the progression of nephropathy in diabetic as well as hypertensive patients.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease,

immunosuppressant treatment, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing renal impairment. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Dermatological Reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity have been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome etc) have been reported following administration of perindopril and may therefore occur. A causal relationship is 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)

Taste disturbances were reported to be common (prevalence up to 12.5%) with high doses of one ACE inhibitor. The actual incidence of taste disturbance is probably low (<0.5%) but data are scarce and difficult to interpret. Taste disturbances with ACE inhibitors have been described as suppression of taste or a metallic sensation in the mouth. Dysgeusia usually occurs in the first weeks of treatment and may disappear in most cases within 1-3 months.

Medicines Causing Renin Release

The effects of perindopril may be enhanced by concomitant administration of antihypertensive agents which cause renin release.

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

As a consequence of inhibiting the RAAS, hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicines that affect this system. Dual blockade of the RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). If dual blockade therapy is considered absolutely necessary, this should be limited to individually defined cases under specialist supervision with frequent close monitoring of renal function, electrolytes and blood pressure. The combination of perindopril with aliskiren is contraindicated in patients with diabetes or renal impairment (GFR < 60 mL/min/1.73 m²) (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). ACE inhibitors and angiotensin receptor blockers should not be used in combination in patients with diabetic nephropathy.

Surgery and Anaesthesia

Perindopril may block angiotensin II formation secondary to compensatory renin release in patients undergoing major surgery or during anaesthesia with agents that produce hypotension and cause further reduction in blood pressure. Treatment should be discontinued one day prior to the surgery. Perioperative hypotension can be corrected with volume expansion.

Aortic or mitral valve stenosis/Hypertrophic cardiomyopathy

There has been some concern on theoretical grounds that patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or with hypertrophic cardiomyopathy 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.

Stable coronary artery disease

If an episode of unstable angina pectoris, regardless of severity, occurs during the first month of perindopril treatment, a careful appraisal of the benefits/risks of continuing treatment should be performed.

Lactose intolerance

Perindopril tablets contain lactose. Patients with an intolerance to lactose, rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Primary aldosteronism

Patients with primary hyperaldosteronism will generally not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, treatment with perindopril is not recommended.

Use in Hepatic Impairment

Biotransformation of perindopril to perindoprilat mainly occurs in the liver. Studies in patients with hepatic impairment have shown that kinetic parameters of perindopril were not modified by hepatic failure. With the exception of bioavailability, which was increased, kinetic parameters of perindoprilat (including T_{max}) were also unchanged. The increase in bioavailability could be due to inhibition of the formation of perindopril metabolites other than perindoprilat (see Section 5.2 PHARMACOKINETIC PROPERTIES). The administration of perindopril leads to the formation of a glucuronoconjugate derivative of perindoprilat by a hepatic first-pass effect. The kinetic parameters of perindoprilat glucuronide are not modified by hepatic failure. The small changes in the kinetics of perindoprilat do not justify the need to change the usual dosage in most patients with hepatic failure.

Use in Renal Impairment

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

In patients with symptomatic heart failure, hypotension following the initiation of treatment with ACE inhibitors may lead to further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis (see Section 4.3 CONTRAINDICATIONS).

In clinical studies in patients with hypertension with unilateral or bilateral renal artery stenosis, increases in blood urea, nitrogen and serum creatinine were observed in 20% of patients. Acute renal insufficiency may also occur. These increases are usually reversible upon discontinuation. Renal function may also be reduced 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. ACE inhibitors can lead to the thrombotic occlusion of a stenosed renal artery.

Some patients with hypertension and with no apparent pre-existing renovascular disease have developed increases in blood urea, nitrogen and serum creatinine, which are usually minor and transient, particularly when perindopril has been given in combination with a diuretic. However, increases in blood, urea nitrogen and serum creatinine are more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dose reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Renal function should always be assessed (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). In the case of renal impairment, the initial perindopril dose should be adjusted according to the patient's creatinine clearance (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Routine monitoring of potassium and creatinine are part of normal medical practice for these patients [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. If 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.

Some ACE inhibitors 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 (NSAID).

Perindopril is dialysable with a clearance of 70 mL/min.

Use in the Elderly

Renal insufficiency is commonly observed in elderly people. Care should therefore be taken when prescribing perindopril to elderly patients. The initial dose of perindopril in the elderly should always be 2 mg daily and patients should be monitored closely during the initial stages of treatment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). In a study of 91 elderly patients with a mean age of 71.9 years, a 6% increase in serum potassium occurred in the first month of treatment and subsequently remained stable. There was no change in the group in blood urea, creatinine or creatinine clearance. Particular care should be taken in elderly patients with congestive heart failure who have renal and/or hepatic insufficiency.

Paediatric Use

Use of perindopril in children is not recommended as no data establishing safety or effectiveness in children are available.

Effects on Laboratory Tests

Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 higher frequency of adverse events such as 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, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.1 PHARMACODYNAMIC PROPERTIES).

Combined use which is CONTRAINDICATED (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Aliskiren

Patients with diabetes or renal impairment (GFR < 60 mL/min/1.73 m²), may be at risk of hypotension, syncope, stroke, hyperkalaemia and changes in renal function (including acute renal failure).

Extracorporeal treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile membranes such as "AN69") and low density lipoprotein apheresis with dextran sulfate are contraindicated due to increased risk of severe anaphylactoid reactions (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If such treatment is required, consideration should be given to using a different type of dialysis membrane [e.g. cuprophane or polysulfone (PSF)] or a different class of antihypertensive agent.

Sacubitril/Valsartan

The combined use of perindopril with sacubitril/valsartan fixed dose combinations is contraindicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan fixed dose combinations must not be started until 36 hours after taking the last dose of perindopril. Perindopril must not be started until 36 hours after the last dose of sacubitril/valsartan fixed dose combination (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Combined use NOT RECOMMENDED (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Aliskiren

Patients other than those with diabetes or renal impairment may be at risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity, and an increase in mortality (see Section 4.3 CONTRAINDICATIONS).

ACE inhibitor and angiotensin receptor blocker

It is reported in the literature that in patients with established atherosclerosis, heart failure, or diabetes with end organ damage, combined use with an ACE inhibitor and an angiotensin receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single RAAS agent. Dual blockade (e.g, by combining an ACE inhibitor with an angiotensin receptor blocker) should be limited to individually defined cases with close monitoring of renal function, serum potassium, and blood pressure.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients on combined treatment with co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk of hyperkalaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during combined use of lithium with ACE inhibitors. Combined use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination is necessary, careful monitoring of serum lithium levels should be performed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Potassium-sparing diuretics (e.g. triamterene, amiloride, potassium salts)

The combined use of perindopril and potassium-sparing diuretics may result in potentially lethal hyperkalaemia especially in patients with renal impairment (additive hyperkalaemic effects). The combination of perindopril with the above-mentioned medicines is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If the combination is required, it should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone and eplerenone in heart failure, see paragraph under 'Combined use which requires SPECIAL CARE'.

Combined use which requires SPECIAL CARE:

Medicines to treat diabetes (e.g. insulin, oral hypoglycaemic medicines)

Reported with captopril and enalapril. ACE inhibitors may add to the glucose lowering effect, with risk of hypoglycaemia, in patients with diabetes who are treated with insulin or with oral hypoglycaemic medicines. Hypoglycaemia is very rare and appears to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Baclofen

Baclofen may increase the antihypertensive effect of perindopril. Monitor blood pressure and adjust the dose of perindopril if necessary.

Non-potassium-sparing diuretics

Patients treated with diuretics, especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of treatment with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, or by increasing volume or salt intake prior to commencing treatment with low and progressive doses of perindopril. If it is not possible to discontinue the diuretic, the starting dose of the ACE inhibitor should be reduced. The patient should be closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised. In arterial hypertension, when prior diuretic treatment has caused salt/volume depletion, the diuretic must be discontinued before commencing treatment with the ACE inhibitor. A non-potassium-sparing diuretic can then be reintroduced, or the ACE inhibitor be commenced at a low dose and progressively increased. In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dose, possibly after reducing the dose of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor treatment.

Potassium-sparing diuretics (eplerenone, spironolactone)

As the combination of perindopril and potassium-sparing medicines (e.g eplerenone and spironolactone), potassium supplements or potassium-containing salt substitutes is general not recommended:

- Ensure patients do not have hyperkalaemia or renal impairment before commencing treatment with this combination.
- There is a risk of potentially lethal hyperkalaemia with this combination in patients treated for NYHA Class II-IV heart failure with a reduced ejection fraction, who have been previously treated with ACE inhibitors and loop diuretics. This risk is particularly high when recommendations for use of this combination have not been followed.
- Weekly monitoring of serum potassium and creatinine levels is recommended in the first month of the treatment and, monthly thereafter.

Non-steroidal anti-inflammatory drugs including aspirin ≥ 3 g/day

Medicines with prostaglandin synthetase inhibitor properties (e.g. indometacin) or an NSAID (i.e. aspirin at anti-inflammatory dose regimens, non-selective NSAIDs or COX-2 inhibitors) may diminish the antihypertensive efficacy of concomitantly-administered ACE inhibitors. However, clinical studies have not demonstrated any interaction between perindopril or indometacin or other non-steroidal anti-inflammatory drugs. Combination use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after commencing treatment with the combination, and periodically thereafter.

Ciclosporin

Hyperkalaemia may occur during the combined use of ACE inhibitors with ciclosporin. Frequent monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during the combined use of ACE inhibitors with heparin. Frequent monitoring of serum potassium is recommended.

Combination use of ACE inhibitors, anti-inflammatory drugs and thiazide diuretics

The combined use of an ACE inhibiting drug (ACE inhibitor or angiotensin receptor blocker), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic increases the risk of renal impairment. This includes use in fixed-combination products. The combination of medicines from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at initiation.

Mammalian target of rapamycin (mTOR) inhibitor (e.g. temsirolimus, sirolimus, everolimus)

Patients on combined treatment with an ACE inhibitor and an mTOR inhibitor may be at increased risk of angioedema (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin, alogliptin)

When an ACE inhibitor and a gliptin are used in combination, there is an increased risk of angioedema due to the decreased activity of the dipeptidyl peptidase IV (DPP-IV).

Combined use which requires SOME CARE:

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 including perindopril.

Antihypertensive medicines and vasodilators

Combined use of these medicines may increase the hypotensive effects of perindopril. Combined use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Tetracycline and other drugs that interact with magnesium

The simultaneous administration of tetracycline with an ACE inhibitor may significantly reduce the absorption of tetracycline, possibly due to the magnesium content in the ACE inhibitor tablets. This interaction should be considered if co-prescribing an ACE inhibitor and tetracycline or other drugs that interact with magnesium.

Medicines Affecting Sympathetic Activity

As the sympathetic nervous system plays an important part in physiological blood pressure regulation, caution should be exercised with combined administration of a medicine with sympathetic activity and perindopril. Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Tricyclic antidepressants/Antipsychotics/Anaesthetics

Combined use of certain anaesthetics, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies in rats showed no impairment of male or female fertility at oral perindopril erbumine doses up to 10 mg/kg/day.

Use in Pregnancy

Australian Pregnancy Categorisation: D

The use of ACE inhibitors is contraindicated during pregnancy (see Section 4.3 CONTRAINDICATIONS).

As with all ACE inhibitors, perindopril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with perindopril and avoided during the treatment. Unless continued treatment with an ACE inhibitor is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. 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.

Perindopril or its metabolites have been shown to cross the placenta and distribute to the foetus in pregnant animals. 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*.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. A historical cohort study in over 29,000 infants born to mothers without diabetes has shown 2.7 times higher risk for congenital malformations in infants exposed to ACE inhibitors during the first trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of foetal and neonatal toxicity: hypotension, hyperkalaemia, renal failure, skull hypoplasia, oligohydramnios 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. Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion.

Use in Lactation

Animal studies have shown that perindopril and its metabolites are excreted in milk during lactation, but there are no human data. It is therefore recommended that perindopril should not be given to lactating women as the possible effect on the newborn is unknown. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The antihypertensive effect in individual cases may be symptomatic. Treatment with any blood pressure lowering agent may, therefore, affect the ability to drive, cross the road safely or operate machinery, especially at the start of treatment or when changing over from other preparations, or during combined use of alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety profile of perindopril is consistent with the safety profile of ACE inhibitors. The most frequent adverse events reported in clinical trials and observed with perindopril are: dizziness, headache, paraesthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, pruritis, rash, muscle cramps, and asthenia. The following adverse effects (see Table 2) have been observed during clinical trials and/or post-marketing use with perindopril are listed below ranked under the following frequency: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000 and including isolated reports).

Table 2: Adverse effects observed during clinical trials and/or post-marketing use with perindopril

ADVERSE EFFECTS (MedDRA System organ class)	Frequency
Blood and lymphatic system disorders	
Eosinophilia	Uncommon[#]
Agranulocytosis or pancytopenia	Very rare
Decreases in haemoglobin and haematocrit	Very rare
Leucopenia/neutropenia	Very rare
An unexplained change in prothrombin ratio was reported in one patient	Very rare
Haemolytic anaemia has been reported in patients with congenital G-6PDH deficiency (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Very rare
Thrombocytopenia	Very rare

ADVERSE EFFECTS (MedDRA System organ class)	Frequency
Endocrine disorders	
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare
Metabolism and nutrition disorders	
Hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)	Uncommon[#]
Hyperkalaemia, reversible on discontinuation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Uncommon[#]
Hyponatraemia	Uncommon[#]
Psychiatric disorders	
Depression	Uncommon[#]
Mood disturbances	Uncommon
Sleep disorders (insomnia, dream abnormality)	Uncommon
Nervous system disorders	
Dizziness	Common
Headache	Common
Paraesthesia	Common
Vertigo	Common
Drowsiness	Common
Somnolence	Uncommon[#]
Syncope	Uncommon[#]
Confusion	Very rare
Hallucinations	Very rare
Eye disorders	
Visual disturbance	Common
Ear and Labyrinth disorders	
Tinnitus	Common
Cardiac disorders	
Palpitations	Common
Tachycardia	Uncommon[#]
Angina pectoris (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Very rare
Arrhythmia	Very rare
Myocardial infarction possibly secondary to excessive hypotension in high risk patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Very rare
Vascular disorders	
Hypotension and effects related to hypotension	Common
Vasculitis	Common

ADVERSE EFFECTS (MedDRA System organ class)	Frequency
Flushing	Common
Impaired peripheral circulation	Common
Stroke possibly secondary to excessive hypotension in high risk patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Very rare
Raynaud's phenomenon	Not known
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Dyspnoea	Common
Epistaxis	Common
Discomfort on exertion	Common
Bronchospasm	Uncommon
Eosinophilic pneumonia	Very rare
Rhinitis	Very rare
Gastrointestinal disorders	
Abdominal pain	Common
Constipation	Common
Diarrhoea	Common
Dysgeusia	Common
Dyspepsia	Common
Nausea	Common
Vomiting	Common
Dry mouth	Uncommon
Pancreatitis	Very rare
Hepato-biliary disorders	
Hepatitis, either cytolytic or cholestatic (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Very rare
Skin and subcutaneous tissue disorders	
Pruritus	Common
Rash	Common
Urticaria (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Uncommon
Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Uncommon
Hyperhidrosis	Uncommon
Photosensitivity reactions	Uncommon[#]
Pemphigoid	Uncommon[#]
Eczema	Uncommon[#]
Psoriasis aggravation	Rare[#]
Erythema multiforme	Very rare
Musculoskeletal and Connective tissue disorders	
Muscle cramps	Common
Arthralgia	Uncommon[#]
Myalgia	Uncommon[#]
Renal and urinary disorders	
Renal insufficiency	Uncommon
Acute renal failure	Rare[#]
Anuria/Oliguria	Rare[#]
Reproductive system and Breast disorders	
Erectile dysfunction	Uncommon
General disorders and administration site conditions	
Asthenia	Common
Chest pain	Uncommon[#]
Malaise	Uncommon[#]

ADVERSE EFFECTS (MedDRA System organ class)	Frequency
Oedema peripheral	Uncommon[#]
Pyrexia	Uncommon[#]
Sweating	Uncommon
Atypical chest pain	Uncommon
Investigations	
Blood urea increased	Uncommon[#]
Blood creatinine increased	Uncommon[#]
Blood bilirubin elevation	Rare
Hepatic enzyme increases	Rare
Injury, Poisoning and Procedural Complications	
Fall	Uncommon[#]

[#] Frequency of these adverse events detected from spontaneous reports is calculated from clinical trial data.

Withdrawals

In total, 56 of 1275 patients (4.4%) studied stopped treatment because of adverse reactions. In a specific study of 632 patients in which 36 patients (5.7%) withdrew because of adverse events. A plausible or probable relationship with perindorpil treatment was considered to exist in 19 cases (3%).

Reporting Suspected Adverse Effects

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

4.9 OVERDOSE

Symptoms

Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Treatment

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. Perindopril may be removed from the general circulation by haemodialysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

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

Perindopril (prodrug), following hydrolysis to perindoprilat, inhibits angiotensin converting enzyme (ACE) both *in vitro* and *in vivo*. It is thought that ACE inhibitors reduce blood pressure by inhibiting the enzyme which catalyses the conversion of angiotensin I to angiotensin II. Decreased plasma angiotensin II leads to increased plasma renin activity and a decrease in aldosterone. In addition to its effects on circulating ACE, perindopril binds to and inhibits tissue converting enzyme, predominantly in the kidney and vascular wall.

The contribution of this mechanism to the overall antihypertensive effect of perindopril is unknown. Animal studies have demonstrated reversal of vascular hypertrophy and an improvement in the ratio of elastin to collagen in the vessel wall.

Studies in man have demonstrated an improvement in the visco-elastic properties of large vessels and in compliance. Studies in animals and humans suggest that specific and competitive suppression of the renin-angiotensin-aldosterone system (RAAS) is the main mechanism by which blood pressure is reduced. However, antihypertensive activity has also been observed in patients with low renin activity. Perindopril may also inhibit the degradation of the potent vasodepressor peptide, bradykinin, and this action may contribute to its antihypertensive action. Perindopril appears to reduce peripheral resistance and may influence arterial compliance.

Studies carried out in animal models of hypertension have shown that perindopril is a specific competitive angiotensin I converting enzyme inhibitor. The administration of perindopril to patients with essential hypertension results in a reduction in supine and standing blood pressure without any significant effect on heart rate. Abrupt withdrawal of perindopril has not been associated with a rebound rise in blood pressure. Single dose studies have demonstrated that peak inhibition of ACE activity and peak reduction in blood pressure occurs 4-6 hours after administration. The durations of these effects are dose related and at the recommended dose range, both effects have been shown to be maintained over a 24-hour period.

In haemodynamic studies carried out in animal models of hypertension, blood pressure reduction after perindopril administration was accompanied by a reduction in peripheral arterial resistance and improved arterial wall compliance. In studies carried out in patients with essential hypertension the reduction in blood pressure was accompanied by a reduction in peripheral resistance with no change, or a small increase in renal blood flow and no change in glomerular filtration rate. An increase in the compliance of large arteries was also observed. When perindopril is administered together with a thiazide-type diuretic, the antihypertensive activity of perindopril may be potentiated in some patients, and this effect is evident after four weeks of treatment. Perindopril, like other ACE inhibitors, may compensate for thiazide-induced hypokalaemia.

In one study of 48 patients in which low-dose perindopril (2 mg) was compared with correspondingly low doses of enalapril (2.5 mg) or captopril (6.25 mg) in patients with congestive heart failure, significantly different blood pressure responses were noted. Blood pressure fell significantly with captopril and enalapril following the first dose. However, whilst perindopril inhibited plasma ACE comparably with enalapril, the blood pressure changes were insignificant and similar to placebo for up to 10 hours of regular observation. Data regarding possibility of a late hypotensive response are not available for perindopril.

Clinical Trials

Patients with stable coronary artery disease

The effects of perindopril were compared to placebo in patients with stable coronary artery disease with no clinical signs of heart failure. The EUROPA (*EU*ropean trial on *R*eduction *O*f cardiac events with *P*erindopril in stable coronary *A*rtery disease) study was a multicentre, international, randomised, double blind, placebo-controlled clinical trial lasting 4 years. 12218 patients aged over 18 were randomised: 6110 patients to perindopril 8 mg and 6108 patients to placebo.

The primary endpoint was the composite of cardiovascular mortality, non-fatal myocardial infarction, and/or cardiac arrest with successful resuscitation.

The trial population had evidence of coronary artery disease documented by previous myocardial infarction at least 3 months before screening, coronary revascularisation at least 6 months before screening, angiographic

evidence of stenosis (at least 70% narrowing of one or more major coronary arteries), or positive stress test in men with a history of chest pain.

Study medication was added to conventional treatment, including medication used for the management of hyperlipidaemia, hypertension and diabetes mellitus. Patients randomised to perindopril were initiated on 2 or 4 mg doses of perindopril for 2 weeks, and then titrated up to 8 mg during the 2 following weeks. The 8 mg dose was then maintained for the whole duration of the study. If this dose was not well tolerated, it could be reduced to 4 mg once daily.

Most of the patients also received platelet inhibitors, lipid-lowering agents and beta-blockers. At the end of the study, the proportions of patients on these concomitant medications were 91%, 69% and 63% respectively.

The results of the EUROPA study, specifically the primary endpoint and its components (cardiovascular mortality, non-fatal myocardial infarction or resuscitated cardiac arrest) for the intention-to-treat (ITT) population are presented in Table 3.

Table 3 EUROPA study results (ITT population)[1]

	Perindopril (N-6110)	Placebo (N=6108)	Absolute Risk Reduction [95% CI]	NNT[2] over 4.2 year trial period (per year)	Relative Risk Reduction [95% CI]	P (log-rank)
Cardiovascular events (*Primary composite endpoint*)	488 (8.0%)	603 (9.9%)	1.9% [0.87; 2.90]	54 (227)	20% [9; 29]	0.0003
Primary endpoint component:						
Cardiovascular mortality	215 (3.5%)	249 (4.1%)	insignificant	-	14% [-3; 28]	0.107
Non-fatal MI[3]	295 (4.8%)	378 (6.2%)	1.4% [0.55; 2.17]	74 (311)	22% [10; 33]	0.001
Cardiac arrest with successful resuscitation	6 (0.1%)	11 (0.2%)	Insignificant	-	46% [-47; 80]	0.223
Secondary endpoints:						
Total mortality	375 (6.1%)	420 (6.9%)	insignificant	-	11% [-2; 23]	0.101
Non-fatal and fatal MI	320 (5.2%)	418 (6.8%)	1.6% [0.76; 2.44]	63 (265)	23.9% [12; 34]	< 0.001

Notes:
1. The EUROPA study was designed to have adequate statistical power to detect a treatment effect on the composite primary endpoint, and not for the individual components
2. NNT = Number of patients needed to be treated to prevent one event
3. MI = Myocardial Infarction

The reduction in the primary composite endpoint was mainly due to a reduction in the number of non-fatal myocardial infarctions. There was no significant reduction in the rate of cardiovascular mortality or total mortality in patients taking perindopril compared to those taking placebo.

After a mean follow-up of 4.2 years, treatment with perindopril 8 mg once daily resulted in a significant relative risk reduction of 20% (95% CI: 9-29) in the primary combined endpoint: 488 patients (8.0%) reported events in the perindopril group compared to 603 patients (9.9%) in the placebo group (p = 0.0003). Improvements in the primary composite endpoint achieved statistical significance after 3 years of continuous treatment on perindopril.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, perindopril is rapidly absorbed and is 61-85% bioavailable. Elimination is rapid, occurring predominantly via the urine. Plasma half-life is approximately 1 hour. Biotransformation of perindopril to the active metabolite perindoprilat is approximately 20%.

Distribution

Peak plasma concentrations of perindoprilat occur 3 to 4 hours after oral administration of perindopril and protein binding of perindoprilat is below 30%. When perindopril is administered chronically, steady-state perindoprilat concentration is reached within 4 days, and perindoprilat does not accumulate. The elimination of perindoprilat is reduced in elderly patients and in patients with cardiac and renal failure (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Metabolism

Apart from perindoprilat, the administration of perindopril leads to the formation of 5 other metabolites, all of which are inactive and exist in very low quantities. One of these is the glucuronoconjugate of perindoprilat, which is formed by a hepatic first pass effect. This effect does not appear to have any influence on the kinetics of perindoprilat. Food intake may reduce hepatic biotransformation to perindoprilat.

Excretion

Perindoprilat binds to plasma and tissue ACE, and free perindoprilat is eliminated through the urine. The elimination half-life of the free fraction is between 3 and 5 hours. The terminal half-life, which corresponds to the dissociation of perindoprilat from ACE, is approximately 25 to 30 hours.

Pharmacokinetic Results of the Bioequivalence Study

An open label, randomised, two-period, two treatment, two sequence, crossover, balanced, single dose comparative bioavailability study was conducted in adults under fasting conditions comparing the generic perindopril erbumine 8 mg tablet with that of the originator.

Perindopril: The generic and originator mean C_{max} for perindopril was 110.449 ng/mL and 101.657 ng/mL respectively. The T_{max} for both the generic and originator tablets was 0.6 and 0.8 hours respectively.

Perindoprilat: The generic and originator mean C_{max} for perindoprilat was 15.615 ng/mL and 15.373 ng/mL respectively. The T_{max} for both the generic and originator tablets was 2.7 and 2.5 hours respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

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 the ACE inhibitor class to cause this effect in man is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when this occurs, it is considered as benign.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- colloidal anhydrous silica
- sodium bicarbonate
- lactose
- chlorophyllin-copper complex aluminium lake
- microcrystalline cellulose
- magnesium stearate

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 in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

All presentations are available in pack sizes of 30 tablets presented in either PA/Al/PVC/Al or PVC/Al blister packs in triple laminated bags with a desiccant in a sachet.

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

Australian Register of Therapeutic Goods (ARTG)

AUST R 176516 - PERISYL perindopril erbumine 2 mg tablet blister pack
AUST R 176518 - PERISYL perindopril erbumine 4 mg tablet blister pack
AUST R 176517 - PERISYL perindopril erbumine 8 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

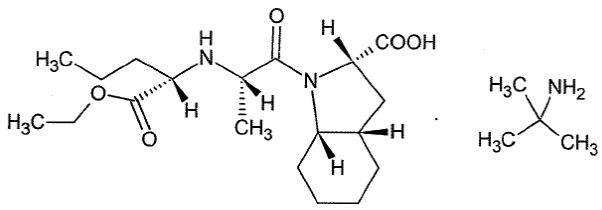
6.7 PHYSICOCHEMICAL PROPERTIES

Perindopril is a dipeptide monoacid monoester with a perhydroindole group and no sulfydryl radical. Perindopril erbumine is a white powder, readily soluble in purified water, 95% ethanol and chloroform. Perindopril has five asymmetric centres and is synthesised stereoselectively so that it is a single enantiomer (all S stereochemistry).

Chemical Structure

Chemical name: tert-butylammonium (2S, 3aS, 7aS)-1-N-[(S)-1-ethoxycarbonyl butyl]-L-alanyl) perhydroindole-2-carboxylate

Structural formula:



Molecular formula: $C_{19}H_{32}N_2O_5$, $C_4H_{11}N$ Molecular weight: 441.6

CAS Number

107133-36-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

12/05/2021

10 DATE OF REVISION

06/06/2022

Summary Table of Changes

Section Changed	Summary of New Information
4.3, 4.4, 4.5	Editorial changes
4.4	Updated information regarding hyperkalaemia risk and dermatological reactions. Relocated information on use in hepatic impairment and renal impairment. Updated information on use in renal impairment. Deleted repetitive text on angioedema.
4.5	Deleted repetitive text on interactions relating to angioedema and hyperkalaemia.
4.8	Added endocrine disorder adverse effect and updated information on psychiatric disorder.

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