NEW ZEALAND DATA SHEET

ACETEC

1. Product Name

Acetec, 5, 10 & 20 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 5 mg, 10 mg, or 20 mg of enalapril maleate.

Excipients with known effect: Maize starch and lactose.

Allergen declaration: sulfites and sugars as lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Acetec 5 mg tablets are white arc triangle shaped biconvex tablets, debossed with “5” over “G” on one side and scoreline on the other side. Each tablet contains 5 mg of the active ingredient, enalapril maleate.

Acetec 10 mg tablets are rusty red, arc triangle shaped biconvex tablets, debossed with “10” over “G” on one side and scoreline on the other side. Each tablet contains 10 mg of the active ingredient, enalapril maleate.

Acetec 20 mg tablets are peach, arc triangle shaped biconvex tablets, debossed with “20” over “G” on one side and scoreline on the other side. Each tablet contains 20 mg of the active ingredient, enalapril maleate.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of:

- All grades of essential hypertension
- Renovascular hypertension
- All degrees of heart failure

  In patients with symptomatic heart failure, enalapril maleate is also indicated to:

  - Improve survival
  - Retard the progression of heart failure
  - Reduce hospitalisation for heart failure

- Prevention of symptomatic heart failure

In asymptomatic patients with left ventricular dysfunction, enalapril maleate is indicated to:

- Retard the development of symptomatic heart failure
- Reduce hospitalisation for heart failure

- Prevention of coronary ischaemic events in patients with left ventricular dysfunction

Enalapril maleate is indicated to:

- Reduce the incidence of myocardial infarction
- Reduce hospitalisation for unstable angina pectoris.

4.2 Dose and method of administration

Dose

Essential hypertension

The initial dose is 5 mg and is given once daily. The usual maintenance dose is one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 40 mg daily.

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 (2.5 - 5 mg). The dosage should then be adjusted according to the needs of the patient. Most patients may be expected to respond to one 20 mg tablet taken once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended (see next paragraph).

Concomitant diuretic therapy in hypertension

Symptomatic hypotension may occur following the initial dose of enalapril maleate; this is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume- or salt-depleted. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with enalapril maleate. If this is not possible, the initial dose of enalapril maleate should be low (2.5 mg) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient.

Dosage in renal insufficiency

Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

Table 1:

Renal Status	Creatinine clearance (mL/min)	Initial dose (mg/day)
Mild impairment	<80 - >30 mL/min	5 mg
Moderate impairment	<30 - >10 mL/min	2.5 – 5 mg
Severe impairment Normally, these patients will be on dialysis*	<10 mL/min	2.5 mg on dialysis days**

* See Warnings and Precautions: Haemodialysis patients

** Enalaprilat is dialysable. Dosage on non-dialysis days should be adjusted depending on blood pressure response.

Heart failure / Asymptomatic left ventricular dysfunction

The initial dose of enalapril maleate in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. Enalapril maleate may be used in the management of symptomatic heart failure usually with diuretics and, where appropriate, digitalis. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with enalapril maleate in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. 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 patients with symptomatic heart failure this dosage regimen was effective in reducing mortality.

Blood pressure and renal function should be monitored closely both before and after starting treatment with enalapril maleate (see Section 4.4) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics the dose should be reduced, if possible, before beginning treatment with enalapril maleate. 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 medicine. Serum potassium also should be monitored (see Section 4.5).

Method of administration

Since absorption of enalapril maleate tablets is not affected by food, the tablets may be administered before, during, or after meals.

4.3 Contraindications

Enalapril maleate is contraindicated in patients who are hypersensitive to any component of this product 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.

All angiotensin-converting enzyme inhibitors, including enalapril maleate, are contraindicated in pregnancy because of the potential risk of foetotoxicity.

Enalapril maleate should not be administered with aliskiren in patients with diabetes (see Section 4.5).

Enalapril maleate is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer enalapril maleate with 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor (see Section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril maleate, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see Section 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril maleate and/or diuretic is adjusted. 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 the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a

contraindication to further doses, which can usually be given without difficulty once the blood pressure has increased after volume expansion.

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

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.

Renal function 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 percent 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 disease, have developed minor and usually transient increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril maleate has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or enalapril maleate may be required.

Hypersensitivity / Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors, including enalapril maleate. This may occur at any time during treatment. In such cases, enalapril maleate should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. 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 epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway, should be administered promptly.

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 a higher incidence of angioedema compared to non-blacks.

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).

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

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy may be at increased risk for angioedema (see Section 4.3 and 4.5).

Patients receiving concomitant ACE inhibitor and vildagliptin may be at increased risk for angioedema (see Section 4.5).

Intestinal angioedema

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including CT scans or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during hymenoptera desensitisation

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

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed 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.

Anaphylactoid reactions during LDL apheresis

Rarely, patients receiving 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.

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

Surgery anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks 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.

Hyperkalaemia

Elevated serum potassium (greater than 5.7 mmol/L) was observed in approximately one percent 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 percent of hypertensive patients. Risk factors for the development of hyperkalaemia include renal

insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes, or other medicines 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, or other medicines that may increase serum potassium, 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 enalapril maleate and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see Section 4.5)

Hypoglycaemia

Diabetic patients treated with oral anti-diabetic 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).

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.

Paediatric use

The safety and effectiveness of enalapril maleate have been established in hypertensive paediatric patients age 1 month to 16 years. Use of enalapril maleate in these age groups is supported by evidence from adequate and well-controlled studies of enalapril maleate in paediatric and adult patients as well as by published literature in paediatric patients.

In multiple dose pharmacokinetic study in 40 hypertensive paediatric patients, excluding neonates, enalapril maleate was generally well tolerated. Pharmacokinetics following oral administration of enalapril are similar in these patients and comparable to historical values in adults.

In a clinical study involving 110 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥ 50 kg received either 1.25, 5 or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. In this study, enalapril maleate was generally well tolerated.

The adverse experience profile for paediatric patients is not different from that seen in adult patients.

Enalapril maleate is not recommended in neonates and in paediatric patients with glomerular filtration rate < 30 mL/min/1.73 m², as no data are available.

Pancreatitis

Pancreatitis may occur with angiotensin converting enzyme inhibitors and patients with abdominal pain on ACE inhibitors should be tested accordingly.

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 increased risks 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 coadminister aliskiren with enalapril maleate in patients with diabetes. Avoid use of aliskiren with enalapril maleate in patients with renal impairment (GFR<60 mL/min).

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin-aldosterone system, is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g, by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function.

Laboratory test findings

Creatine Blood Urea Nitrogen:
In controlled clinical trials minor increases in blood urea and serum creatinine 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.

Serum Electrolytes:
Hyperkalaemia and hyponatraemia have occurred.

Haemoglobin and Haematocrit:
Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, 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 percent of patients discontinued therapy due to anaemia.

Other (Causal Relationship Unknown):
In marketing experience, rare cases of pancreatitis, neutropenia, thrombocytopenia, bone marrow depression, and agranulocytosis have been reported.

A few cases of haemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests:
Elevations of liver enzymes and/or serum bilirubin have occurred.

4.5 Interaction with other medicines and other forms of interaction

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 4.2 and Section 4.4).

Agents Causing Renin Release

The antihypertensive effect of enalapril maleate 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

In clinical trials, serum potassium usually remained within normal limits. In hypertensive patients treated with enalapril maleate alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate plus a thiazide diuretic, the potassium-losing effect of the diuretic was attenuated usually by the effect of enalapril.

If enalapril maleate is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

Enalapril maleate may attenuate potassium loss caused by thiazide-type diuretics. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride) potassium supplements, or potassium-containing salt substitutes, or other medicines that may increase serum potassium (e.g., trimethoprim-containing products), which may lead to significant increases in serum potassium. If concomitant use of enalapril maleate with potassium supplements, potassium-sparing diuretics or potassium containing salt substitutes is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium (see section 4.4).

Anti-diabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and anti-diabetic 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 anti-diabetic 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 medicines which eliminate sodium, lithium clearance may be reduced. Therefore, the serum lithium levels should be monitored carefully if lithium salts are to be administered.

Non-steroidal anti-inflammatory medicines including selective cyclooxgenase-2 inhibitors

Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other anti-hypertensive medicines. Therefore, the anti-hypertensive effect of angiotensin II receptor antagonists or ACE inhibitors 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 non-steroidal anti-inflammatory medicines, including selective cyclooxgenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute 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 increased risks 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 enalapril maleate in patients with diabetes. Avoid use of aliskiren with enalapril maleate 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) inhibitor

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

Neprilysin inhibitors

Patients taking a concomitant neprilysin inhibitor (e.g., sacubitril) may be at risk for angioedema (see Section 4.3 and 4.4).

Vildagliptin

Patients taking concomitant vildagliptin may be at increased risk of angioedema (see Section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

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 foetus. ACE inhibitors have also been associated with foetal death in utero. There have been reports of foetal 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 foetal hypotension, decreased birth weight and decreased renal perfusion or anuria in the foetus from in utero exposure to ACE inhibitors. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the foetus 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 foetal toxicity occurred in some rabbits at doses of 1mg/kg/day or more. Saline supplementation prevented the maternal and foetal 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 foetotoxicity of teratogenicity in rats treated with up to 200mg/kg/day of enalapril. Foetotoxicity expressed as a decrease in average foetal weight occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline

Breastfeeding

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 breast feeding should be discontinued.

Fertility

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

For pre-clinical fertility data refer to section 5.3.

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).

4.8 Undesirable effects

Summary of the safety profile

Enalapril maleate has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. Enalapril maleate has been found to be generally well tolerated in controlled clinical trials involving 2677 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 have been mild and transient in nature. Discontinuation of therapy was required in 6.0% 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

	Enalapril maleate (n=2677[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] See 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 percent of patients in 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), syncope, orthostatic hypotension, chest pain, palpitations, rhythm disturbances, angina pectoris, Raynaud's phenomenon.

Endocrine
Syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Gastrointestinal
Ileus, pancreatitis (see Section 4.4), hepatic failure, hepatitis – either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

Metabolic
Cases of hypoglycaemia in diabetic patients on oral anti-diabetic agents or insulin have been reported (see Section 4.5).

Nervous system / psychiatric
Depression, confusion, somnolence, insomnia, nervousness, paresthesia, vertigo, dream abnormality.

Renal
Renal failure, oliguria, renal dysfunction.

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

Skin
Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritius, urticaria, alopecia.

Psoriasis/psoriasis aggravation has been reported. Frequency not known.

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

A symptom complex has been reported which may include fever, serositis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic 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). 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 effect) 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 percent and syncope occurred in 0.5 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients (See Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Limited data are available for overdosage in humans. The most likely manifestation of overdosage would be hypotension, beginning some 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 fifteen minute period. No adverse effects, other than those associated with recommended dosages, were observed.

Enalaprilat may be removed from the general circulation by haemodialysis (see Section 4.4).

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain, ATC code: C09A

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

Mechanism of action

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. 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.

ACE is identical to kininase II. Thus enalapril maleate may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril maleate remains to be elucidated.

While the mechanism through which enalapril maleate 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 maleate is anti-hypertensive even in patients with low-renin hypertension.

The onset of action of oral enalapril maleate is gradual and smooth; it begins within one hour and its effects usually continue for 24 hours. Consequently, enalapril maleate may be administered on a once-daily basis, with the advantages this brings in convenience and compliance.

The Studies of (patients with) Left Ventricular Dysfunction (SOLVD) was a multicentre, placebo controlled, double blind study of 6797 patients assessed as having Left Ventricular Dysfunction. All patients had a Left Ventricular Ejection Fraction of < 35% and were classified as New York Heart Association Class I-IV (NYHA).

The 2569 symptomatic patients (primarily NYHA Class II and III) were randomised into a Treatment arm, whilst the 4228 asymptomatic patients (NYHA Class I) were randomised into the Prevention arm. The combined results demonstrated an overall reduced risk for the development of major ischaemic events. Enalapril maleate decreased the incidence of myocardial infarction and reduced the number of hospitalisations for unstable angina pectoris in patients with left ventricular dysfunction.

In the Prevention arm, enalapril maleate significantly prevented the development of symptomatic heart failure and reduced the number of hospitalisations for heart failure. Enalapril maleate in the Treatment arm, as an adjunct to conventional therapy, significantly reduced overall mortality and hospitalisation for heart failure and improved NYHA functional class. In CONSENSUS, a similar study involving 253 patients with severe heart failure (NYHA Class IV), enalapril maleate was shown to improve symptoms and reduce mortality significantly.

The cardio-protective properties of enalapril maleate were demonstrated in these studies by the beneficial effects on survival and retardation of the progression of heart failure in patients with symptomatic heart failure; retardation of the development of symptomatic heart failure in asymptomatic patients with left ventricular dysfunction; and prevention of coronary ischaemic events in patients with left ventricular dysfunction, specifically reduction in the incidence of myocardial infarction and reduction in hospitalisation for unstable angina pectoris.

Pharmacodynamic effects

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 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of anti-hypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4-6 hours after administration. The duration of effect is dose related. However, at recommended doses, anti-hypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

Antihypertensive treatment with enalapril maleate leads to a significant regression of left ventricular hypertrophy with preservation of left ventricular systolic performance.

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 in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.

Chronic administration of enalapril maleate to patients with essential hypertension and renal insufficiency may be associated with improvements in renal function, evidenced by increased glomerular filtration rate.

In short term clinical studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

Treatment with enalapril maleate has been associated with favourable effects on plasma lipoprotein fractions and favourable or no effect on total cholesterol levels.

In patients with mild to moderate heart failure, enalapril retarded progressive cardiac dilatation/enlargement and failure, as evidenced by reduced left ventricular end diastolic and systolic volumes and improved ejection fraction.

Clinical data have shown that enalapril reduced the frequency of ventricular arrhythmias in patients with heart failure, although the underlying mechanisms and clinical significance are not known.

5.2 Pharmacokinetic properties

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 tablet is approximately 60%.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Similar peak serum concentrations of enalaprilat occur about four hours after an oral dose of enalapril. 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. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were achieved by the fourth day of administration of oral enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. 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.

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of oral enalapril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Radioactivity was found to cross the placenta following administration of ^{14}C enalapril maleate to pregnant hamsters.

There is no significant change in the plasma half-life of enalapril maleate in elderly patients.

No pharmacokinetic data is available on the effect of enalapril maleate in patients with hepatic dysfunction.

5.3 Preclinical safety data

Animal toxicity

Studies were performed to assess the teratogenic potential of enalapril in rats and rabbits and its effect on reproduction and postnatal development in rats.

Enalapril given to pregnant rats at doses up to 1200 mg/kg/day (2000 times the maximum human dose) from Day 6 through Day 17 of gestation did not reveal any evidence of embryo lethality or teratogenicity. Decreased average foetal weight occurred at 1200 mg/kg/day, but did not occur at this dosage level if the pregnant animals were given physiological saline for drinking instead of tap water during the dosing period. Average foetal weights were not affected in unsupplemented rats given up to 120 mg/kg/day.

Decreased maternal weight gain during the dosing period occurred at doses as low as 12 mg/kg/day, but did not occur in saline-supplemented rats given 1200 mg/kg/day. Saline supplementation in rats given 1200 mg/kg/day also prevented increases in serum urea nitrogen which occurred at doses as low as 100 mg/kg/day in unsupplemented rats (lowest dose level examined in pregnant rats), but only partially inhibited increases in serum potassium. In supplemented rats serum potassium was elevated in rats given 200 mg/kg/day, but not 100 mg/kg/day.

Enalapril was not teratogenic to saline-supplemented rabbits given doses up to 30 mg/kg/day (50 times the maximum human dose) from Day 6 through Day 18 of gestation. At 30 mg/kg/day (50 times the maximum human dose), enalapril produced maternal and foetal toxicity. Doses of 3 and 10 mg/kg/day were without maternotoxic or foetotoxic effects in saline-supplemented rabbits.

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

An *in vitro* Coombs' test of enalapril and its active metabolite (enalaprilat) did not show a positive Coombs' reaction within the range of concentrations tested (which did not induce direct haemolysis).

Neither enalapril nor enalaprilat 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 micro-nucleus test with mice, as well as an *in vivo* cytogenic study using mouse bone marrow.

There was no evidence of a carcinogenic effect when enalapril was administered for 106 weeks to rats at a dose up to 90 mg/kg/day (150 times the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively (150 and 300 times the maximum daily dose for humans) and showed no evidence of carcinogenicity.

6. Pharmaceutical Particulars

6.1 List of excipients

Acetec tablet also contains

- Sodium hydrogen carbonate
- Pregelatinized starch
- Maize starch
- Lactose monohydrate
- Magnesium stearate

Acetec 10 mg tablet also contains:

- Iron oxide red

Acetec 20 mg tablet also contains:

- Iron oxide brown

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

6.5 Nature and contents of container

HDPE bottle with a PP closure and a silica gel desiccant. Pack-sizes of 90, 100 & 500 tablets.

Polyamide / Al / PVC / Al blister. Pack size of 30 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

18 May 2000

10. Date of Revision of the Text

1 December 2025

Summary table of changes

Section	Summary of new information

4.4	Additional warning added regarding Intestinal Angioedema.