New Zealand Data sheet

1 PRODUCT NAME

RENITEC® 10 mg tablet
RENITEC® 20 mg tablet
RENITEC® M 5 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RENITEC 10 mg tablet contains 10 mg enalapril maleate
Each RENITEC 20 mg tablet contains 20 mg enalapril maleate
Each RENITEC M 5 mg tablet contains 5 mg enalapril maleate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

RENITEC M 5 mg tablet: A white, barrel-shaped, biconvex tablet. The tablet is scored on one side and is engraved RENITEC on the other. Each tablet contains 5 mg of enalapril maleate. Dimensions are 8 mm x 7 mm.

RENITEC 10 mg tablet: A rust-red coloured, barrel-shaped, biconvex tablet. The tablet is scored on one side and is engraved with the product name on the other side. Each tablet contains 10 mg of enalapril maleate. Dimensions are 8 mm x 7 mm.

RENITEC 20 mg tablet: A peach coloured, barrel-shaped, biconvex tablet. The tablet is plain on one side and is engraved MSD 714 on the other side. Each tablet contains 20 mg of enalapril maleate. Dimensions are 8 mm x 7 mm.

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, RENITEC 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, RENITEC 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.

RENITEC 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 RENITEC; 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 RENITEC. If this is not possible, the initial dose of RENITEC 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.

Special populations

Dosage in Renal Insufficiency

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

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 Section 4.4 - 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 RENITEC 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. RENITEC 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 RENITEC 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 RENITEC (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 RENITEC. The appearance of hypotension after the initial dose of RENITEC does not imply that hypotension will recur during chronic therapy with RENITEC and does not preclude continued use of the medicine. Serum potassium also should be monitored (see Section 4.5).

Paediatric population
See section 4.4.

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

4.3 Contraindications

RENITEC 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 RENITEC, are contraindicated in pregnancy because of the potential risk of foetotoxicity.

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

RENITEC is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer RENITEC within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor (See Sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

<u>Symptomatic Hypotension</u>
Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving RENITEC, 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 Sections 4.8 and 4.5). 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 RENITEC 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 be given usually 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 RENITEC. 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 RENITEC 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

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

Patients with renal insufficiency may require reduced and/or less frequent doses of RENITEC (see Section 4.2). In some patients, with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Some patients, with no apparent pre-existing renal disease, have developed minor and usually transient increases in blood urea and serum creatinine when RENITEC has been given concomitantly with a diuretic. Dosage reduction and/or discontinuation of the diuretic and/or RENITEC may be required.

Hypersensitivity/Angioneurotic Oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including RENITEC. This may occur at any time during treatment. In such cases, RENITEC 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.

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 (also 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 for angioedema.

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

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

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 anti-hypertensive agent.

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

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered part of the differential diagnosis of cough.

Surgery Anaesthesia

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

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, potassium-containing salt substitutes, or other medicines that may increase serum potassium (e.g., trimethoprim-containing products).

The use of potassium supplements, potassium-sparing diuretics, 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 RENITEC 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, Serum Potassium).

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).

Use in Pregnancy

The use of RENITEC during pregnancy is contraindicated. When pregnancy is detected, RENITEC should be discontinued as soon as possible.

In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor medicine during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor medicines. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. Use of ACE inhibitors during this period has been associated with foetal and neonatal injury including hypotension, renal failure, hyperkalaemia, and/or skull hypoplasia in the newborn. Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

These adverse effects to the embryo and foetus do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester.

Infants whose mothers have taken RENITEC should be closely observed for hypotension, oliguria and hyperkalaemia. Enalapril, which crosses the placenta, has been removed from

the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Nursing Mothers

Enalapril and enalaprilat are secreted in human milk in trace amounts. ACE inhibitors and angiotensin II receptor antagonists should not be used by breastfeeding mothers in the first few weeks after delivery because of possible profound neonatal hypotension; preterm babies may be at particular risk. In mothers who are breastfeeding older infants, the use of captopril, enalapril, or quinapril may be considered.

Paediatric Use

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

In a multiple dose pharmacokinetic study in 40 hypertensive paediatric patients, excluding neonates RENITEC tablets 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 anti-hypertensive 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 anti-hypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. In this study, RENITEC was generally well tolerated.

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

RENITEC 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

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 rennin-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.

4.5 Interaction with other medicines and other forms of interaction

Anti-hypertensive Therapy

The combination of RENITEC with other anti-hypertensive medicines may increase the anti-hypertensive effect, especially in combination with diuretics.

The combination of RENITEC with beta-adrenergic blocking agents, methyldopa, or calcium entry blockers has been shown to improve the efficacy of lowering the blood pressure.

Ganglionic blocking agents or adrenergic blocking agents, combined with RENITEC, should only be administered under careful observation of the patient.

A possible drop in serum-potassium due to thiazide-containing diuretics may be reduced by simultaneous administration of RENITEC.

There are no clinically significant pharmacokinetic medicine interactions between enalapril maleate and the following compounds: hydrochlorothiazide, furosemide, digoxin, timolol, methyldopa, warfarin, indomethacin and sulindac. Propranolol co-administered with enalapril maleate reduces serum enalaprilat concentrations, but this does not appear to be of any clinical significance. Since cimetidine does not interact with enalapril maleate in animals, it is not anticipated that a medicine interaction will occur in humans.

Serum Potassium

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

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

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, potassium-containing salt substitutes, or other medicines that may increase serum potassium (e.g., trimethoprim-containing products).

The use of potassium supplements, potassium-sparing diuretics, 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.

If concomitant use of RENITEC and the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (See Section 4.4, Hyperkalaemia).

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.

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 Warnings and Precautions).

Neprilysin inhibitors

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

Vildagliptin

Patients taking concomitant vildagliptin may be at increased risk for angioedema (see Sections 4.4).

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 RENITEC and other agents that affect the RAAS. Do not coadminister aliskiren with RENITEC in patients with diabetes. Avoid use of aliskiren with RENITEC in patients with renal impairment (GFR <60 ml/min).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of RENITEC during pregnancy is contraindicated (see Sections 4.3 and 4.4).

Breast-feeding

See Section 4.4.

Fertility

See Section 5.3.

4.7 Effects on ability to drive and use machines

Individual responses to medication may vary. Certain adverse effects that have been reported with RENITEC may affect some patient's ability to drive or operate machinery (see Section 4.8).

4.8 Undesirable effects

Summary of the safety profile

RENITEC has been demonstrated to be generally well tolerated. For the most part, adverse experiences have been mild and transient in nature, and have not required discontinuation of therapy.

The following adverse effects have been associated with the use of RENITEC tablets:

Dizziness and headache were the more commonly reported adverse effects. Fatigue and asthenia were reported in 2-3% of patients. Other adverse effects occurred in less than 2% of patients and included hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, and cough. Skin rash was reported in 1.2% of patients and taste disturbances in 0.5% of patients.

Less frequently renal dysfunction, renal failure and oliguria have been reported.

Adverse effects which occurred very rarely, either during controlled clinical trials or after the medicine was marketed, include:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see Warnings and Precautions), 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

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

Other: Impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Laboratory Test Findings

Clinically important changes in standard laboratory parameters were rarely associated with administration of RENITEC. Increases in blood urea and serum creatinine, and elevations of liver enzymes and/or serum bilirubin have been seen. These are usually reversible upon discontinuation of RENITEC. Hyperkalaemia and hyponatraemia have occurred.

Decreases in haemoglobin and haematocrit have been reported.

Since the medicine was marketed a small number of cases of neutropaenia, thrombocytopaenia, bone marrow depression, and agranulocytosis have been reported in which a causal relationship to therapy with RENITEC could not be excluded.

Description of selected adverse reactions

Hypersensitivity/Angioneurotic Oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (see Section 4.4). In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
Limited data are available for overdosage in humans. The most prominent feature of overdosage reported to date is marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Serum enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg of 440 mg of enalapril, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If available, angiotensin II infusion may be beneficial. If ingestion is recent, induce emesis. Enalaprilat may be removed from the general circulation by haemodialysis. (See Section 4.4, Haemodialysis Patients.)

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE INHIBITORS, PLAIN, ATC code: C09A

RENITEC 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 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 RENITEC may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of RENITEC remains to be elucidated.

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

The onset of action of oral RENITEC is gradual and smooth; it begins within one hour and its effects usually continue for 24 hours. Consequently, RENITEC 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 & 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. RENITEC 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, RENITEC significantly prevented the development of symptomatic heart failure and reduced the number of hospitalisations for heart failure. RENITEC 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), RENITEC was shown to improve symptoms and reduce mortality significantly.

The cardio-protective properties of RENITEC 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 RENITEC 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 RENITEC 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.

Anti-hypertensive treatment with RENITEC 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 RENITEC 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 RENITEC 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 RENITEC 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 RENITEC 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 14C enalapril maleate. Radioactivity was found to cross the placenta following administration of 14C enalapril maleate to pregnant hamsters.

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

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

5.3 Preclinical safety data

Animal Toxicology

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

RENITEC M 5 mg, RENITEC 10 mg, RENITEC 20 mg tablets contain:
sodium bicarbonate
lactose monohydrate
starch-maize
starch-pregelatinised maize
magnesium stearate

RENITEC 10 mg tablets also contain:
iron-oxide red

RENITEC 20 mg tablets also contain:
iron-oxide red
iron-oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C and avoid transient temperatures above 50°C. Store in a dry place.

6.5 Nature and contents of container

RENITEC M 5 mg, RENITEC 10 mg and 20 mg tablets are available in blister platforms of 10 tablets with 3 platforms per outer carton (30 tablets).

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription

8 SPONSOR

Organon New Zealand Limited
P O Box 99 851
Newmarket
Auckland
NEW ZEALAND
Tel: 0800 111 700

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 17 May 1984.

10 DATE OF REVISION OF THE TEXT

13 January 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Additional text addressing the precaution of increased risk for angioedema with concomitant use of vildagliptin
4.5	Additional text addressing the increased risk for angioedema from drug interaction with vildagliptin