Approved Professional Information for Medicines for Human Use:

Please note: This application is submitted as a duplicate and hence [PRODUCT NAME] is used to indicate the approved proprietary names as per below:

Master	Duplicate 1	Duplicate 2
Austell Enalapril 5 mg, 10 mg and 20 mg	Apex Enalapril 5 mg, 10 mg and 20 mg	Camox Enalapril 5 mg, 10 mg and 20 mg

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

[PRODUCT NAME] 5 mg TABLET

[PRODUCT NAME] 10 mg TABLET

[PRODUCT NAME] 20 mg TABLET

COMPOSITION:

Each **[PRODUCT NAME] 5 mg** tablet contains 5 mg enalapril maleate.

Each **[PRODUCT NAME] 10 mg** tablet contains 10 mg enalapril maleate.

Each **[PRODUCT NAME] 20 mg** tablet contains 20 mg enalapril maleate.

Other ingredients:

Maleic acid, lactose monohydrate, hypromellose E 464, croscarmellose sodium, sodium lauryl fumarate.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicines – other hypotensives.

PHARMACOLOGICAL ACTION:

PHARMACODYNAMICS

Mechanism of action

Enalapril is an ACE inhibitor used in the treatment of hypertension.

The inhibition of angiotensin converting enzyme (ACE) lowers systemic vascular resistance and mean, diastolic and systolic blood pressures in various hypertensive states.

Alone, treatment with ACE inhibitors normalise blood pressure in 50 % of patients with mild to moderate hypertension, and this is increased to 90 % when used in combination with a calcium channel blocker, β adrenergic receptor blocker, or a diuretic.

Duiretics are particularly effective in combination therapy due to rendering the patient's blood pressure renin-dependent.

Increasing evidence shows superiority of ACE inhibitors as the choice of antihypertensive for diabetics, resulting in improved endothelial function and reduced cardiovascular events, when compared to therapy with calcium channel blockers, β adrenergic receptor blockers or diuretics.

PHARMACOKINETICS

Absorption

Enalapril is a prodrug, hydrolysed by esterases in the liver to the active diacid form, enalprilat. Enalaprilat is a highly potent inhibitor of ACE, although poorly absorbed orally.

Enalapril is rapidly absorbed via oral administration, with 60 % oral bioavailability unaffected by food, and peak plasma concentrations achieved within 1 hour. Enalaprilat peak concentrations are then achieved within 3 to 4 hours after extensive hydrolysis of enalapril in the liver.

Distribution

Enalaprilat is 50-60 % bound to plasma proteins, with a volume of distribution of approximately 2 litres/kg.

Metabolism and elimination

Enalapril is extensively hydrolysed in the liver, and excreted as enalaprilat and unchanged drug primarily via the urinary route. 90 % of intravenous enalaprilat is also excreted via the kidneys.

The effective half-life of enalaprilat is reported as 11 hours.

Special populations

Renal clearance is decreased in renal dysfunction, the elderly and in congestive heart failure. The half-life increases in renal dysfunction. Cirrhosis causes decreased oral bioavailability and urinary excretion, with an increase in half-life.

INDICATIONS:

[PRODUCT NAME] is indicated in:

- **Hypertension**

Treatment of hypertension

- **Heart failure**

[PRODUCT NAME] is indicated for the treatment of symptomatic congestive heart failure, in combination with diuretics and when appropriate, digitalis. In these patients enalapril improves symptoms, increases survival, and decreases the frequency of hospitalization.

- **Asymptomatic left ventricular dysfunction**

[PRODUCT NAME] may be given prophylactically to patients with asymptomatic left ventricular dysfunction to delay the onset of symptomatic heart failure, and has been used in these patients to reduce the incidence of coronary ischaemic events, including myocardial infarction.

CONTRA INDICATIONS:

Hypersensitivity to enalapril or any of the other ingredients.

Patients with a history of angioneurotic oedema relating to previous treatment with an angiotensin converting enzyme inhibitor.

Patients with hereditary or idiopathic angioedema.

Pregnancy (see **PREGNANCY AND LACTATION**).

Renal artery stenosis.

Concomitant use of **[PRODUCT NAME]** with fluoroquinolones in patients with moderate to severe renal impairment.

WARNINGS:

Should a woman become pregnant while receiving **[PRODUCT NAME]**, the treatment should be stopped promptly and switched to a different class of medicine (See **CONTRAINDICATIONS** and **PREGNANCY AND LACTATION**)

ACE-inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the 2nd and 3rd trimesters (See **PREGNANCY AND LACTATION**). ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios, which may result in limb contractures, craniofacial deformities and hypoplastic lung development, as well as hypotension, hyperkalaemia, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

Infants whose mothers have taken **[PRODUCT NAME]** should be closely observed for hypotension, oliguria and hyperkalaemia. These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE-inhibitor exposure limited to the first trimester.

Enalapril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit.

Concomitant use of fluoroquinolones with ACE inhibitors, such as **[PRODUCT NAME]**, may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **CONTRAINDICATIONS**). Renal function should be assessed before initiating treatment, and monitored during concomitant treatment with **[PRODUCT NAME]** and fluoroquinolones.

INTERACTIONS:

Antihypertensive therapy

The combination of **[PRODUCT NAME]** with other antihypertensive medicines may increase the antihypertensive effect, especially in combination with diuretics, and agents such as alcohol which lower blood pressure.

The combination of **[PRODUCT NAME]** with beta-adrenergic blocking agents and methyldopa or calcium entry blockers, potentiates the hypotensive effects of **[PRODUCT NAME]**.

Ganglionic blocking agents or adrenergic blocking agents, combined with **[PRODUCT NAME]**, should only be administered with careful observation of the patient.

Because of lack of experience, concomitant treatment of **[PRODUCT NAME]** with calcium antagonists is not recommended.

Serum potassium

Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium containing salt substitutes.

In patients with renal failure, the administration of **[PRODUCT NAME]** may lead to elevation of serum potassium. 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. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Serum lithium

The lithium elimination may be reduced. Therefore the lithium levels of serum should be carefully compared if lithium salts are to be administered.

Non-steroidal anti-inflammatory drugs

In patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of **[PRODUCT NAME]** may result in a further deterioration of renal function. These effects are usually reversible.

Indomethacin, aspirin and possibly other NSAIDS have been reported to reduce the hypotensive action of ACE inhibitors.

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors, such as **[PRODUCT NAME]**, may precipitate acute kidney injury (see **CONTRAINDICATIONS**).

PREGNANCY AND LACTATION:

See **CONTRAINDICATIONS** and **WARNINGS**.

Pregnancy

Safety in pregnancy and lactation has not been established.

[PRODUCT NAME] passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of **[PRODUCT NAME]** in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur. In addition, use of **[PRODUCT NAME]** during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system (See **CONTRAINDICATIONS** and **WARNINGS**).

Breastfeeding mothers

Enalapril and enalaprilat are secreted in human milk. Caution should be exercised if **[PRODUCT NAME]** is given to a breastfeeding mother.

DOSAGE AND DIRECTIONS FOR USE:

Since its absorption is not affected by food, **[PRODUCT NAME]** tablets may be administered before, during or after meals.

Treatment for hypertension

The initial dose is 10 mg to 20 mg depending on the degree of hypertension and is given once daily. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of

hypertension the initial dose is 20 mg daily. The dosage should be adjusted according to the needs of the patient.

Concomitant diuretic therapy in hypertension

Symptomatic hypotension may occur following the initial dose of **[PRODUCT NAME]**; 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 **[PRODUCT NAME]**. If this is not possible, the initial dose of **[PRODUCT NAME]** should be low (5 mg or less) 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.**

Renal status	**Creatinine clearance ml/min**	**Initial dose mg/day**
Mild impairment	Less than 80, greater than 30.	5
Moderate Impairment	Less than or equal to 30, greater than 10.	2,5
Severe Impairment. Normally, these patients will be on dialysis*.	Less than or equal to 10	2,5 mg on dialysis days**

*****See **SPECIAL PRECAUTIONS** – Haemodialysis patients

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

Heart Failure/Asymptomatic Left Ventricular Dysfunction

The initial dose of **[PRODUCT NAME]** 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. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with **[PRODUCT NAME]** 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 before and after starting treatment with **[PRODUCT NAME]** (See **SPECIAL PRECAUTIONS**) because hypotension and consequent renal failure have been reported. In patients treated with diuretics, the dosage should be reduced if possible before beginning treatment with **[PRODUCT NAME]**. The appearance of hypotension after the initial dose of **[PRODUCT NAME]** does not imply that hypotension will recur during chronic therapy with **[PRODUCT NAME]** and does not preclude continued use of **[PRODUCT NAME]**.

Serum potassium also should be monitored (see INTERACTIONS).

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side Effects

Most of the adverse effects of ACE inhibitors are reversible on withdrawing therapy.

Blood and lymphatic disorders

Less frequent: decreased haemoglobin, decreased haematocrit. Neutropenia and agranulocytosis have also been reported in patients taking enalapril.

Metabolism and nutrition disorders

Frequent: hyperkalaemia

Less frequent: hyponatraemia

Nervous system and psychiatric disorders

Frequent: headache, depression, taste alteration

Less frequent: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, dream abnormality

Eye disorders

Frequent: blurred vision

Ear and labyrinth disorders

Less frequent: tinnitus

Cardiac and vascular disorders

Frequent: dizziness (more frequently reported side effect), hypotension (including orthostatic hypotension), syncope, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see **SPECIAL PRECAUTIONS**), chest pain, rhythm disturbances, angina pectoris

Less frequent: orthostatic hypotension, palpitations, flushing, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders

Frequent: cough, dyspnoea

Less frequent: rhinorrhoea, sore throat, hoarseness, bronchospasm/asthma, pulmonary infiltrates

Gastrointestinal disorders

Frequent: nausea, diarrhoea, abdominal pain

Less frequent: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, stomatitis, glossitis

In very rare cases intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.

Hepatobiliary disorders

Less frequent: hepatic failure, hepatitis – either hepatocellular or cholestatic, jaundice

Skin and subcutaneous tissue disorders

Frequent: rash, angioneurotic oedema which may be fatal, of the face, extremites, lips, tongue, glottis and/or larynx have been reported. (see **SPECIAL PRECAUTIONS**)

Less frequent: diaphoresis, pruritus, urticaria, alopecia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive anti-nuclear antibody, elevated erythrocyte sedimentation rate, eosinophilila, and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Musculoskeletal and connective tissue disorders

Less frequent: muscle cramps

Renal and urinary disorders

Less frequent: renal dysfunction, renal failure, oliguria

Reproductive system and breast disorders

Less frequent: impotence

General disorders and administration site disorders

Frequent: asthenia, fatigue

Investigations

Frequent: increases in serum creatinine

Less frequent: increases in blood urea, elevations of liver enzymes and/or bilirubin

These are usually reversible upon discontinuation of **[PRODUCT NAME]**.

Special Precautions

Symptomatic hypotension

Symptomatic hypotension may occur in patients with uncomplicated hypertension. 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 **INTERACTIONS** and **SIDE EFFECTS**). In patients with heart failure, with or without associated renal insufficiency, symptomatic

hypotension has been observed. This is the 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 those patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of **[PRODUCT NAME]** 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 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 or 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 congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with **[PRODUCT NAME]**. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of **[PRODUCT NAME]** may be necessary.

Aortic stenosis/hypertrophic cardiomyopathy

[PRODUCT NAME] should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Renal function impairment

Patients with renal insufficiency may require reduced and/or less frequent doses of **[PRODUCT NAME]**. Careful dose titration and monitoring of renal function should be done (see **DOSAGE AND DIRECTIONS FOR USE**).

Hypersensitivity/angioneurotic Oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including **[PRODUCT**

NAME]. This may occur at any time during treatment. In such cases, **[PRODUCT NAME]** should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in receiving symptoms.

Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy 1:1 000 (0,3 ml to 0,5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE – inhibitors, including **[PRODUCT NAME]**, 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 ACE-inhibitors including **[PRODUCT NAME]** (see also **CONTRAINDICATIONS**).

Anaphylactoid reactions during hymenoptera desensitization

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

Haemodialysis patients

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

Cough

Cough has been reported with the use of ACE-inhibitors, including **[PRODUCT NAME]**. 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.

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

Serum potassium – see **INTERACTIONS**

Effects on ability to drive and use machines:

Experience with enalapril indicates that **[PRODUCT NAME]** is unlikely to impair a patient's ability to drive or use machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULAR OF ITS TREATMENT

There have been reports of overdosage with enalapril.

The main adverse event 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.

The recommended treatment of overdosage is supportive and volume expansion such as intravenous infusion of normal saline solution. If available, angiotensin II infusion may be beneficial. If ingestion is recent, induce emesis.

Activated charcoal may be given within one hour of ingestion.

Enalaprilat may be removed from the general circulation by haemodialysis (see **SPECIAL PRECAUTIONS**, Haemodialysis Patients).

IDENTIFICATION:

[PRODUCT NAME] 5 is a white to off-white, round, flat-face bevelled edge tablet with "5" debossed on the one side and a breakline on the other.

[PRODUCT NAME] 10 is a white to off-white round, flat-face bevelled edge tablet with “10” debossed on the one side and a breakline on the other.

[PRODUCT NAME] 20 is a white to off-white round, flat-face bevelled edge tablet with “20” debossed on the one side and a breakline on the other.

PRESENTATION:

[PRODUCT NAME] 5, 10 and 20 tablets are available in blister packs (alu-alu blister foil and aluminium foil) of 10 or 14 packed in an outer carton of 30 or 28 tablets.

STORAGE INSTRUCTIONS:

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

Do not remove tablets from blisters until required for use.

Keep blisters in the original carton until required for use.

KEEP THIS MEDICINE OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

[PRODUCT NAME] 5 mg: 48/7.1.3/0922

[PRODUCT NAME] 10 mg: 48/7.1.3/0923

[PRODUCT NAME] 20 mg: 48/7.1.3/0924

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown, Johannesburg

2193, South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date on the registration certificate: 01 October 2015

Date of revision: 19 September 2020