AUSTRALIAN PRODUCT INFORMATION

ACETEC®

(enalapril maleate) tablets

1 NAME OF THE MEDICINE

enalapril maleate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACETEC tablets contain 2.5 mg, 5 mg, 10 mg or 20 mg enalapril maleate as the active ingredient.

Excipients of known effect: sugars as lactose and sulfites.

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

3 PHARMACEUTICAL FORM

ACETEC 2.5 tablets	:	White, oval shaped, biconvex and debossed with “2.5” score line “G” on one side and score line on the other side.
ACETEC 5 tablets	:	White, arc triangle shaped, biconvex and debossed with “5” over “G” on one side and score line on the other side.
ACETEC 10 tablets	:	Rusty red, arc triangle shaped, biconvex and debossed with “10” over “G” on one side and score line on the other side.
ACETEC 20 tablets	:	Peach, arc triangle shaped, biconvex and debossed with “20” over “G” on one side score line on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- **Hypertension:** All grades of essential hypertension and renovascular hypertension.

- **Congestive Heart Failure***:* Treatment of all degrees of symptomatic heart failure. In such patients, it is recommended that enalapril maleate be administered together with a diuretic.

- **Left Ventricular Dysfunction**: All degrees of left ventricular dysfunction where the left ventricular ejection fraction is less than 35%, irrespective of the presence or severity of obvious symptoms of heart failure.

4.2 DOSE AND METHOD OF ADMINISTRATION

Essential hypertension

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of enalapril maleate. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with enalapril maleate to reduce the likelihood of hypotension (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If the patient's blood pressure is not controlled with enalapril maleate alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued an initial dose of 2.5 mg should be used under medical supervision for at least one hour to determine whether excess hypotension will occur (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg/day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with enalapril maleate alone, a diuretic may be added.

Concomitant administration of enalapril maleate with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

To date there is insufficient experience with enalapril maleate in the treatment of accelerated or malignant hypertension. Enalapril maleate, therefore, is not recommended in such situations.

Use in the elderly (over 65 years)

The starting dose should be 2.5 mg. Some elderly patients may be more responsive to enalapril maleate than younger patients.

Renovascular hypertension

Since blood pressure and renal function in such patients may be particularly sensitive to ACE inhibition, therapy should be initiated with a lower starting dose (e.g. 5 mg or less). The dosage should then be adjusted according to the needs of the patient. Most patients may be expected to respond to 20 mg taken once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended (see next paragraph).

Congestive heart failure

Therapy with enalapril maleate must be started under close medical supervision.

Blood pressure and renal function should be monitored closely both before and after starting treatment with enalapril (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)** because severe hypotension and (more rarely) consequent renal failure have been reported.

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. If possible, the dose of diuretic should be reduced before beginning treatment.

The initial dose of enalapril maleate in patients with congestive heart failure (especially renally impaired or sodium- and/or volume-depleted patients) should be lower (2.5 mg or less), and it should be administered under close medical supervision to determine the initial effect on the blood pressure. The appearance of hypotension after the initial dose of enalapril maleate does not imply that hypotension will recur during chronic therapy with enalapril maleate and does not preclude continued use of the drug.

In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with enalapril maleate in congestive heart failure, the dose should be gradually increased, depending on the patient's response, to the usual maintenance dose (10-20 mg) given in a single or divided dose. This dose titration may be performed over a 2 to 4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure. In clinical trials in which mortality and morbidity was reduced, dosage was divided in two doses.

Left ventricular dysfunction without symptoms of overt heart failure

In the SOLVD-Prevention trial, the initial dose was 2.5 mg twice daily and titrated as above (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Congestive heart failure), to the usual maintenance does of 20 mg in two divided doses.

Dosage Adjustment in Renal Impairment

The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance $\leq$30 mL/min (serum creatinine $\geq$3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Table 1

Renal Status	Creatinine Clearance (mL/min)	Initial Dose (mg/day)
Normal Renal Function	>80 mL/min	5 mg
Mild Impairment	≤80, >30 mL/min	5 mg
Moderate to Severe Impairment	≤30 mL/min	2.5 mg
Dialysis Patients	-	2.5 mg on dialysis days[1]
[1] Dosage on non-dialysis days should be adjusted depending on blood pressure response.		

4.3 CONTRAINDICATIONS

1. History of previous hypersensitivity to enalapril maleate or to any component of the formulation and in patients with a history of angioneurotic oedema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

2. Pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use In Pregnancy).

3. ACETEC should not be administered with aliskiren in patients with diabetes (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4. ACETEC is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer ACETEC within 36 hours of switching to or from sacubitril/valsartan, or a product containing a neprilysin inhibitor. (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

General

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril maleate. This may occur at any time during treatment. In such cases enalapril maleate should be promptly discontinued and the patient carefully observed until the swelling disappears. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous adrenaline (epinephrine) solution 1:1,000 (0.3 to 0.5mL) and/or measures to ensure a patent airway should be promptly administered** (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS.))

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.

Black patients receiving ACE inhibitors have been reported to have higher incidence of angioedema compared to non-blacks.

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

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy may be at increased risk for angioedema (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients receiving concomitant ACE inhibitor and vildagliptin may be at increased risk for angioedema (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Anaphylactoid reactions during hymenoptera desensitization

Rarely, patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitization.

Hypotension

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis or dietary salt restriction or those suffering from diarrhoea or vomiting (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) In patients with heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotaemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression (including leucopenia/neutropenia). These reports generally involve patients who have pre-existing renal dysfunction and/or collagen vascular disease, some of whom have received concomitant immunosuppressant therapy. Most reports describe transient episodes for which a causal relationship to the ACE inhibitor could not be established. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. International marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded.

It is recommended that periodic haematologic monitoring be considered in patients with diseases known to affect bone marrow function (e.g., renal dysfunction, collagen vascular disease, etc) and/or who are taking concomitant therapy known to be associated with bone marrow depression.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Evaluation of the hypertensive patient should always include assessment of renal function (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Hyperkalaemia

(See also Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Agents Increasing Serum Potassium).

Elevated serum potassium (greater than 5.7 mmol/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalaemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalaemia may include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements and/or potassium-containing salt substitutes, or other drugs that may increase serum potassium (e.g., trimethoprim-containing products),which should be used cautiously, if at all, with enalapril maleate.

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.

If concomitant use of ACETEC and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Hypoglycaemia

Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Antidiabetics).

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Cough

A persistent non-productive, ticklish cough has been reported in some patients undergoing treatment with enalapril and other ACE inhibiting drugs. The cough is often worse when lying down. The cough is commoner in women (who account for about two thirds of reported cases). The patients who cough may have increased bronchial reactivity compared to those who do not cough. It may disappear in some patients with continued use or diminish or disappear if the dose of the drug is reduced.

In those in whom cough persists, the drug should be discontinued. The cough usually returns on rechallenge. No residual effects have been reported.

Use in Renal Impairment

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

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given

concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Use in the elderly

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric Use

Enalapril maleate has not been studied in children.

Effects on Laboratory Tests

Serum electrolytes

Hyperkalaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hyperkalaemia), hyponatraemia.

Creatinine, blood urea nitrogen

In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with enalapril maleate alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Haemoglobin and haematocrit

Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with enalapril maleate but are rarely of clinical importance unless another cause of anaemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anaemia.

Other (causal relationship unknown)

In marketing experience, rare cases of pancreatitis, neutropenia, thrombocytopenia, agranulocytosis and bone marrow depression have been reported. A few cases of haemolysis have been reported in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Liver Function Tests

Elevations of liver enzymes and/or serum bilirubin have occurred.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Hypotension; patients on diuretic therapy

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimised by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Agents causing renin release

The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Other cardiovascular agents

Enalapril maleate has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents increasing serum potassium

(See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hyperkalaemia).

Enalapril maleate may attenuate potassium loss caused by thiazide type diuretics. Risk factors for the development of hyperkaelemia include renal insufficiency and diabetes mellitus. Potassium sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements, potassium containing salt substitutes or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) may lead to significant increases in serum potassium. Therefore, if concomitant use of enalapril with these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored for hypoglycaemia, especially during the first month of treatment with an ACE inhibitor.

Serum lithium

As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, the serum lithium levels should be monitored carefully if lithium salts are to be administered.

Nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors)

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of ACE inhibitors or angiotensin II receptor antagonists may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with NSAIDs including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

These interactions should be considered in patients taking NSAIDs, including selective COX-2 inhibitors concomitantly with diuretics and ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.

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

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers, ACE inhibitors, or direct renin inhibitors (such as aliskiren) is associated with an increased risk of hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on enalapril maleate and other agents that affect the RAAS. Do not co-administer aliskiren with ACETEC in patients with diabetes. Avoid use of aliskiren with ACETEC in patients with renal impairment (GFR <60 mL/min).

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 enalapril.

Mammalian Target of Rapamycin (mTOR) Inhibitors

Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Neprilysin Inhibitors

Patients taking a concomitant inhibitor (e.g., sacubitril) may be at increased risk for angioedema (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Vildagliptin

Patients taking concomitant vildagliptin may be at increased risk for angioedema (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Use in Pregnancy

Pregnancy Category: D

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

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

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

There are no adequate and well-controlled studies of enalapril in pregnant women. Data, however, show that enalapril crosses the human placenta. Post marketing experience with all ACE inhibitors suggest that exposure in utero may be associated with hypotension and decreased renal perfusion in the fetus. ACE inhibitors have also been associated with fetal death in utero. There have been reports of fetal hypotension, renal failure, hyperkalaemia, skull hypoplasia and death when ACE inhibitors have been used during the second and third trimesters of 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 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.

There is a potential risk of fetal hypotension, decreased birth weight and decreased renal perfusion or anuria in the fetus from in utero exposure to ACE inhibitors. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus and may result in limb contractures, craniofacial deformations and hypoplastic lung development. Any neonate exposed to enalapril in utero should be observed closely for adequate urine output, blood pressure and hyperkalaemia. If required, appropriate medical measures should be initiated including administration of fluids or dialysis to remove enalaprilat from the circulatory system.

The maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day. Enalapril was not teratogenic in rabbits. There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril. Fetotoxicity expressed as a decrease in average fetal weight occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline.

Use in Lactation

It is not known if enalapril maleate is secreted in human milk. However, enalapril maleate has been demonstrated to be secreted into the milk of lactating rats. In view of this and a lack of knowledge of the effects of enalapril on neonates, this product should not be used during lactation or else breastfeeding should be discontinued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Enalapril maleate has been evaluated for safety in more than 10,000 patients, including over 1,000 patients treated for one year or more. Enalapril maleate has been found to be generally well tolerated in controlled clinical trials involving 2,677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8 %), dizziness (4.6 %) and fatigue (2.8 %). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0 percent of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with enalapril maleate reporting adverse experiences was comparable to placebo.

Adverse experiences occurring in greater than one percent of patients treated with enalapril maleate in controlled clinical trials are shown below:

Table 2

Percent of Patients in Controlled Studies

Adverse Event	Enalapril Maleate (n=2,667[1]) Incidence (discontinuation)	Placebo (n=230) Incidence
Headache	4.8 (0.3)	9.1
Dizziness	4.6 (0.4)	4.3
Fatigue	2.8 (<0.1)	2.6
Diarrhoea	1.6 (0.2)	1.7
Rash	1.5 (0.3)	0.4
Hypotension	1.4 (0.3)	0.4

Cough[2]	1.3 (0.2)	0.9
Nausea	1.3 (0.2)	1.7
Orthostatic Effects	1.3 (<0.1)	0.0
[1]Includes 363 patients treated for congestive heart failure receiving concomitant digoxin and diuretic therapy. [2] Refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE		

Clinical adverse experiences occurring since the drug was marketed or in 0.5 to 1.0% of patients in the controlled trials are listed below and, within each category, are in order of decreasing severity.

Cardiovascular

Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hypotension); syncope, orthostatic hypotension, palpitations, chest pain, rhythm disturbances, angina pectoris, Raynaud's phenomenon.

Endocrine

Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Gastrointestinal system

Ileus, pancreatitis, hepatic failure, hepatitis either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

Metabolic

Cases of hypoglycaemia in diabetic patients on oral antidiabetic agents or insulin have been reported (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Nervous system/psychiatric

Depression, confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, dream abnormality.

Renal

Renal failure, oliguria, renal dysfunction (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Respiratory

Pulmonary infiltrates, bronchospasm/asthma, dyspnoea, rhinorrhoea, sore throat and hoarseness.

Skin

Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, alopecia, psoriasis/psoriasis aggravation.

Other

Vasculitis, muscle cramps, hyperhidrosis, impotence, asthenia, photosensitivity, flushing, taste alteration, tinnitus, glossitis, blurred vision.

A symptom complex has been reported which may include fever, serositis, myalgia and arthralgia/arthritis; an elevated erythrocyte sedimentation rate (ESR), a positive antinuclear antibody (ANA), eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema

Angioedema has been reported in patients receiving enalapril maleate (0.2%). Angioedema associated with laryngeal oedema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalapril maleate should be discontinued and appropriate therapy instituted immediately (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.

Hypotension

Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension, and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension, beginning approximately six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor, which can be treated, if necessary, by intravenous infusion of normal saline solution.

Several hypertensive patients in clinical studies have received as much as 80 mg of enalaprilat intravenously over a 15-minute period. No adverse effects, other than those associated with recommended dosages, were observed.

Enalaprilat may be removed from the general circulation by haemodialysis.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Enalapril maleate is a prodrug, which, when administered orally is hydrolysed to release the active converting enzyme inhibitor, enalaprilat. The liver appears to be the main site for this conversion.

Administration of enalapril maleate to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients, the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril maleate has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity usually occurs two to four hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by four to six hours after administration.

The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate.

Following administration of enalapril maleate there was an increase or no change in renal blood flow; glomerular filtration rate was unchanged. However, in patients with low pretreatment glomerular filtration rates, the rates were usually increased.

When given together with thiazide-type diuretics, the blood pressure lowering effects of enalapril maleate are at least additive. Enalapril maleate may reduce or prevent the development of thiazide-induced hypokalaemia.

In patients with heart failure on therapy with digitalis and diuretics, treatment with oral or parenteral enalapril maleate was associated with decreases in peripheral resistance and blood pressure. Cardiac output increased, while heart rate (usually elevated in patients with heart failure) decreased. Pulmonary capillary wedge pressure was also reduced. Exercise tolerance and severity of heart failure, as measured by New York Heart Association criteria, improved. These actions continued during chronic therapy.

Mechanism of Action

How enalapril or converting enzyme inhibitors generally lower blood pressure is not entirely clear. The mechanism most favoured is inhibition of the angiotensin converting enzyme (ACE), a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure, enalapril is antihypertensive even in patients with low-renin hypertension. Enalapril maleate may also block the degradation of bradykinin, a potent vasodepressor peptide; however, the role that this plays in the therapeutic effect of enalapril remains to be elucidated.

Clinical Trials

In a multicentre, placebo-controlled clinical trial (SOLVD), 2,569 patients with all degrees of symptomatic heart failure and ejection fraction less than or equal to 35% were randomised to placebo or enalapril and followed for up to 55 months (SOLVD-Treatment).

A second multicentre trial used the SOLVD protocol for a study of patients with minimal or no symptoms of heart failure. SOLVD-Prevention patients, who had left ventricular ejection fraction less than or equal to 35% and no history of symptomatic heart failure were randomised to placebo (n=2,117) or enalapril (n=2,111) and followed for up to five years. These patients had little or no limitation of exercise tolerance due to dyspnoea or fatigue at randomisation and did not require treatment with digitalis, diuretics or vasodilators for heart failure at entry into the trial. The majority of patients in the trial had a history of ischaemic heart disease. A history of myocardial infarction was present in 80% of patients, current angina pectoris in 34% and a history of hypertension in 37%. Patients who had a recent myocardial infarction (i.e. within the preceding 30 days) were not included in the SOLVD trials.

In patients with left ventricular ejection fractions of less than 35%, enalapril maleate has been shown to retard the progression of heart failure, reduce hospitalisations for heart failure and reduce the risk of myocardial infarction. In addition, in patients who have significant symptoms of heart failure (New York Heart Association Classes 2 to 4) and also left ventricular ejection fractions of less than 35%, enalapril maleate has been shown to improve survival and reduce hospitalisations for unstable angina pectoris.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. The oral bioavailability of enalaprilat is approximately 40%. Protein binding is approximately 50%.

The absorption of oral enalapril maleate is not influenced by the presence of food in the gastrointestinal tract. The extent of absorption and hydrolysis of enalapril are similar for the various doses in the recommended therapeutic range.

Metabolism

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate.

Excretion

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril maleate. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to angiotensin converting enzyme (ACE).

In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril. The plasma concentration time profile of enalaprilat was complex with several exponentials including a very prolonged terminal phase ($t^{1}/_{2}$>30 hr). The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

Carcinogenicity

There was no evidence of a carcinogenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day. Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 mg and 180 mg/kg/day, respectively, and showed no evidence of carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium bicarbonate, pregelatinised maize starch, maize starch, lactose monohydrate and magnesium stearate. ACETEC 10 tablets also contain iron oxide red and ACETEC 20 tablets contain Iron Oxide Brown 70 IC07460 brown (ID 3792).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Al/Al

Pack sizes:

ACETEC 2.5: 10 tablets.

ACETEC 5, 10 and 20: 30 tablets.

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

Australian Register of Therapeutic Goods (ARTG)

AUST R 75457 - ACETEC 2.5 enalapril maleate 2.5mg tablet blister pack

AUST R 75497 - ACETEC 5 enalapril maleate 5mg tablet blister pack

AUST R 75498 - ACETEC 10 enalapril maleate 10mg tablet blister pack

AUST R 75499 - ACETEC 20 enalapril maleate 20mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Enalapril maleate is a white to off-white crystalline powder. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol and dimethylformamide

Enalapril maleate is the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. Following oral administration, enalapril is rapidly absorbed and then hydrolysed to enalaprilat, which is a specific, long acting angiotensin converting enzyme (ACE) inhibitor.

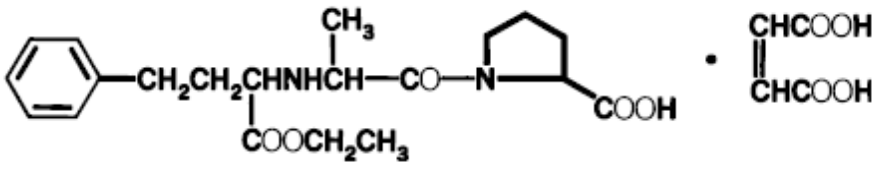
Enalapril tablets contain the maleate salt of enalapril, the ethyl ester of the parent diacid, enalaprilat.

Chemical name: The chemical name of enalapril maleate is (S)-1-[1-(ethoxycarbonyl)-3-phenylpropyl1]-L-alanyl]-L-proline,(Z)-2-butenedioate salt (1:1)

Molecular weight: 492.52

Molecular formula: $C_{20}H_{28}N_2O_5.C_4H_4O_4$

Chemical Structure



CAS Number

76095-16-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

18/08/2000

10 DATE OF REVISION

27/10/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.8	Add psoriasis/psoriasis aggravation

ACETEC® is a Viatris company trade mark

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