

## NEW ZEALAND DATA SHEET

### Name of Medicine

#### **CO-RENITEC<sup>®</sup>**

*enalapril maleate (USP) plus hydrochlorothiazide (BP/USP)*  
20 mg/12.5 mg tablets

### Presentation

CO-RENITEC (20 mg enalapril/12.5 mg HCTZ), a yellow, round fluted biconvex tablet engraved MSD718 on one side and scored on the other. Diameter 9 mm.

### Therapeutic Class

CO-RENITEC is a combination of an angiotensin converting enzyme inhibitor (enalapril maleate) and a diuretic (hydrochlorothiazide).

CO-RENITEC is highly effective in the treatment of hypertension. The anti-hypertensive effects of the two components are additive and sustained for at least 24 hours. A higher percentage of patients with hypertension respond satisfactorily to CO-RENITEC than to either component administered alone.

### Indications

CO-RENITEC is indicated for the treatment of patients with hypertension who are not adequately controlled on monotherapy.

### Dosage and Administration

CO-RENITEC is supplied as tablets for oral administration.

CO-RENITEC 20/12.5 contains enalapril maleate 20 mg and hydrochlorothiazide 12.5 mg.

### Hypertension

In hypertension, the usual dose of CO-RENITEC is either half or one tablet administered once daily, depending on the dose of RENITEC being taken prior to initiating therapy. If necessary the dosage may be increased to two tablets administered once daily.

### Prior Diuretic Therapy

Symptomatic hypotension may occur following the initial dose of CO-RENITEC; this is more likely in patients who are volume or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with CO-RENITEC.

### Dosage in Renal Insufficiency

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/min or below (i.e. moderate or severe renal insufficiency).

The recommended initial dose of enalapril maleate, when used alone, in mild renal insufficiency is 5 to 10 mg.

In patients with creatinine clearance of >30 and <80 mL/min, CO-RENITEC should be used only after titration of the enalapril component.

## Contraindications

- Anuria.
- CO-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.
- Hypersensitivity to other sulfonamide-derived medicines.
- All angiotensin converting enzyme inhibitors, including CO-RENITEC, are contraindicated in pregnancy because of the potential risk of foetotoxicity. (See also Use in Pregnancy and the Nursing Mother under Warnings and Precautions.)

## Warnings and Precautions

### Hypotension and Electrolyte/Fluid Imbalance

As with all anti-hypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Particular consideration should be given when therapy is administered to patients with ischaemic heart or cerebrovascular disease because 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. Following restoration of effective blood volume and pressure reinstatement of therapy at reduced dosage may be possible or either of the components may be used appropriately alone.

### 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

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/min or below (i.e. moderate or severe renal insufficiency).

In patients with creatinine clearance of >30 and <80 mL/min, CO-RENITEC should be used only after titration of the enalapril component.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when enalapril has been given concomitantly with a diuretic. If this occurs during therapy with CO-RENITEC, the combinations should be discontinued. Reinstatement of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

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In some patients, with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen with angiotensin converting enzyme (ACE) inhibitors.

### **Hepatic Disease**

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

### **Surgery/Anaesthesia**

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

### **Metabolic and Endocrine Effects**

Thiazide therapy may impair glucose tolerance. Dosage adjustment of anti-diabetic agents including insulin, may be required.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy; however, at the 12.5 mg dose contained in CO-RENITEC, minimal or no effect was reported.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, enalapril may increase urinary uric acid and thus attenuate the hyperuricaemic effect of hydrochlorothiazide.

### **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 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 before 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 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 angio-oedema unrelated to ACE inhibitor therapy may be at

increased risk of angio-oedema while receiving an ACE inhibitor (see also Contraindications).

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosis has been reported with the use of thiazides.

### **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.

### **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.

### **Haemodialysis Patients**

The use of CO-RENITEC is not indicated in patients requiring dialysis for renal failure (see Dosage and Administration). 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.

### **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 as part of the differential diagnosis of cough.

### **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, or potassium-containing salt substitutes.

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 CO-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 Interactions, *Serum Potassium*.)

### **Use in Pregnancy**

The use of CO-RENITEC during pregnancy is contraindicated. When pregnancy is detected, CO-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.

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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.

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

Infants whose mothers have taken CO-RENITEC should be closely observed for hypertension, 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. There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.

### **Nursing Mothers**

Both enalapril and thiazides appear in human milk. If the use of the product is deemed essential, the patient should stop nursing.

### **Paediatric Use**

Safety and effectiveness in children have not been established.

### **Use in the Elderly**

In clinical studies the efficacy and tolerability of enalapril maleate and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

### **Pancreatitis**

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

### **Animal Toxicology**

#### Carcinogenesis/Mutagenesis

##### *Enalapril*

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 embryoletality 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

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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 unsupplemented rats serum potassium was elevated in rats given 200 mg/kg/day, but not 100 mg/kg/day.

There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2½ times the maximum human dose). At these doses, foetotoxicity, expressed as a decrease in average foetal weight, occurred in both species. No foetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril and hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril and hydrochlorothiazide in mice.

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 this dosage level (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, nor enalapril in combination with hydrochlorothiazide, was mutagenic in the Ames microbial mutagen test with or without metabolic activation.

The combination of enalapril and hydrochlorothiazide was also negative in an *in vitro* alkaline elution assay in rat hepatocytes and in an *in vitro* chromosome aberration assay.

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 in 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.

### *Hydrochlorothiazide*

Two year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains Ta 98, Ta 100, Ta 1535, TA 1537 and TA 1538 and in the

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Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

### **Effect on the Ability to Drive and use Machinery**

Individual responses to medication may vary. Certain side effects that have been reported with CO-RENITEC may affect some patients' ability to drive or operate machinery (see Adverse Effects).

### **Adverse Effects**

CO-RENITEC is usually well-tolerated. In clinical studies, adverse effects have usually been mild and transient, and in most instances have not required interruption of therapy.

The most common clinical adverse effects were dizziness and fatigue, which generally responded to dosage reduction and seldom required discontinuation of therapy.

Other side effects (1-2%) were: muscle cramps, nausea, asthenia, orthostatic effects including hypotension, headaches, cough and impotence.

Less common side effects which occurred either during controlled trials or during marketed use include:

*Cardiovascular:* Syncope, non-orthostatic hypotension, palpitation, tachycardia, chest pain

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

*Gastrointestinal:* Pancreatitis, diarrhoea, vomiting, dyspepsia, abdominal pain, flatulence, constipation

*Nervous System/Psychiatric:* Insomnia, somnolence, paraesthesia, vertigo, nervousness

*Respiratory:* Dyspnoea

*Skin:* Stevens-Johnson Syndrome, rash, pruritus, diaphoresis

*Other:* Renal dysfunction, renal failure, decreased libido, dry mouth, gout, tinnitus, arthralgia

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.

### **Hypersensitivity/Angioneurotic Oedema**

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

### **Laboratory test Findings**

Clinically important changes in standard laboratory parameters were rarely associated with administration of CO-RENITEC. Occasional hyperglycaemia, hyperuricaemia and hypokalaemia have been noted. 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 CO-RENITEC. Hyperkalaemia has occurred.

Decreases in haemoglobin and haematocrit have been reported.

## **Interactions**

### **Other Anti-hypertensive Therapy**

Additive effects may occur when enalapril maleate is used together with other anti-hypertensive therapy.

### **Serum Potassium**

The potassium losing effect of thiazide diuretics is usually attenuated by the effect of enalapril. Serum potassium usually remains within normal limits.

The use of potassium supplements or potassium-sparing agents or potassium containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If concomitant use of CO-RENITEC and any of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium. (See Precautions, *Hyperkalaemia*.)

### **Lithium**

Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended. Refer to the package inserts for lithium preparations before use of such preparations.

### **Non-Steroidal Anti-Inflammatory Medicines Including Selective Cyclooxygenase-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 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 acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

### **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, hyperkalemia, 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.

### **Non Depolarising Muscle Relaxants**

Thiazides may increase the responsiveness to tubocurarine.

### **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.

### **Overdosage**

No specific information is available on the treatment of overdosage with CO-RENITEC. Treatment is symptomatic and supportive. Therapy with CO-RENITEC should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

### **Enalapril Maleate**

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 and 440 mg of enalapril maleate, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If available, angiotensin II infusion may be beneficial. Enalaprilat may be removed from the general circulation by haemodialysis. (See Warnings and Precautions, *Haemodialysis Patients*.)

### **Hydrochlorothiazide**

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloreaemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

### **Actions**

CO-RENITEC provides anti-hypertensive and diuretic activity. Enalapril maleate and hydrochlorothiazide have been used singly and concomitantly for the treatment of hypertension. The anti-hypertensive effects of these two agents are additive and are sustained for at least 24 hours. The enalapril maleate component of CO-RENITEC has been shown to attenuate the potassium loss associated with hydrochlorothiazide.

Enalapril maleate and hydrochlorothiazide have similar dosage schedules. Therefore, CO-RENITEC provides a convenient formulation for the concomitant administration of enalapril maleate and hydrochlorothiazide.

## **Enalapril maleate**

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 may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated. 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 anti-hypertensive even in patients with low-renin hypertension.

## **Enalapril maleate-Hydrochlorothiazide**

Hydrochlorothiazide is a diuretic and anti-hypertensive agent which increases plasma renin activity. Although enalapril alone is anti-hypertensive even in patients with low-renin hypertension, concomitant administration of hydrochlorothiazide in these patients leads to greater reduction of blood pressure.

## **Pharmacokinetics**

### **Enalapril maleate**

Oral enalapril maleate 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%.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate.

Excretion of enalapril 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 enalapril maleate. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril maleate 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.

### **Hydrochlorothiazide**

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

## **Enalapril maleate – Hydrochlorothiazide**

Concomitant multiple doses of enalapril maleate and hydrochlorothiazide have little or no effect on the bioavailability of these medicines. The combination tablet is bioequivalent to concomitant administration of the separate entities.

### **Pharmacodynamics**

#### Enalapril Maleate

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 to 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.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with a slight 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. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.

Anti-hypertensive treatment with enalapril leads to a significant regression of left ventricular hypertrophy with preservation of left ventricular systolic performance.

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

#### Enalapril Maleate - Hydrochlorothiazide

In clinical studies the extent of blood pressure reduction seen with the combination of enalapril maleate and hydrochlorothiazide was greater than that seen with each individual component given alone. In addition, the anti-hypertensive effect of CO-RENITEC was sustained for at least 24 hours.

### **Pharmaceutical Precautions**

Store in a dry place below 30°C.

### **Medicine Classification**

Prescription Medicine

## Package Quantities

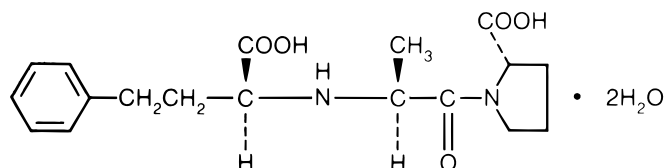
CO-RENITEC tablets will be available in aluminium foil blisters containing 30 tablets per pack.

## Further Information

### Chemistry

#### Enalapril Maleate

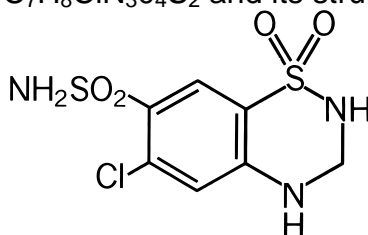
Enalapril maleate is the ethyl ester of the parent diacid, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxy-carbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is  $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$ , and its structural formula is:



Enalapril maleate is a white to off-white crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol and dimethylformamide.

#### Hydrochlorothiazide

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1, 1-dioxide. Its empirical formula is  $C_7H_8ClN_3O_4S_2$  and its structural formula is:



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

## Name and Address

Merck Sharp & Dohme (New Zealand) Limited  
 P O Box 99 851  
 Newmarket  
 Auckland  
 NEW ZEALAND  
 Tel. 0800 500 673

## Date of Preparation

21 November 2011

DP-CRN-1111(211111)

