Approved Professional Information for Medicines for Human Use:

[PRODUCT NAME]

Please note: This application for registration is submitted as a triplicate and hence [PRODUCT NAME] is used in 1.3 to indicate the registered names as on the registration certificates:

Master (Proposed proprietary name)	**Duplicate 1 (Proposed proprietary name)**	**Duplicate 2 (Proposed proprietary name)**
ACENTEN 20/12,5	**RENLIN 20/12,5**	**ENALAPRIL HCTZ 20/12,5 AUSTELL**

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

[PRODUCT NAME] 20/12,5 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of enalapril maleate and 12,5 mg of hydrochlorothiazide.

Contains sugar.

Each [PRODUCT NAME] tablet contains lactose monohydrate 130,10 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

[PRODUCT NAME] is pale yellow in colour, approximately 8,5 mm, circular, biconvex uncoated tablet with a non-functional break line on one side and plain on the other side. The break line is not intended for division of the tablet. The tablet should be swallowed whole.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[PRODUCT NAME] is indicated for the treatment of hypertension in patients where fixed combination therapy is considered more appropriate than monotherapy.

4.2 Posology and method of administration

Posology

Hypertension

The usual dosage is one tablet, administered once daily. If necessary, the dosage may be increased to a maximum of two tablets, administered once daily.

Special populations

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).

[PRODUCT NAME] is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of greater than 30 and less than 80 mL/min, [PRODUCT NAME] may be used but only after titration of the individual components.

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.

Paediatric population

Safety and efficacy in children have not been established.

Method of administration

Oral use.

The tablet should be swallowed whole.

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the ingredients of [PRODUCT NAME] (see section 6.1).
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Anuria
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Hypersensitivity to sulfonamide-derived medicines.
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria
- Lithium therapy: Concomitant administration with [PRODUCT NAME] may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).

- The concomitant use of [PRODUCT NAME] with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5).
- Severe hepatic impairment.
- Combination with sacubitril/valsartan due to the increased risk of angioedema. Do not administer [PRODUCT NAME] within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor. (See sections 4.4 and 4.5).
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers in patients with moderate to severe renal impairment and in the elderly (see section 4.4).
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving [PRODUCT NAME], the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and section 4.6).

Austell Pharmaceuticals (Pty) Ltd, 491087-9, Acenten, Renlin, Enalapril HCTZ Austell, 20/12,5 mg, Tablets

Enalapril Maleate-Hydrochlorothiazide

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors such as enalapril, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers and aliskiren is therefore contraindicated (see sections 4.3, 4.5 and 5.1). [PRODUCT NAME] should not be used concomitantly with aliskiren (see section 4.3).

Hypotension and Electrolyte Fluid Imbalance

Symptomatic hypotension may occur following the initial dose of [PRODUCT NAME]. In hypertensive patients receiving [PRODUCT NAME], symptomatic hypotension is more likely to occur if the patient has been volume - depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhoea or vomiting (see sections 4.5 and 4.8). Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. Special attention should be paid to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. In hypertensive 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 [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 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 contra-indication 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 [PRODUCT NAME]. 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 [PRODUCT NAME] may be necessary.

Renal Function Impairment

Renal failure has been reported in association with enalapril, as contained in [PRODUCT NAME], and has been mainly in patients with severe heart failure or underlying renal disease, including renal

artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible. [PRODUCT NAME] should not be administered to patients with renal insufficiency (creatinine clearance <80 mL/min. and >30 mL/min) until titration of enalapril has shown the need for the dose present in this formulation (see section 4.2).

Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic (see Special warnings and precautions for use, Enalapril Maleate, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4). If this occurs, therapy with [PRODUCT NAME] should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see Special warnings and precautions for use, Enalapril Maleate, Renovascular Hypertension in section 4.4).

Hyperkalaemia

The combination of enalapril and a low-dose diuretic cannot exclude the possibility of a hyperkalaemia to occur (see Special warnings and precautions for use, Enalapril Maleate, Hyperkalaemia in section 4.4).

Lithium

The combination of lithium with enalapril and diuretic medicines is generally not recommended (see sections 4.3 and 4.5).

Lactose

[PRODUCT NAME] contains less than 200 mg of lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

Safety and efficacy in children has not been established.

Enalapril Maleate

Aortic Stenosis/Hypertrophic Cardiomyopathy

[PRODUCT NAME] should be given with caution in patients with left ventricular valvular outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal Function Impairment

Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4).

Renovascular Hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors such as enalapril. Loss of renal function may occur with only mild changes in serum creatinine. [PRODUCT NAME] is contraindicated in these patients (see section 4.3)

Haemodialysis Patients

The use of enalapril is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor such as enalapril. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine.

Kidney Transplantation

There is no experience regarding the administration of enalapril in patients with a recent kidney transplantation. Treatment with enalapril is therefore not recommended.

Hepatic failure

ACE inhibitors such as enalapril, have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood.

Patients receiving ACE inhibitors such as enalapril, who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor such as enalapril and receive appropriate medical follow-up (see Special warnings and precautions for use, Hydrochlorothiazide, Hepatic Disease in section 4.4).

[PRODUCT NAME] is contraindicated in patients with severe hepatic impairment (see section 4.3).

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors such as enalapril. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril.

Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, inter-current events in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g., heparin, trimethoprim-containing products such as cotrimoxazole).

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, dysrhythmias. If concomitant use of enalapril and any of the above-mentioned medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see Special warnings and precautions for use, Enalapril Maleate-

Hydrochlorothiazide, Hyperkalaemia; Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 and section 4.5).

Hypoglycaemia

Diabetic patients treated with oral antidiabetic medicines or insulin starting an ACE inhibitor such as enalapril, should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see Special warnings and precautions for use, Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 and section 4.5).

Hypersensitivity/Angioneurotic Oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with enalapril maleate. 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. 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.

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 1:1 000 (0,3 mL to 0,5 mL) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors such as enalapril, have been reported to have a higher incidence of angioedema compared to Whites. However, in general it appears that Blacks have an increased risk for angioedema.

Patients with a history of angioedema unrelated to ACE inhibitor therapy such as enalapril, may be at increased risk of angioedema while receiving an ACE inhibitor such as enalapril (see section 4.3).
Patients receiving coadministration of ACE inhibitor such as enalapril 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 such as enalapril and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.5). The combination of enalapril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of enalapril therapy. If treatment with sacubitril/valsartan is stopped, enalapril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Anaphylactoid Reactions during Hymenoptera Desensitisation
Patients receiving ACE inhibitors such as enalapril during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy such as enalapril prior to each desensitisation.

Anaphylactoid Reactions during LDL-Apheresis
Patients receiving ACE inhibitors such as enalapril during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactic reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy such as enalapril prior to each apheresis.

Cough

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

Surgery/Anaesthesia

Enalapril blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or anaesthesia with medicines that produce hypotension to compensate via the renin-angiotensin system. Hypotension which occurs due to this mechanism can be corrected by volume expansion (see section 4.5).

Ethnic Differences

Enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Use with Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors such as enalapril/angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiation of treatment and monitored during treatment with fluoroquinolones and ACE inhibitors such as enalapril/angiotensin receptor blockers.

Hydrochlorothiazide

Renal Function Impairment

Hydrochlorothiazide 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) (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Enalapril Maleate, Renal Function Impairment in section 4.4).

[PRODUCT NAME] should not be administered to patients with renal insufficiency (creatinine clearance ≤80 mL/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

Hepatic Disease

Hydrochlorothiazide 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 (see Special warnings and precautions for use, Enalapril Maleate, Hepatic Failure in section 4.4).

Metabolic and Endocrine Effects

Hydrochlorothiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required (see Special warnings and precautions for use, Enalapril Maleate, Diabetic Patients in section 4.4). Hydrochlorothiazide may decrease serum sodium, magnesium and potassium levels.

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide diuretic therapy; however, at the 12,5 mg dose of hydrochlorothiazide contained in [PRODUCT NAME], minimal or no effect was reported. In addition, in clinical studies with 6 mg of hydrochlorothiazide no clinically significant effect on glucose, cholesterol, triglycerides, sodium, magnesium or potassium was reported.

Hydrochlorothiazide may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of latent hyperparathyroidism. Hydrochlorothiazide should be discontinued before testing parathyroid function.

Hydrochlorothiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. This effect on hyperuricemia appears to be dose-related. In addition, enalapril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide. As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Hydrochlorothiazide can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are xerostomia, thirst, weakness, lethargy, somnolence, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Although hypokalaemia may develop during use of hydrochlorothiazide diuretics, concurrent therapy with enalapril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not usually require treatment.

Hydrochlorothiazide may have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Anti-doping test

Hydrochlorothiazide contained in this product can produce a positive analytic result in an anti-doping test.

Hypersensitivity

In patients receiving hydrochlorothiazide, sensitivity reactions may occur with or without a history of allergy and bronchial asthma.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochlorothiazide.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking ARBIN CO should be informed of the risk of NMS C and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in the case of exposure, adequate protection should be advised to the patients to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. ARBIN CO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Enalapril Maleate-Hydrochlorothiazide

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Clinical trial data have shown that dual blockade of the renin angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors such as enalapril, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting medicines (see sections 4.3, 4.4 and 5.1).

Other Antihypertensive Medicines

Concomitant use of these medicines may increase the hypotensive effects of enalapril and hydrochlorothiazide. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors such as enalapril. Concomitant use of hydrochlorothiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors such as enalapril.

Use of [PRODUCT NAME] with lithium is contraindicated (see section 4.3).

Non-Steroidal Anti-Inflammatory Medicines including selective cyclooxygenase-2 (COX-2) inhibitors

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

The coadministration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors such as enalapril, exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy). Therefore, the combination should be administered with caution in patients with compromised renal function.

Enalapril Maleate

Potassium-sparing Diuretics, Potassium Supplements, or other medicines that may increase serum potassium

ACE inhibitors such as enalapril, attenuate diuretic induced potassium loss. 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., heparin, trimethoprim-containing products such as cotrimoxazole) may lead to significant increases in serum potassium. See also section 4.3.

Diuretics (hydrochlorothiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see sections 4.2 and 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake.

Tricyclic Antidepressants/Antipsychotics/Anaesthetics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors such as enalapril, may result in further reduction of blood pressure (see section 4.4).

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril.

Mammalian Target of Rapamycin (mTOR) inhibitors

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

Neprilysin Inhibitors

Patients receiving concomitant ACE inhibitor such as enalapril and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.4). The concomitant use of enalapril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema.

Sacubitril/valsartan must not be started until 36 hours after taking the last dose of enalapril therapy. Enalapril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan. (See sections 4.3 and 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors such as enalapril (see section 4.5).

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors such as enalapril.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors such as enalapril and antidiabetic medicines (insulins, oral hypoglycaemic medicines) 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 (see sections 4.4 and 4.8).

Acetyl Salicylic Acid (Aspirin), Thrombolytics and β-blockers

Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β- blockers.

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury (see sections 4.3 and 4.4).

Hydrochlorothiazide

Non-depolarising Muscle Relaxants

Hydrochlorothiazide may increase the responsiveness to tubocurarine.

Alcohol, Barbiturates, or Opioid Analgesics

Potentiation of orthostatic hypotension may occur.

Antidiabetic Medicines (Oral Medicines and Insulin)

Dosage adjustment of the antidiabetic medicine may be required (see sections 4.4 and 4.8).

Cholestyramine and Colestipol Resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85 and 43 percent, respectively.

Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)

Increased risk of torsades de pointes.

Digitalis Glycosides

Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalaemia.

Kaliuretic Diuretics (e.g., Furosemide), Carbenoxolone, or Laxative Abuse

Hydrochlorothiazide may increase the loss of potassium and/or magnesium.

Pressor Amines (e.g., Noradrenaline (Norepinephrine))

The effect of pressor amines may be decreased.

Cytostatics (e.g., Cyclophosphamide, Methotrexate)

Hydrochlorothiazide may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of [PRODUCT NAME] is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take [PRODUCT NAME] during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with [PRODUCT NAME] should be stopped immediately and if appropriate, alternative therapy should be started.

ACE inhibitors:

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly

spins bifida) and of kidney malformations. [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 new-borns, have been reported after administration of [PRODUCT NAME] during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breastfeeding

This medicine is contraindicated in lactating women (see section 4.3).

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or somnolence/fatigue may occur (see section 4.8).

4.8 Undesirable effects

Side effects reported with enalapril/hydrochlorothiazide combination [PRODUCT NAME], enalapril alone or hydrochlorothiazide alone either during clinical studies or after the medicine was marketed include:

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and Infestations			sialadenitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders		anaemia (including aplastic and haemolytic), neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia,	

		agranulocytosis, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases	
Immune system disorders			anaphylactic reactions
Endocrine disorders			syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	hypokalaemia, increase of cholesterol, increase of triglycerides, hyperuricaemia	hypoglycaemia (see section 4.4), hypomagnesemia, gout*, increase in blood glucose, hypercalcaemia (see section 4.4)	electrolyte imbalance, including hyponatraemia
Nervous system and psychiatric disorders	headache, depression, syncope, taste alteration	confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, decreased libido**, Dream abnormality, sleep disorders, paresis (due to hypokalaemia)	restlessness

Eye disorders	blurred vision		xanthopsia
Ear and labyrinth disorders		tinnitus	
Cardiac and vascular disorders	dizziness, hypotension, orthostatic hypotension, rhythm disturbances, angina pectoris, tachycardia	flushing, palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high-risk patients (see section 4.4) Raynaud's phenomenon	necrotising angiitis (vasculitis)
Respiratory, thoracic and mediastinal disorders	cough, dyspnoea	rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma pulmonary infiltrates, respiratory distress (including pneumonitis and pulmonary oedema), rhinitis, allergic alveolitis/eosinophilic pneumonia	
Gastrointestinal disorders	nausea, diarrhoea, abdominal pain	ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia,	

		gastric irritations, dry mouth, peptic ulcer, flatulence**, stomatitis/aphthous ulcerations, glossitis, intestinal angioedema	
Hepatobiliary disorders		hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)	
Skin and subcutaneous tissue disorders	rash (exanthema), hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4).	diaphoresis, pruritus, urticaria, alopecia erythema multiforme, stevens-johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, 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 ANA (antinuclear antibody), elevated ESR (erythrocyte sedimentation rate), eosinophilia, and leukocytosis. rash, photosensitivity or

			other dermatologic manifestations may occur.
Musculoskeletal and connective tissue disorders	muscle cramps†	arthralgia**	
Renal and urinary disorders		renal dysfunction, renal failure, proteinuria, oliguria, interstitial nephritis	glycosuria
Reproductive system and breast disorders		impotence, gynecomastia	
General disorders and administration site conditions	asthenia, chest pain, fatigue	malaise, fever	
Investigations	hyperkalaemia, increases in serum creatinine	increases in blood urea, hyponatraemia elevations of liver enzymes, elevations of serum bilirubin	

* Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

** Only seen with doses of hydrochlorothiazide 12,5 mg and 25 mg

† The frequency of muscle cramps as common pertains to doses of hydrochlorothiazide 12,5 mg and 25 mg, whereas, the frequency of the event is uncommon as it pertains to 6 mg doses of hydrochlorothiazide.

Description of Selected Adverse Reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. (See also sections 4.4 and 5.1).

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 to SAHPRA via the “6.04 Adverse Medicine Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific information is available on the treatment of overdosage with [PRODUCT NAME]. Treatment is symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage and correction of dehydration, electrolyte imbalance and hypotension by established procedures introduced within 2 hours after ingestion.

Enalapril Maleate

The most prominent feature of overdosage is 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 intravenous infusion of normal saline solution. If available, angiotensin II infusion may be beneficial. Enalapril may be removed from the general circulation by haemodialysis (see section 4.4, Haemodialysis patients).

Hydrochlorothiazide

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE-inhibitors and diuretics

ATC Code: C09 BA02

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, which leads to increased plasma renin activity (due to removal of negative feedback on renin release), and decreased aldosterone secretion.

ACE is identical to kininase II. Thus, enalapril may also block the degradation of bradykinin, a potential vasodepressor peptide.

However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

Mechanism of Action

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the reninangiotensin-aldosterone system, which plays a major role in the regulation of blood pressure, enalapril is antihypertensive even in patients with low-renin hypertension.

Enalapril maleate - hydrochlorothiazide

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Enalapril crosses the placental barrier. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Biotransformation

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

Elimination

Excretion of enalapril is primarily renal. The principal components in urine are enalaprilat, accounting for about 40 % of the dose, and intact enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril maleate is 11 hours. When plasma levels of hydrochlorothiazide 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.

Renal impairment

Enalaprilat may be removed from the general circulation by haemodialysis.

Lactation

After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1,7 µg/L (range 0,54 to 5,9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1,7 µg/L (range 1,2 to 2,3 µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breast-fed infant would be about 0,16 % of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 1 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0,75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24-hour period was 1,44 µg/L and 0,63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (< 0,2 µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10 mg in two mothers; enalapril levels were not determined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

pregelatinized starch

maleic acid

iron oxide yellow (E172)

dried maize starch

sodium stearyl fumarate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container.

6.5 Nature and contents of container

Aluminium/Aluminium blisters

[PRODUCT NAME] is packed in Aluminium/Aluminium blisters of 10 tablets; the blisters are then packed in an outer carton containing 30 tablets.

HDPE bottle pack:

[PRODUCT NAME] is packed in white opaque HDPE (High Density Polyethylene) containers with cap and liner.

Pack size: 100 tablets.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

Austell Pharmaceuticals (Pty) Ltd, 491087-9, Acenten, Renlin, Enalapril HCTZ Austell, 20/12,5 mg, Tablets

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER

ACENTEN 20/12,5: 49/7.1.3/1087

RENLIN 20/12,5: 49/7.1.3/1088

ENALAPRIL HCTZ 20/12,5 AUSTELL: 49/7.1.3/1089

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10. DATE OF REVISION OF THE TEXT

23 December 2022