Approved Professional Information for Medicines for Human Use:

COVENAP 5 mg and 10 mg

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

COVENAP 5 mg tablets

COVENAP 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COVENAP 5 mg tablet contains: 5 mg enalapril maleate.

Each COVENAP 10 mg tablet contains: 10 mg enalapril maleate.

Contains lactose monohydrate

Each COVENAP 5 mg tablet contains 129,8 mg lactose monohydrate.

Each COVENAP 10 mg tablet contains 125,8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

COVENAP 5 mg Tablets

Oval, convex, white snap tab tablets, one side scored with markings of EN 5.

COVENAP 10 mg Tablets

Oval, convex, white snap tab tablets, one side scored with markings of EN 10.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COVENAP is indicated in:

• Hypertension

Treatment of hypertension

• Heart failure

COVENAP is indicated for the treatment of symptomatic congestive heart failure, in combination with diuretics and when appropriate digoxin. In these patients COVENAP improves symptoms, increases survival, and decreases the frequency of hospitalisation.

• Asymptomatic Left Ventricular Dysfunction

In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction less than or equal to 35 %), COVENAP may decrease the rate of development of overt heart failure and may decrease the incidence of hospitalisation for heart failure.

4.2 Posology and method of administration

Posology

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 usual maintenance dose is one 20 mg tablet taken once 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 COVENAP; 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

COVENAP. If this is not possible, the initial dose of COVENAP 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.

Heart Failure / Asymptomatic Left Ventricular Dysfunction

The initial dose of COVENAP in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2,5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with COVENAP 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 COVENAP (see section 4.4) 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 COVENAP. The appearance of hypotension after the initial dose of COVENAP does not imply that hypotension will recur during chronic therapy with COVENAP and does not preclude continued use of COVENAP.

Serum potassium also should be monitored (see section 4.5).

Special populations

Renal impairment

Dosage in Renal Insufficiency

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

Enalaprilat is dialysable

Renal Status	**Creatinine Clearance mL/min**	**Initial Dose mg/day**
Mild to moderate Impairment	Less than 80, greater than 30	2,5 - 5

Method of administration

COVENAP is for oral administration.

Since its absorption is not affected by food, COVENAP tablets may be administered before, during or after meals.

4.3 Contraindications

• Hypersensitivity to enalapril or to any of the components of COVENAP

• A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARB's): These patients must never again be given these medicines

• Hereditary or idiopathic angioedema

• Hypertrophic obstructive cardiomyopathy (HOCM)

• Severe renal function impairment (creatinine clearance less than 30 mL/min)

• 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

• Porphyria

• Lithium therapy: Concomitant administration with COVENAP may lead to toxic blood concentration of lithium.

• Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving COVENAP, the treatment should be stopped promptly and switched to a different class of antihypertensive medicines, (see section 4.2 and 4.6).

COVENAP should be used with caution in the following conditions:

- Cerebrovascular disease or ischaemic heart disease – Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents.
- Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting) – Although it may occur in normo volaemic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of COVENAP induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion with or without hyponatraemia should have these conditions

corrected before therapy with COVENAP. Monitoring is required after initiating therapy and the patients should be monitored closely whenever the dose of COVENAP 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 of 0,9 % sodium chloride solution. 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 congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with COVENAP.

  If hypotension becomes symptomatic, a reduction of dose or discontinuation of COVENAP may be necessary.
- Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma: Increased risk for development of neutropenia or agranulocytosis.
- Neutropenia/ Agranulocytosis: Neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. COVENAP 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 COVENAP 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.

- In acute myocardial infarction, treatment with COVENAP should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 µmol/L or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 µmol/L or doubling of the pre-treatment value) then COVENAP may need to be withdrawn (see section 4.3).
- Hypotension in acute myocardial infarction-treatment with COVENAP must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2,5 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then COVENAP should be withdrawn.
- Bone marrow depression – Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia –COVENAP may cause an increase in serum potassium levels.
- Renal function impairment – Decreased elimination of COVENAP resulting in an increased risk of hyperkalaemia. These patients may require lower doses (see sections 4.2 and 4.3). In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and serum creatinine (see section 4.3). Some patients with no apparent pre-existing renal disease have developed minor and usually transient increases in blood urea and

serum creatinine when COVENAP has been given concomitantly with a diuretic. Dosage reduction of COVENAP and/or discontinuation of the diuretic may be required.

- Anaphylactoid reactions have occurred in patients using ACE inhibitors as in COVENAP during desensitising protocols involving for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption. Rarely, patients receiving ACE inhibitors as in COVENAP during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily with-holding ACE inhibitor as in COVENAP therapy prior to each desensitisation.
- Hypersensitivity/angioedema - If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with COVENAP, COVENAP should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms. 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 relieving symptoms.
- Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis, or larynx, it is likely to cause airway obstruction, and appropriate emergency therapy should be administered. This may include the administration of epinephrine (adrenaline) solution 1:1000 (0,3 to 0,5 ml) promptly and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. **These patients should never receive any COVENAP or any other ACE inhibitor or angiotensin receptor blockers again.**

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor (including COVENAP). (see section 4.3).

- COVENAP causes a higher rate of angioedema in black patients than in non-black patients.
- Concomitant therapy with potassium sparing diuretics such as spironolatone, triamterene, amiloride may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysrhythmias and cardiac arrest. (see section 4.5).
- Cough:

  Cough has been reported with the use of COVENAP. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. COVENAP 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.
- *Dual blockade of the renin-angiotensin-aldosterone system (RAAS)* There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of COVENAP and aliskiren is therefore contraindicated (see section 4.3). COVENAP should not be used concomitantly with aliskiren. (see section 4.3).

- Concomitant use of fluoroquinolones and ACE inhibitors/renin-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 initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers

COVENAP contains lactose; thus, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take COVENAP.

Paediatric population

Safety and efficacy in children has not been established.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of COVENAP with:

Antihypertensive therapy:

- The combination of COVENAP with other antihypertensive medicines may increase the antihypertensive effect, especially in combination with diuretics.
- Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- With loop, thiazide or related diuretics – “First dose hypotension” may occur (see section 4.2).
- The combination of COVENAP with beta-adrenergic blocking agents and methyldopa or calcium entry blockers potentiates the hypotensive effects of COVENAP.
- Ganglionic blocking agents or adrenergic blocking agents, combined with COVENAP, should only be administered with careful observation of the patient.

- Because of lack of experience, concomitant treatment of COVENAP 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, epleronone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes.

In patients with renal failure, the administration of COVENAP 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.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors as in COVENAP and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored for hypoglycaemia.

Non-steroidal anti-inflammatory agents including Selective Cyclooxygenase-2 Inhibitors:

• Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) – reduce the antihypertensive effects

of COVENAP. Blood pressure monitoring should be increased when any NSAID (including a selective COX-2 inhibitor) is added or discontinued in a patient treated with COVENAP**.**

In patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs including selective cyclooxgenase-2 inhibitors, the co-administration of COVENAP may result in a further deterioration of renal function. These effects are usually reversible.

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 as in COVENAP therapy including enalapril.

Serum lithium:

- The lithium elimination may be reduced with increases in serum lithium concentrations reported. Concomitant administration with COVENAP may lead to toxic blood concentrations of lithium (see section 4.3).

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

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

Fluoroquinolones

- Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3). This may lead to renal impairment due to altered renal haemodynamics in particular clinical situations.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of COVENAP is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take COVENAP 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 COVENAP should be stopped immediately and if appropriate, alternative therapy should be started. Foetal exposure to ACE inhibitors as in COVENAP 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. COVENAP 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 COVENAP 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).

Breastfeeding

Enalapril and enalaprilat are excreted in breast milk but their effect on the breastfeeding infant has not been determined. Therefore, the use of COVENAP is not recommended in women breastfeeding their babies (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 weariness may occur.

4.8 Undesirable effects

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with Enalapril Maleate.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders		Anaemia (including aplastic and haemolytic), neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, and lymphadenopathy, autoimmune diseases	
Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders	Hyperkalaemia	Hypoglycaemia including cases of hypoglycaemia in diabetic patients on oral antidiabetic medicine or insulin, hyponatraemia	
Psychiatric disorders	Depression	Confusion, insomnia, nervousness, dream abnormality, sleep disorders	
Nervous system disorders	Dizziness, headache, syncope, taste alteration	Somnolence, paraesthesia, vertigo	
Eye disorders	Blurred vision.		
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders	Chest pain, rhythm disturbances, angina pectoris, tachycardia,	Palpitations	

	myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients		
Vascular disorders	Hypotension (including orthostatic hypotension)	Flushing, orthostatic hypotension, Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders	Cough, dyspnoea	Rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia	
Gastrointestinal disorders	Nausea, diarrhoea, abdominal pain	Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritation, dry mouth, peptic ulcer, stomatitis/aphthous ulcerations, glossitis, and intestinal angioedema.	

Hepatobiliary disorders		Hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice).	
Skin and subcutaneous tissue disorders	Rash, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx	Diaphoresis, pruritus, urticaria, alopecia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma.	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 leucocytosis. Rash, photo sensitivity or

			other dermatologic manifestations may occur.
Musculoskeletal and connective tissue disorders		Muscle cramps	
Renal and urinary disorders		Renal dysfunction, renal failure, proteinuria, oliguria.	
Reproductive system and breast disorders		Impotence, gynaecomastia	
General disorders and administration site conditions	Asthenia, fatigue	Malaise, fever.	
Investigations	increases in serum creatinine	Increases in blood urea, elevations of liver enzymes, elevations of serum bilirubin	

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 Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms:

Severe hypotension, electrolyte disturbances and renal failure.

Treatment:

Treatment is symptomatic and supportive. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion by intravenous infusion of 0,9 % sodium chloride solution to correct hypotension and treating dehydration and electrolyte imbalances.

Enalaprilat may be removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 7.1.3 Vascular medicines - other hypotensives

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors

ATC Code: C09A A02

Enalapril (prodrug), following oral absorption, is hydrolysed to enalaprilat (active form), which is an angiotensin-converting enzyme (ACE) inhibitor. The essential effect of enalaprilat on the renin-angiotensin system is to inhibit the conversion of the inactive angiotensin I to the active angiotensin II. The principal pharmacological and clinical effects of ACE inhibitors arise from the fact that the synthesis of angiotensin II is suppressed.

5.2 Pharmacokinetic properties

Absorption

Enalapril is absorbed from the gastro-intestinal tract and has an oral bio-availability of approximately 60 %. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Distribution

Peak plasma of enalapril occur within an hour and it has a plasma half-life of approximately 1,3 hours, while the active form, enalaprilat, only peaks after 3-4 hours and has a plasma half-life of up to 11 hours. Enalaprilat is 50-60 % bound to plasma proteins.

Biotransformation

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

Elimination

Elimination is mainly via the kidneys (60 %) as intact enalapril and enalaprilat accounting for about 40 % of the dose. The remainder is eliminated in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose,

Magnesium stearate,

Maize starch,

Sodium hydrogen carbonate

Talc.

Lactose monohydrate

Isopropyl alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Do not remove blisters from the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN**.**

6.5 Nature and contents of container

COVENAP 5 mg and 10 mg tablets are packed in aluminium/aluminium blisters and packed into cardboard cartons.

COVENAP is available in pack sizes of 28's or 30's.

Not all pack sizes may be 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, 2193

Tel: +27 11 611 1400 or +27 860 287 835

8. REGISTRATION NUMBERS

COVENAP 5 mg tablets: 56/7.1.3/1176

COVENAP 10 mg tablets: 56/7.1.3/1177

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 April 2023

10. DATE OF REVISION OF THE TEXT